Technical Report No. 5

Sterile Pharmaceutical Packaging: Compatibility and Stability

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FOREWORD

THIS IS THE FIFTH IN A SERIES OF TECHNICAL REPORTS.[1-4] This Technical Report was prepared by Dr. Y. John Wang and Dr. Yie W. Chien under the auspices of the PDA Research Committee. It provides a comprehensive review of sterile pharmaceutical packaging systems with regard to product–package interactions, stability and compatibility.

In the selection of pharmaceutical packaging systems one must be aware of the potential physicochemical interactions with the product. These interactions are discussed in detail from both a practical application and a theoretical point of view.

R. M. Enzinger, Ph.D.
Chairman
Research Committee

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[1] "Validation of Steam Sterilization Cycles," Parenteral Drug Association Inc., Technical Monograph No. 1.

[2] "Validation of Aseptic Filling for Solution Drug Products," Parenteral Drug Association Inc., Technical Monograph No. 2.

[3] "Validation of dry Heat Processes Used for Sterilization & Depyrogenation," Parenteral Drug Association Inc., Technical Report No. 3.

[4] "Design Concepts for the Validation of a Water for Injection System," Parenteral Drug Association Inc., Technical Report No. 4.

PREFACE AND ACKNOWLEDGEMENT

The aim of this book is to provide for persons working with sterile pharmaceutical products a detailed account of the compatibility and stability of sterile formulations and packaging components. The intention is to present what is known in concise form, and to indicate how to avoid or resolve problems.

For hospital pharmacists, it is hoped that this book will serve as a valuable handy reference to assist them in identifying and solving the problems of sterile packaging. The tremendous increase in popularity of intravenous admixture programs makes it imperative that greater attention be paid to recognizing such problems. For manufacturing chemists involved in developing sterile pharmaceutical products, it is hoped that their awareness of the current knowledge of relevant physicochemical principles will enable them to design products that will have only minimal problems of compatibility and stability, both for the shelf life of the product and during its preparation and administration in hospital.

The book is arranged by type of interaction between formulation and packaging component, ie., sorption, leaching, and permeation, thus permitting an efficient presentation and analysis of common factors. Some important concepts are presented more than once, to ensure that they are not overlooked.

Ortho Pharmaceutical Corporation provided extensive assistance in the preparation of this book. We thank the Ortho librarians for their efficient help, the operators in the Ortho Word Processing Center, Mrs. Katie McAllister and Miss Karen Daniels for their patience and skill, and Miss Carol Neuwiesinger for her skillful drawing of the figures. Dr. Glenn Van Buskirk's thorough review of the manuscript lessened markedly the number of errors that may appear in the book.

Dr. Joseph Robinson and Dr. Michael Enzinger, as well as other members of the Research Committee of the Parenteral Drug Association, provided valuable comments and criticisms of the manuscript. Mr. Robert L. Buchanan of Tompkins Rubber Co. and Mr. Joseph Wong of Endo Laboratories Inc. provided helpful assistance in the initial literature search. Dr. David Frost, consultant editor, improved the readability of the text considerably.

Yu-chang John Wang
Yie W. Chien

TABLE OF CONTENTS

I. Introduction 1
II. Primary Packaging Systems 3
A. Containers 3
1. Glass containers 3
a. Nature and composition of glass 3
1) Soda-lime glasses 4
2) Borosilicate glasses 5
3) Amber glass 7
b. Classification of glass containers by USP 7
1) Type I 7
2) Type II 7
3) Type III 7
4) Type NP 8
2. Plastic containers 8
a. Polymerization 8
1) Polymerization by addition 8
2) Polymerization by condensation 11
b. Additives (Adjuvants) 13
1) Lubricants 13
2) Stabilizers 14
3) Plasticizers 14
4) Antioxidants 14
5) Antistatic agents 15
6) Slip agents 15
7) Dyes and pigments 15
c. Potential problems with plastic containers 15
B. Closure Systems 18
1. General 18
2. Composition of rubber closures 18
a. Primary ingredients 18
b. Adjuvants 18
3. Natural rubber 19
4. Synthetic elastomers 19
a. Polyisoprene rubber 19
b. Butyl rubber 19
c. Halogenated butyl rubber 20
d. Chloroprene rubber 20
e. Silicone rubber 20
f. Nitrile butadiene rubber 20

III. Potential Physicochemical Interactions 21
A. Sorption 22
1. Introduction 22
2. Mathematical Models 23
a. Freundlich equation 25
b. Simple linear equation 25
c. Langmuir equation 26
d. Diffusion equation—general 27
e. Diffusion equation—constant drug concentration .. 29
f. Diffusion equation—varying drug concentration ... 31
g. Diffusion equation—half-saturation time 33
h. First-order equation 34
i. Reversible first-order equation 35
j. Bi-exponential equation 37
3. Factors Influencing Sorption 38
a. Effect of concentration 38
b. Partition coefficient 40
c. pH of the solution 40
d. Effect of excipients 43
e. Effect of temperature 44
f. Structure of the polymeric sorbent 46
g. Structure of the sorbate 47
4. Drug-Plastic Interactions 49
a. General 49
b. Insulin 59
c. Nitroglycerin 60
d. Diazepam 62
5. Drug-Rubber Closure Interactions 63
6. Sorption of Antimicrobial Agents by Plastics 63
a. General 63
b. Benzalkonium chloride 71
c. Phenylmercuric compounds 73
7. Sorption of Antimicrobial Agents by Rubber Closures . 74
a. General 74
b. Benzyl alcohol 77
c. Phenol 79
d. Chlorobutanol 79
e. Parabens 80
f. Mercuric compounds 80
8. Adsorption onto Glass Surfaces 80
a. General 80

b. Biological compounds 81
c. Nonbiological compounds 85
B. Leaching 87
1. General 87
2. Mathematical Models 87
a. Square-root-of-time equation 87
b. First-order equation 89
c. Log-log equation 89
d. Linear equation 91
e. Desorption equation 91
3. Factors Influencing Leaching 93
a. Temperature 93
b. pH 94
c. Excipients 94
4. Leaching from Rubber Closures 95
5. Leaching from Plastic Containers 99
6. Corrosion of Glass Surface 102
a. Etching process 105
b. Leaching process 106
C. Permeation 107
1. General 107
2. Mathematical Models 108
a. Diffusion equation 108
b. Compartmental equations 111
3. Factors Influencing Permeation 113
a. Concentration 113
b. Partition coefficient 114
c. pH of the solution 115
d. Formulation components 116
e. External environment 117
f. Diffusion in polymers 117
g. Temperature 119
4. Permeation through Plastic Materials 119
5. Permeation through Elastomers 122
IV. References 126

I. INTRODUCTION

Sterile pharmaceutical packaging is defined as a primary packaging system that holds and is in direct contact with a sterile pharmaceutical formulation throughout the shelf life of the product. It consists of a container, possibly with a closure, and is considered an integral part of the pharmaceutical product. Examples of sterile pharmaceutical packaging are vials, ampules, plastic bags, plastic bottles, etc. This report encompasses primary packaging systems for such sterile pharmaceutical products as small- and large-volume parenterals, sterile irrigating solutions, and ophthalmic products, but not those for sterile diagnostic products and medical devices.

The primary packaging system should provide adequate protection against any ingress of foreign matter or egress of its contents, and it should possess acceptable physicochemical compatibility and long-term stability with the drug formulation within it until the drug formulation has been administered. Maintenance of a 2- to 3-year shelf-life is desirable. It is worth remembering that no container or closure is completely inert.

To make an intelligent selection of a primary packaging system that is compatible, both physically and chemically, with a sterile drug formulation, one should know about all potential instability/incompatibility problems of a packaging system with a particular drug formulation. This knowledge should derive from careful evaluation of: (*1*) the composition of the packaging system; (*2*) the treatment to which it will be subjected; and (*3*) the composition of the drug formulation.

Physicochemical interactions between sterile pharmaceutical products and their packaging components have been reported in the literature. We discuss these interactions, offering a quantitative analysis of them. Interactions are discussed in three categories: sorption, leaching, and permeation. In each category, discussion of the mathematical equations that are pertinent to an interaction is followed by evaluation and discussion of those critical parameters, such as temperature, that have been shown to influence the interaction. Finally, details of the interactions related to various packaging materials are presented as a handy guide for those involved in selecting a suitable primary packaging system for a formulation to achieve maximum compatibility and stability.

Numerous reviews have discussed interactions between pharmaceutical products and packaging components (Autian, 1963a,b; Polack, 1967; Busse and Hughes, 1969; Coates, 1973; Armstrong, 1974; Varsano and Gilbert, 1969). Autian (1963a,b) treated the subject in great depth and provided some guidance for quantitative analysis. Since the early '60s, however, a

better understanding of these interactions has resulted from developments in other fields, such as permeation through plastic films, pharmacokinetic modeling, absorption through biological membranes, and sustained-released dosage forms. This report provides a comprehensive review of those publications that discuss the concepts and mechanisms of these physicochemical interactions and the utilization of these concepts in the development of sterile pharmaceutical products.

II. PRIMARY PACKAGING SYSTEMS

The primary packaging system for a sterile pharmaceutical product consists of a container and a closure system:

A. Containers

Depending on composition of the materials used, containers may be classified as either glass or plastic. Their physicochemical and mechanical properties, as well as the processes involved in their manufacture, may be described as follows:

1. Glass containers

Glass has traditionally been considered the container material of choice for most sterile pharmaceutical products. However, it should not be assumed that glass is a totally inert material or that it is the ideal primary packaging component, either technically or commercially. General reviews on glass container for sterile products were provided by Adams (1977) and Anschel (1977).

a. Nature and composition of glass

Glass is a noncrystalline solid and, thus, shows only short-range order to 10 Å. It is also called a supercooled liquid because, under certain conditions, it can order itself and crystallize, a process known as "devitrification."

Glass consists of a mixture of oxides. The primary glass-forming (network-forming) oxides are SiO_2, B_2O_3, GeO_2, P_2O_5, V_2O_5, and Al_2O_3. Among these, SiO_2 is by far the major component for practically all commercial glasses. Silicone oxide is known to be the component responsible for the three-dimensional network of glass, the silicon dioxide tetrahedron.

Additionally, fluxes such as CaO, Na_2O, K_2O, BaO, or Li_2O, are needed to decrease the softening temperature of glass and, thereby, make it easier to process (Holloway, 1973). A stabilizer, such as Al_2O_3, Sb_2O_3, PbO_2, or ZnO, is also added to make the glass less prone to crystallization or devitrification and, thus, more durable. The general functions of glass formers, fluxes, and stabilizers are shown in Table I. Except for boric oxide, which can enter into the silicon dioxide tetrahedron structure, most of the inorganic oxides, such as those of sodium, potassium, calcium, magnesium, aluminum, barium, and iron, are only loosely bound in the network interstices and are, thus, relatively free to migrate. These migratory oxides can leach into a drug solution that is in intimate contact with the glass container, particularly during the process of thermal sterilization. The dissolved or

TABLE I
Common Constituents of Glasses and Their Effect on Properties

Constituent	Function	Physical and Chemical Properties
SiO_2	Network former	Crystalline silica has very high melting point and liquid silica has very high viscosity. High concentration of silica in a glass confers high softening temperature, low thermal expansion, good chemical durability.
B_2O_3	Network former	Will join network structure of silica glasses and reduce viscosity without producing adverse changes in thermal expansion and durability. Is a component of all heat-resisting and "Chemical" glasses.
PbO_2	Stabilizer	Can link SiO_4 tetrahedrons.
Al_2O_3	Stabilizer	Can join network in AlO_4 tetrahedron which are different in size from SiO_4. Strongly suppresses devitrification; increases process viscosity.
Na_2O	Network modifier (flux)	Markedly lowers softening temperature. Raises thermal expansion and ionic conductivity. Reduces durability.
K_2O	Network modifier (flux)	Similar to Na_2O, but the larger K^+ ion is less mobile than the Na^+ ion.
Li_2O	Network modifier (flux)	Similar to Na_2O, but the smaller Li^+ ion is more mobile than the Na^+ ion.
CaO	Network modifier (flux)	Inhibits mobility of alkali ions, hence increases resistivity and durability of alkali glasses. Shortens the working range.

Source: Holloway (1973).

extracted oxides may affect solution pH, catalyze physicochemical reactions, or even enter into the reactions themselves. Additionally, some components of glass are also prone to attack by drug solutions; as a result, flakes may be dislodged into the solution (Avis, 1975).

A true glass can be formed from the combination of SiO_2 and Na_2O. A true glass is, however, soluble in water and is thus called water glass. With the addition of a stabilizer, the water solubility of true glass is greatly reduced and an insoluble soda-lime glass is formed.

1) Soda-lime glasses

Soda-lime glasses account for approximately 90% of all commercial glasses. They are fairly resistant to chemicals, but cannot withstand sudden changes in temperature. Depending on the concentration of Na_2O, B_2O_3,

TABLE II
Major Chemical Constituents of Container Glasses and Glasses Used for Handling Ultrapure Solutions

Glass Type	Typical Concentration (wt %)[a]									
	SiO_2	Al_2O_3	ZrO_2	Na_2O	K_2O	Li_2O	B_2O_3	CaO	MgO	BaO
Soda-lima A	73	1	—	17	0.5	—	—	5	4	—
Soda-lime B	74	2	—	13	0.5	—	3	11	0.5	—
Borosilicate A	81	2	—	4	0.5	—	13	—	—	—
Borosilicate B	73	6	—	7	0.5	—	10	1	—	2
Alkali-resistant	71	1	15	11	0.5	1	—	—	—	—
Chemically Strengthened	66	20	—	9	—	5	—	—	—	—
High-silica	96	0.5	—	—	—	—	3	—	—	—
Vitreous-silica	100	—	—	—	—	—	—	—	—	—

[a] In all except high-silica and vitreous-silica glasses, F, Cl, SO_4, As, and Sb can be present in the range 0.05–0.5%.

CaO, and MgO in the glass network, soda-lime glasses are further classified into A and B types (Table II).

The chemical resistance of soda-lime glass containers can be increased by de-alkalization of the glass surface, generally by exposing the glass to SO_2 gas to remove Na_2O prior to use:

$$Na_2O + SO_2 + \tfrac{1}{2} O_2 \rightarrow Na_2SO_4$$

The sodium sulfate formed remains on the surface of the glass as a fine precipitate that is water soluble and can be rinsed off easily. The de-alkalization treatment can be accelerated if SO_2 is used in the presence of H_2O. This treatment reduces the extractable alkali by a factor of 25. By means of SO_2 treatment, a soda-lime B glass (USP Type III or Type NP glass) can be upgraded to a USP Type II glass.

The chemical resistance of de-alkalized glass is comparable to that of borosilicate glass in acidic and neutral solutions, but resistance to alkaline solutions is increased only slightly by de-alkalization treatment. De-alkalized glass containers are widely used for intravenous infusion solutions.

2) Borosilicate glasses

Borosilicate glasses are chemically highly resistant and are known commercially as Pyrex® and Kimax®. Typical compositions of these glasses are shown in Tables III and IV.

TABLE III
Typical Compositions (in %) of Chemically Resistant Borosilicate Glasses Manufactured by Kimble

Component	Code KG-33	KG-34	N51A	A 203
SiO_2	80.3	74.6	74.4	71.6
B_2O_3	13.0	11.3	9.5	9.2
Al_2O_3	2.4	5.0	5.5	5.3
CaO	0.1	—	0.9	0.8
MgO	—	—	0.3	0.1
BaO	—	2.7	2.2	2.1
Na_2O	4.2	6.0	6.6	6.4
K_2O	—	—	0.6	0.7
TiO_2	—	—	—	2.8
Fe_2O_3	—	—	—	0.3
Uses:	Scientific ware, process pipe	Blown bottles	Ampuls vials	Amber ampuls Amber vials

Source: Bacon (1968).

TABLE IV
Typical Composition (in %) of Alkali-Resistant Glasses Manufactures by Corning

Component	Code 7280	7740
SiO_2	71.3	80.3
B_2O_3	—	13.0
Al_2O_3	—	2.4
CaO	0.1	0.1
MgO	0.1	—
Li_2O	0.8	—
Na_2O	11.5	4.2
K_2O	0.1	—
ZrO_2	15.8	—

Source: Bacon (1968).

Borosilicate glasses, are also known as USP Type I glasses, can be divided into A and B subclasses (Table II). Class A, Pyrex glass, is more difficult to fabricate and has a lower thermal expansion coefficient than class B. Class B borosilicate glass, as exemplified by the so-called neutral glass, is

commonly used in the manufacture of chemically resistant ampuls and vials for pharmaceuticals.

3) Amber glass

Certain metals can be added to glass to produce such colors as amber, which results from an interaction between added ferric oxides and ferrous oxides and sulfur. Additional components are used to produce three types of amber glass for pharmaceutical use: reddish amber, 4% MnO_2 and 0.01% CrO_3; greenish amber, 0.1% to 1% SO_3; and brownish amber, 2% to 3% TiO_2.

Other colors can be produced by incorporating CoO for blue, NiO for gray, Cr_2O_3 for green, and CuO for bluish-green. These coloring metals in amber glass are potential sources of trace ions, particularly of iron.

b. Classification of glass container by USP

The United States Pharmacopeia (USP) has classified glass containers, according to their degree of chemical resistance, into four types:

1) *Type I* is made from a chemically high resistant borosilicate glass, composed principally of silicon dioxide and boric oxides. This glass has low leachability and a low thermal coefficient of expansion. In general, it is suitable for all parenteral drug products although sulfur dioxide treatment is sometimes utilized to increase its chemical resistance still more.
2) *Type II* is made from de-alkalized soda-lime glass, composed of relatively high levels of sodium oxide (13–17%) and calcium oxide (5–11%) (Table II). The existence of these two oxides makes Type II glass containers chemically less resistant than Type I (which contains 4–7% Na_2O and 1% CaO). A Type II glass container, however, has a lower concentration of migratory oxides than does Type III, and its chemical resistance can be increased by sulfur dioxide treatment, under controlled conditions of temperature and humidity to de-alkalize the internal surface of the glass containers. However, this de-alkalized surface will break down if it is repeatedly exposed to heat sterilization, depyrogenation or alkaline detergents. Thus, Type II glass containers possess relatively good chemical resistance for one-time use. A Type II glass container melts at a lower temperature, can more easily be molded, and has a higher coefficient of thermal expansion than does a Type I glass container. It may be suitable for use as a container for a drug solution that has been buffered to a pH below 7 or one that is not reactive with the glass.
3) *Type III* is also made from a soda-lime glass that contains relatively high levels of sodium oxide and calcium oxide, as do Type II glass containers. However, a Type III glass container has a higher concentration

of migratory oxides than does a Type II container, and it has not been subjected to de-alkalization treatment. It is usually suitable only for anhydrous liquids or for dry drug products.

4) *Type NP* is also made from a soda-lime glass and is not suitable for parenteral drug products.

2. Plastic containers

Plastics fall into two general classes: thermosets and thermoplastics. Because of their unusual versatility, thermoplastics have found wider application than thermosets, especially in the medical/pharmaceutical field.

Thermoplastic polymers are gradually finding use as packaging materials for sterile preparations, such as parenterals and ophthalmic solutions. One of the principal advantages of plastic containers is that they are not as fragile as glass. In addition, the flexibility of polyvinyl chloride IV bags is an advantage in the intravenous administration of large volumes of drug solution, because no air interchange is required.

Prior to the recognition of the potential of plastic materials in health care practice, glass was the dominant material used in the primary packaging of pharmaceutical products. The fragility and weight of glass, coupled with the broad range of properties offered by plastics, have resulted in marked increases in the use of plastics for pharmaceutical packaging during the last two decades (Giles and Pecina, 1975). Today, for example, plastics are used in such sterile primary packaging systems as syringes, bottles, vials, and ampuls (Table V). Fifteen years ago, only glass would have been considered for these uses.

a. Polymerization

Plastic materials are prepared from monomers by polymerization. To achieve polymerization, the monomers must be bifunctional, i.e., the monomers must be capable of forming two covalent bonds. There are two classical ways in which a monomer can achieve bifunctionality: first, a monomer may contain an unsaturated C=C bond, e.g., ethylene ($CH_2{=}CH_2$); second, a monomer may possess two different organic functional groups that can react with one another, e.g., an amino acid ($NH_2{-}CHR{-}COOH$).

Polymerization can proceed by either of two basic processes, determined largely by the way in which the monomer has attained bifunctionality.

1) Polymerization by addition

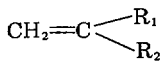
Polymerization by addition (or free radical reaction) is commonly performed with monomers that contain an unsaturated C=C bond. These

TABLE V
Sterile Plastic Devices for Parenteral Drug Administration

Sterile Plastic Device	Plastic Material
Containers for blood product	Polyvinyl chloride
Disposable syringe	Polycarbonate Polyethylene Polypropylene
Irrigating solution container	Polyethylene Polyolefins Polypropylene
I.V. infusion fluid container	Polyvinyl chloride Polyolefins
Administration set	Nylon (spike) Polyvinyl chloride (tube) Polymethylmethacrylate (needle adapter) Polypropylene (clamp)
Catheter	Teflon Polypropylene

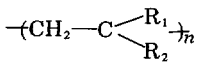
Adapted from Turco and King (1979).

monomers have the general chemical structure



where R_1 and R_2 can be H, CH_3, phenyl, COOH, COOR, $OCOCH_3$, C≡N, F, Cl, $CONH_2$, or pyrrolidone.

The polymer produced by addition polymerization may be represented as:



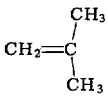
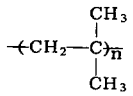
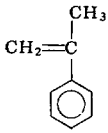
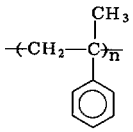
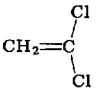
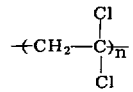
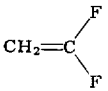
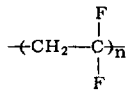
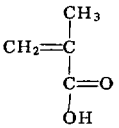
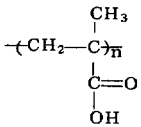
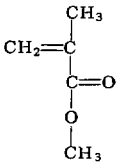
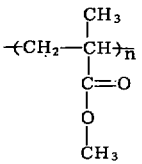
when n refers to the average number of monomer units in the polymer molecule. Depending on the chemical types of R_1 and R_2, a great variety of polymers can be produced (Tables VI and VII). Teflon®, also known as polytetrafluoroethylene $\text{+}CF_2\text{—}CF_2\text{+}_n$, is a unique polymer produced

TABLE VI
Polymers Produced by Addition Polymerization of Vinyl-Type Monomers

Monomer Structure	Monomer Name	Polymer Structure	Common Polymer Name
$H_2C{=}CH_2$	Ethylene	$-(CH_2-CH_2)_n-$	Polyethylene (PE)
$CH_2{=}CH(CH_3)$	Propylene	$-(CH_2-CH(CH_3))_n-$	Polypropylene (PP)
$CH_2{=}CH(Cl)$	Vinyl chloride	$-(CH_2-CH(Cl))_n-$	Polyvinylchloride (PVC)
$H_2C{=}CH$	Styrene	$-(CH_2-CH)_n-$	Polystyrene (PS)
$H_2C{=}CH-C{=}O(OH)$	Acrylic acid	$-(CH_2-CH(C{=}O(OH)))_n-$	Polyacrylic acid (PAA)
$H_2C{=}CH-C{=}O(OR)$	Acrylic acid ester	$-(CH_2-CH(C{=}O(OR)))-$	Polyacrylic acid ester
$H_2C{=}CH-C{\equiv}N$	Acrylonitrile	$-(CH_2-CH(C{\equiv}N))_n-$	Polyacrylonitrile (PAN)
$CH_2{=}CH(F)$	Vinyl fluoride	$-(CH_2-CH(F))_n-$	Polyvinyl fluoride (PVF)
$H_2C{=}CH-O-C{=}O-CH_3$	Vinyl acetate	$-(CH_2-CH(O-C{=}O-CH_3))_n-$	Polyvinyl acetate (PVAc)
$H_2C{=}CH-C{=}O(NH_2)$	Acrylamide	$-(H_2C-CH(C{=}O(NH_2)))_n-$	Polyacrylamide (PAAm)
$H_2C{=}CH-N(CH_2-CH_2-C{=}O)$	Vinyl pyrrolidone	$-(H_2C-CH(N(CH_2-CH_2-C{=}O)))_n-$	Polyvinyl pyrrolidone (PVP)

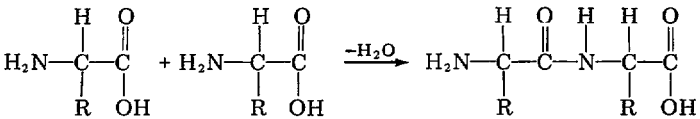
by addition polymerization from a monomer called tetrafluoroethylene, $CF_2{=}CF_2$, in which all four hydrogen atoms in ethylene have been substituted by fluorine.

TABLE VII
Polymers by from Addition Polymerization of Monomers with both R_1 and R_2 that are Not Hydrogen Atoms

Monomer Structure	Monomer Name	Polymer Structure	Polymer Name
	Isobutylene		Polyisobutylene (PIB)
	Methyl styrene		Polymethylstyrene (PMS)
	Vinylidene chloride		Polyvinylidene chloride (PVC_2)
	Vinylidene fluoride		Polyvinylidene fluoride (PVF_2)
	Methacrylic acid		Polymethylacrylic acid (PMAc)
	Methyl methacrylate		Polymethyl methacrylate (PMMA)

2) Polymerization by condensation

Condensation (or step-reaction) polymerization commonly occurs with monomers that contain two different types of organic functional groups. It may be illustrated by the reaction of two amino acid monomers:



During the reaction, an amide (C—N) bond is formed and a molecule of water is condensed out. The free carboxylic (—COOH) group remaining can react with the amino group (—NH_2) of another molecule of amino acid, and the free NH_2 group can also react with the COOH group of another amino acid monomer. The polymer chain thus grows from both ends. In fact, a variety of functional group pairs can be involved to form a number of polymers via condensation polymerization (Tables VIII and IX).

The most common examples of condensation-type polymers are polyesters, like Dacron® and Mylar®, polyamides, such as the majority of Nylons® (polypeptide is a form of polyamide), and cellulose, a condensation product of monosaccharide units.

Some monomers, such as acrylic acid (CH_2=CH—COOH), can react

TABLE VIII
Some Functional Group Pairs Involved in Condensation Polymerization Reactions

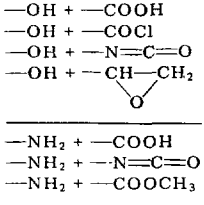


TABLE IX
Some Polymers Produced by Condensation Polymerization

Polymer Type	Typical Monomer(s)	Polymer Repeat Unit
Polyester	HO-R-COOH	(-O-R-CO-)
	HO-R-OH + HOOC-R′-COOH	(-O-R-O-CO-R′-CO-)
	HO-R-OH + ClCO-R′COCl	(-O-R-O-CO-R′-CO-)
Polyamide	H_2N-R-NH_2 + HOOC-R′-COOH	(-NH-R-NHCO-R′-CO-)
	H_2N-R′-NH_2 + ClOCR′COCl	(-NH-R-NHCO-R′-CO-)
Polyurea	H_2N-R-NH_2 + OCN-R′-NCO	(-NH-R-NH-CO-NH-R′-NH-CO-)
Polyurethane	HO-R-OH + OCN-R′-NCO	(-O-R-O-CO-NH-R′-NH-CO-)
Polyanhydride	HOOC-R-COOH	(-O-CO-R-CO-)
Polycarbonate	HO-R-OH + $COCl_2$	(-R-O-CO-O-)

Source: Jenkins and Stannet (1972).

TABLE X
Comparison of Addition and Condensation Polymerization

Addition Polymerization	Condensation Polymerization
Growth occurs by rapid addition of monomer to a small number of active centers.	Growth occurs by coupling of any two species (monomer or polymer).
Monomer concentration decreases slowly during reaction.	Monomer disappears well before any high polymer is formed.
High molecular weight polymer is present at low conversions.	Polymer molecular weight increases continuously during polymerization; high polymer is present only at very high conversions.
Polymer backbone usually consists exclusively of carbon atoms.	Polymer repeat units normally linked by oxygen and/or nitrogen atoms.

Source: Jenkins and Stannet (1972).

through either the C=C bond or the carboxylic acid group, depending on the polymerization conditions used (Table VI).

Basically, addition polymerization occurs very rapidly after initiation and is essentially a chain reaction, whereas condensation polymerization is a much slower, stepwise reaction process. Some of the fundamental differences between these two major processes of polymerization are shown in Table X.

b. Additives (Adjuvants)

The composition of plastic materials is quite complex. A number of plastics can be prepared for specific applications without the addition of any other ingredient to the polymer, whereas others may contain, besides the polymers, several additives to impart definite quality to the final plastic product. Specific additives are frequently used to modify the mechanical and physicochemical properties of the plastic products. The additives routinely used in thermoplastic materials may be classified as follows (Giles, 1975):

1) Lubricants

Lubricants are used primarily to improve the processibility of plastic materials by lowering the viscosity of melt or by preventing the polymer from sticking to the metal surfaces of the processing equipment.

Most lubricants are used in the processing of polyvinyl chloride, where they are critical to extrusion, calendering, injection molding, etc. Additionally, lubricants have been used in the polyolefins, styrenics, and some thermosets. Considerable activity has recently been noted in the development of lubricants for engineering thermoplastics.

The general chemical class of lubricants used in plastic materials is alkyl acids, e.g., stearic acids, and such derivatives as esters, amides, alcohols and metallic salts. For instance, a commonly used lubricant in the processing of polyethylene is zinc stearate. Paraffin waxes and polyethylene waxes are other popular lubricants. The quantities of lubricant used vary significantly from one plastic material to another.

2) Stabilizers

Stabilizers are used to retard or to prevent the deterioration of plastic materials that may result from exposure to light, heat, and pressure and to improve their aging characteristics. The commonly used families of stabilizers include epoxy compounds (epoxidized soybean oil), organotins (octyltin), and mixed metals (barium and cadmium benzoate). Some of the stabilizers have some solubility in aqueous media, and, consequently, could be extracted into a drug solution.

3) Plasticizers

Plasticizers are materials of low volatility that are added to plastic materials to enhance flexibility, resiliency, and melt flow. They are generally high-boiling organic liquids. They act to reduce the glass transition temperature (Tg) or brittleness of the plastic to a temperature lower than that at which it will be used in an actual application. Rigid PVC (polyvinyl chloride), for example, has a Tg of about 80 °C. Sufficient amounts of plasticizer will produce flexible PVC and decreased the Tg to below 0 °C.

More than 80% of all plasticizers are used with PVC; the rest go into such plastics as cellulosics, nylon, polyolefins, and styrenics. Phthalates are the most popular plasticizers. For example, 30–40% of phthalate ester is added to PVC material to produce a flexible intravenous fluid bag, such as the Viaflex (Travenol/Baxter) and Lifecare (Abbott).

As is true of stabilizers, plasticizers can migrate to the surface of a plastic container and are, therefore, potentially extractable into a drug solution.

4) Antioxidants

Many plastic materials are susceptible to oxidative degradation and require antioxidants to slow down the process and to give them a longer shelf life.

Degradation of a plastic material starts with the initiation of free radicals on exposure to heat, ultraviolet radiation, and mechanical shear, or in the presence of reactive impurities. Antioxidants act by intercepting the radicals or by preventing radical initiation during the shelf life of the plastic materials.

There are two types of antioxidants: *Primary antioxidants* act to in-

terrupt oxidative degradation of plastics by tying up the free radicals. Such primary antioxidants as the hindered phenolics and the aromatic amines both have a reactive NH or OH group and can donate hydrogen to the free radicals. Phenolics, such as butylate hydroxytoluene (BHT), are the most popular of the primary antioxidants. BHT has a broad FDA approval and is used in polyolefins, styrenics, vinyls, and elastomers, among others.

Secondary antioxidants function by reducing the unstable hydroperoxides formed in the plastics degradation process to inert products, thus preventing the proliferation of radicals. They are used in conjunction with primary antioxidants to provide added stability to the plastic materials. The most popular ones are thioesters and phosphites.

Antioxidants can also migrate to the surface of plastic materials and then leach out. Further, the combination of antioxidants with other additives may produce or initiate some undesirable chemical reactions with the drug solution.

5) Antistatic agents

Antistatic agents, such as quaternary ammonium compounds are used to prevent the build-up of static charges on the surface of plastics that causes the plastic materials to cling.

6) Slip agents

Slip agents are added primarily to polyolefin type plastic materials, such as polyethylene and polypropylene, in order to reduce the coefficient of friction of the plastics. These agents impart antitack and antiblock characteristics to the end products.

7) Dyes and pigments

Dyes and pigments impart color to plastic materials. They may leach or be extracted into a drug solution. They are used only infrequently for parenteral products.

The above-mentioned additives may vary in concentration from a few parts per million to as much as 60% of the total weight of the plastic material.

c. Potential problems with plastic containers

During storage the additives described above may possibly be extracted by or leached into a drug solution that is in intimate contact with the plastic container. It is, therefore, important to evaluate the physicochemical compatibility of a final drug formulation in a selected primary packaging system under various storage and time conditions to assure safety and stability of the drug product. Whenever possible, evaluations should be conducted under conditions simulating those to which the product will probably be exposed. Evaluations should take into consideration not only the physical and chemical compatibility of the drug formulation with the

primary packaging system, but should also include an investigation of the mechanical properties of the primary packaging system, e.g., the cracking and stress-cracking of a plastic container that could occur under attack by the drug product, the storage environment, or both. Prolonged exposure to ultraviolet light has been shown to promote the migration of certain additives that could, in turn, accelerate the aging characteristics of the plastic and decrease shelf life of the product.

The use of plastic material for primary packaging systems of parenteral drug products has grown very rapidly during the last two decades. With this phenomenal growth in the use of plastic containers, three potential problems have arisen:

a. Loss of drug potency and the efficacy of preservation because of sorption of active drug ingredients and preservatives onto the plastic material. Such sorption has been most common in containers made of polyamides, such as nylon.

b. Egress of volatile constituents, the protective gas in the headspace, or some selective drug species through the wall of the container to the exterior, resulting in decreases in drug potency and stability; or, conversely ingress of atmospheric oxygen, water vapor, or other gases to the interior of the container, causing oxidative or hydrolytic degradation of some susceptible constituents.

c. Leaching of additives or constituents from plastic containers into the drug formulation, leading to a change in purity, physicochemical instability of the product, formation of particulate matter, or the causation of some adverse effect when the drug is administered.

The use of a plastic material as the primary packaging system for either a pharmaceutical or a food product demands a number of extra considerations that may not be critical to plastics employed for other purposes. Although packaging systems for food products require considerations similar to those for pharmaceuticals, the food products usually have a relatively rapid rate of turnover and, hence, relatively short shelf-life requirements. On the other hand, pharmaceutical products require an extremely long shelf-life stability and the most critical technical and toxicological data for regulatory approval.

The pharmaceutical industry requires, in most instances, a level of safety that is more stringent than that required in the food industry. This is logical when one considers that drugs are taken by a person who is suffering from an illness; any untoward side effects may complicate the existing illness and be detrimental to health. This consideration is of particular relevance for parenteral drug products, which are to be administered directly into the systemic circulation.

Although the thermosetting resins have been widely used for making closure systems and also a few specialized containers (e.g., menthol sticks, for almost 50 years), the use of thermoplastics for packaging pharmaceuticals did not start until the late '40s and early '50s. It is widely recognized today that plastics deservedly play a significant role in all facets of pharmaceutical packaging, provided that their advantages can be properly exploited and their potential disadvantages, in terms of physicochemical interactions with the pharmaceutical formulations, are fully evaluated and controlled.

B. Closure Systems

1. General

A closure system should serve one or more of the following purposes: *a*) to contain and retain the contents in the primary packaging system; *b*) to protect the contents from potential contamination or exposure to hazardous materials during storage and transportation; *c*) to prevent leakage or seepage of contents and unnecessary exposure to patients; *d*) to assist in continued use of the product (reclosability). A rubber closure is normally needed to provide the necessary reclosability or resealing property in parenteral products.

A closure is, therefore, an essential and integral part of a primary packaging system and, as such, it must assist in providing a product with protection, retention, convenience, and presentation in an economical fashion for the proposed shelf life of the product. An ideal closure system should have the following properties: *a*) it should be nonreactive, physically and chemically, with the drug formulation, not affecting adversely the quality of the formulation by sorption of the formulation ingredients, by interaction with the contents, or by allowing any of its components to leach into the formulation; *b*) it should provide a complete barrier to the ingress of any vapors or reactive gases into the container; *c*) it must not be so rigid as to resist insertion of a hypodermic needle or a plastic spike from an IV administration set; *d*) it must not fragment as a needle passes through it; *e*) it must have sufficient elasticity to provide a snug fit between the closure and the lip and neck of the vial and to reseal the hole made by a hypodermic needle as soon as the needle is withdrawn.

The aforementioned properties are not met perfectly by any rubber closure formulations currently available in the marketplace. It is, therefore, essential to determine the physicochemical compatibility of a specific rubber closure with each drug formulation with which it is to be used (Hopkins, 1965). In addition to undergoing physical tests of elasticity, hardness, fragmentation, and vapor transfer, closures should be exposed to the drug formulation for prescribed periods of time under designated conditions of temperature and humidity to permit evaluation of their physicochemical compatibility and stability.

2. Composition of rubber closures

a. Primary ingredients—natural rubber (latex), synthetic polymer; a combination of natural rubber and synthetic polymer.

b. Adjuvants—*1*) vulcanizing agent, such as sulfur or phenolic resin; *2*) accelerator, such as 2-mercaptobenzothiazole; *3*) activator, such as zinc

oxide; *4*) fillers, such as carbon black or limestone; *5*) antioxidants; *6*) lubricants.

These ingredients are compounded together and then vulcanized into a desired shape under high pressure and temperature. An extensive list of possible adjuvants in closures can be found in the Technical Methods Bulletin on "Extractable from Elastomeric Closures" published by the Parenteral Drug Association.

In the use of rubber closures for sterile drug products, the important factors to be considered are aging, deterioration on autoclaving, force needed to pierce, self-sealability, hardness, coring and fragmentation, sorption of active drugs and preservatives, levels of extractable ingredients, permeability to oxygen and moisture, particulate contamination, and chemical compatibility with the product formulation.

The choice of natural rubber as the closure system for sterile preparations began with a demand for a self-sealable closure system for multiple-dose injectable products. Several synthetic elastomers have recently emerged to provide the same self-sealing capability as does natural rubber. The characteristics of these pharmaceutical rubber closure systems are described below.

3. Natural rubber

The chemical name of natural rubber is *cis*-1,4-polyisoprene. It was high elasticity and excellent self-resealability, low coring, high permeability to oxygen, but poor resistance to aging, especially with autoclaving. Its flexibility enables its removal from the mold without tearing. It is used in the stoppers for insulin preparations, intravenous infusion fluids, and multidose parenteral formulations.

4. Synthetic Elastomers

a. Polyisoprene rubber The physical characteristics of polyisoprene rubber closely resemble those of natural rubber, but the synthetic elastomer is generally more uniform in texture.

b. Butyl rubber The chemical name of butyl rubber is poly(isobutylene-co-isoprene). It has excellent resistance to aging and to the penetration of oxygen and water vapors and has good temperature stability. However, its low elasticity leads to poor resealability and to coring. It requires evaluation of the potential of leachable extractives. Butyl rubber has been used as a closure system for antibiotic products, reconstituted solutions for freeze-dried products, and intravenous infusion fluids, and as plungers in unit-dose disposable syringes.

c. Halogenated butyl rubber The properties of halogenated butyl rubber are similar to those of butyl rubber, but with improvement in potential leachable ingredients. It has good resistance against solvents and an excellent compatibility with mercurial preservatives. This elastomer has been used in stoppers for antibiotic products and intravenous infusion fluids, in pistons for prefilled syringes, as well as in dental plungers.

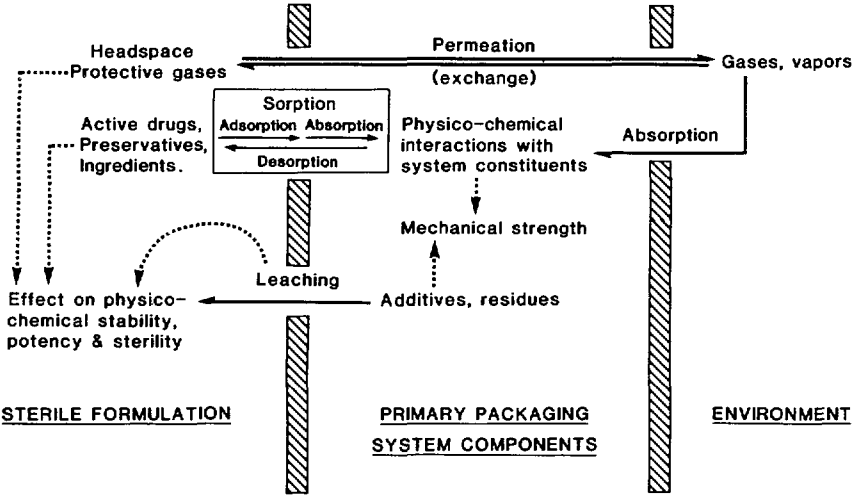
d. Chloroprene rubber Chloroprene rubber is resistant to a broad range of solvents and has excellent aging property.

e. Silicone rubber The chemical name of silicone rubber is polydimethylsiloxane. It is physiologically inert and, therefore, offers negligible hazards from leaching. Although it is recognized for its water-repellent properties, it is relatively permeable to water vapor and highly permeable to gases and preservatives. Silicone rubber also has low resistance to deformation and shows high coring. It has limited use as a piston in syringes, where a smooth action is required.

f. Nitrile butadiene rubber Nitrile butadiene rubber has shown excellent compatibility with mineral oils and with many fatty acid derivatives.

III. POTENTIAL PHYSICOCHEMICAL INTERACTIONS

It is known that no container or closure system is totally inert. Additionally, drug products optimally require a shelf-life stability as long as 3–5 years. During this extremely long storage period, a variety of physicochemical interactions between the drug formulation and the primary packaging system (container and closure system) can occur during their intimate, sustained contact. As illustrated in Scheme I, active drugs, preservatives, and other ingredients in the sterile formulation can be first adsorbed by the contact surface, then absorbed into the primary packaging system by diffusion, and subsequently desorbed into the environment or back to the formulation. Additives in the primary packaging system can also be leached into the sterile formulation, protective gases in the headspace of the container can egress from the container, and atmospheric oxygen, vapors, and other reactive gases can ingress into the interior of the container, causing oxidative and/or hydrolytic degradation of susceptible constituents. All of these physicochemical interactions are analyzed in detail below.



Scheme 1

A. Sorption

1. Introduction

On the surface of a solid or liquid, molecular forces are in a state of imbalance or unsaturation. As a result, solid or liquid surfaces tend to satisfy their residual forces by attracting gases, solvents, or dissolved solutes with which they come in contact. This phenomenon of concentration of a substance on the surface of a solid or liquid is called *ad*sorption.

*Ab*sorption, on the other hand, is the process whereby a substance is not only retained on the surface but passes through the surface to become distributed throughout the body of a solid or liquid.

When a solution is in contact with a plastic material, the following can occur: solvent, solute (drug substance or preservative), or both, can be adsorbed onto the surface, because of surface unsaturation. Stronger interaction between solute (or solvent) molecules and the polymeric material can also occur at reactive sites, if the plastic material is made of chemicals that may attract any specific solute (or even solvent) molecules. When a sufficient amount of solute has accumulated on the surface or when most of the surface reactive sites are filled, a concentration gradient is established and absorption begins; as a result, solute (or solvent) molecules begin to penetrate the surface and interact with new reactive sites inside the plastic material. The rate of penetration of these molecules into the plastic material is governed by diffusion process, as described by Fick's first law of diffusion. When all available sites have been filled, equilibrium is established. Therefore, one may distinguish *ad*sorption from *ab*sorption by noting that *ad*sorption takes up a smaller quantity and requires less energy than does *ab*sorption. In the attainment of an overall equilibrium state, *ab*sorption is usually the rate-limiting process.

In physiochemical interactions between a sterile formulation and the packaging material, both adsorption and absorption can occur. The literature on such interactions in parenteral formulations generally does not make a clear distinction between adsorption and absorption. In the case of glass containers, we know intuitively that only surface adsorption is operative. To prevent confusion, the noncommittal term *sorption* is used in the following discussion to indicate that either adsorption, absorption, or both are operative, even though one of them may predominate.

The substance that is attracted to a surface is defined as the adsorbate, whereas the substance to which the adsorbate is attached is termed the adsorbent. Correspondingly, a sorption process takes place between a sorbate (the drug) and a sorbent (the plastic material).

In general, sorption phenomena are investigated by soaking a piece of

plastic material of known quantity in a solution of sterile formulation of known composition or simply by placing the final drug formulation into a plastic container. One method of studying solute-plastic interaction is to measure the quantity of solute removed from the formulation, at equilibrium, by the plastic material. The data may then be analyzed by any of three mathematical models: Freundlich, simple linear equation, or the Langmuir equation. Another method of studying solute-plastic interaction is to measure the amount of solute taken up at various time intervals by the plastic material. The resultant kinetic data permit determination of diffusion parameters, since the rate-determining step of the sorption process is diffusion of the solute inside the plastic matrix. Based on various assumptions, a variety of equations have been developed for analyzing the kinetic data.

Although the preceding paragraphs refer only to interactions between drug and plastic, one should be aware of other similar interactions, such as the uptake of preservatives by rubber closures and by plastic containers, and uptake of drug by membrane filters. All these interactions should follow the same physicochemical principles. Therefore, the mathematical models and the factors influencing sorption, outlined in the subsequent two sections, are applicable to any interactions between drug or preservatives, on the one hand, and plastic or rubber on the other.

After a general discussion of mathematical model and of the factors influencing sorption, the remaining analysis of sorption consists of five sections that analyze various types of interactions, e.g., drug-plastic interactions, drug-rubber interactions, etc. Each distinctive interaction is discussed in depth. In each section relevant data are reviewed.

2. Mathematical Models

a. Freundlich equation

If a finely divided solid adsorbent is dispersed in a dilute dye solution with stirring, one observes that the color intensity of the dye solution is gradually reduced. If the finely divided solid adsorbent is exposed to a gas at low pressure, the pressure decreases noticeably. The magnitude of the effect depends primarily on the concentration of the dye or the pressure of the gas. The Freundlich equation is one of the first equations proposed to relate empirically the amount of adsorbate taken up by the adsorbent to the concentration of adsorbate in the solution at equilibrium. Although this equation was developed for surface adsorption, it also complied well with the data generated in those studies (Browne and Steele, 1956; Yuen et al., 1979; Powell et al., 1969) in which, in addition to adsorption, a con-

comitant absorption, controlled by the diffusion process, was taking place. To study sorption phenomena in a sterile product, one would determine the amount of solute, q (in mg/g or mole/kg), taken up by a plastic material as a function of solute concentration, C_{eq} (mg/ml or mole/liter), at equilibrium. The data may be expressed as:

$$q = k_f C_{eq}^{1/n} \qquad \text{(Eq. 1)}$$

or

$$\log q = \log k_f + (1/n) \log C_{eq} \qquad \text{(Eq. 2)}$$

where k_f, the Freundlich binding constant, and n, an empirical constant, can be determined, respectively, from the intercept and the reciprocal of the slope of a plot of $\log q$ vs. $\log C_{eq}$. Browne and Steele (1956) established a log-log linear relationship for organic acids, such as salicylic acid, benzoic acid, and phenol, taken up by a polyamide (Nylon 66) yarn (Fig. 1). Others also found that the data for sorption of benzalkonium chloride by polyamide (Nylon 66) sheets (Powell et al., 1969) and for the sorption of nitroglycerin by IV bags (Yuen et al., 1979) can be fitted in the same manner. For comparison, binding constants are shown in Table XI.

The values of k_f in Table XI can be used to predict the trend of sorption. The higher the k_f values, the greater the tendency for the solute to reside in a plastic/rubber phase. When $n = 1$, as appears to be the case for a number of the substances reported, the Freundlich equation is reduced to the distribution equation (see section b. below), and k_f is then equivalent to the partition coefficient.

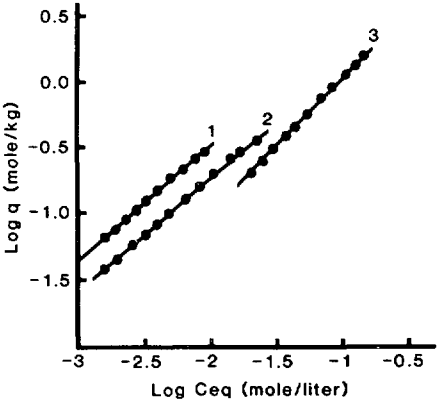


Figure 1—Sorption of organic acids by polyamide (Nylon) yarn at 30 °C. Key: 1, Salicylic Acid; 2, Benzoic Acid; 3, Phenol [Source: Browne and Steele, 1956].

TABLE XI
Binding Constants for Freundlich Equation

Compound	Plastic	Temp (°C)	k_f	n	Reference
Warfarin	Nitrocellulose[a]	29	600	1.55	Chiou and Smith (1970)
Griseofulvin	Nitrocellulose[a]	29	280	0.91	Ibid
Nitroglycerin	Polyvinyl Chloride[b]	35	166	0.92	Yuen et al. (1979)
Salicylic acid	Polyamide[c]	30	19.5	1.14	Browne and Steel (1956)
Benzoic Acid	Polyamide[c]	30	10.8	1.14	Ibid
Phenol	Polyamide[c]	30	10.4	1.00	Ibid
Butyric acid	Polyamide[c]	50	1.62	1.13	Berg et al. (1965)

[a] Millipore GS-type membrane filter with assumed weight of 40 mg. [b] PVC IV bag. [c] Nylon.

b. Simple linear equation

As shown above, sorption phenomena can be described by a simple distribution law. Richardson and Meakin (1974) reported the sorption of benzocaine by polyamide (Nylon 6) powder from aqueous solution. Here, a linear relationship, as described by Eq. (3), was observed over the concentration range studied (Fig. 2):

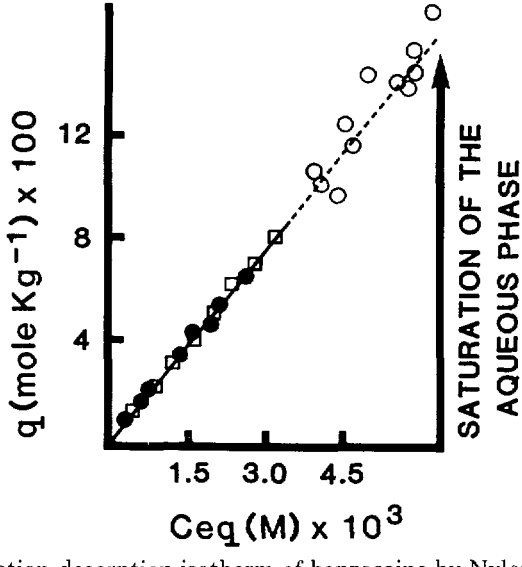


Figure 2—Sorption-desorption isotherm of benzocaine by Nylon 6 powder from 0.5 M potassium chloride solution at 30 °C. Ceq is the solute concentration at the state of equilibrium, q is the amount taken up by a plastic material. Key: Open squares, sorption; closed circles, desorption; open circles, sorption at high benzocaine concentrations [Source: Richardson and Meakin, 1974].

$$q = K_{app} \times C_{eq} \qquad \text{(Eq. 3)}$$

q and C_{eq} were defined earlier in Eq. (1) and K_{app} is the apparent partition coefficient.

This equation was also used to follow the sorption of methylparaben by polyamide (Nylon) membrane (Patel and Kostenbauder, 1958), dehydroacetic acid by polymethylmethacrylate (Nagabhushan et al., 1969), benzodiazepines by polyvinyl chloride infusion bags (Illum and Bundgaard, 1982), and chlorobutanol by polyhydroxyethylmethacrylate (Richardson et al., 1975). Since

$$C_{eq} = C_i - q \times (\text{plastic weight/solution volume}) \qquad \text{(Eq. 4)}$$

substituting for C_{eq} in Eq. (3) gives

$$q = K_{app}[1 + K_{app}(\text{solution volume/plastic weight})]^{-1}C_i \qquad \text{(Eq. 5)}$$

Thus, some workers have plotted the amount of uptake vs. initial concentration (C_i). One example is the uptake of insulin in a glass infusion bottle (Weber et al., 1977).

c. Langmuir equation

When curvature shows up in a plot of the amount sorbed vs. the equilibrium concentration or when one observes that the percent uptake is reduced with increasing initial concentration, it is probable that sorption has approached the limiting capacity of the plastic. This situation differs from that in the Freundlich and simple linear equations discussed earlier, both of which suggest an unlimited capacity.

Langmuir (1917) developed an equation based on the theory that molecules or atoms of gas are adsorbed on the active site of a solid to form a layer one molecule thick (monolayer). The equation developed is also applicable to the adsorption of solute molecules from solution.

$$\frac{1}{q} = \frac{1}{S_\ell} + \frac{1}{k_\ell S_\ell} \times \frac{1}{C_{eq}} \qquad \text{(Eq. 6)}$$

where k_ℓ (liter mole^{-1}) is the ratio of adsorption rate to desorption rate and S_ℓ is a theoretical saturation value that represents the saturation concentration when all binding sites are occupied by a monolayer of molecules. The amount of uptake and the equilibrium concentration are represented by q (mole kg^{-1}) and C_{eq} (mole Liter^{-1}), respectively. A plot of $1/q$ vs. $1/C_{eq}$ will produce a straight line from which S_ℓ and k_ℓ can be determined from the intercept and the slope. As an illustration, the data of Wing (1955) for the sorption of phenol by rubber stoppers are plotted in Fig. 3. Table XII summarizes the literature values for sorption parameters, as determined by the Langmuir equation.

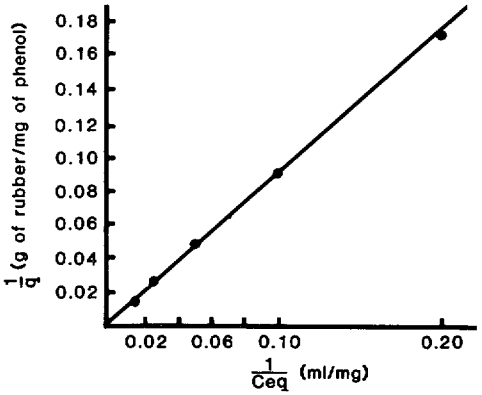


Figure 3—Langmuir isotherm for the uptake of phenol by rubber stopper at 37 °C, slope $(1/k_\ell S_\ell) = 0.88$; intercept $(1/S_\ell) = 0.003$ [Source: Plotted from data given by Wing, 1955].

From comparison of these reported values, it is clear from the definition that the higher the value of S_ℓ, the greater the adsorptive power of the plastic. However, the reader should be cautious in accepting the k_ℓ and S_ℓ values reported. Because the intercepts of the Langmuir curve are often very close to the origin, saturation values, which are the reciprocals of the intercept, often show great variation. For this reason, it would be very difficult, unless numerical data were presented, to calculate the sorption parameters in a Langmuir equation from any graphical presentation.

In practical situations, one may not find the clear-cut data that fit nearly any one of the three equations discussed. Schoenwald and Belcastro (1969) presented data that could fit either the Freundlich or the Langmuir equation. Marcus et al. (1959) showed that, for the sorption of sorbic acid, propylparaben and methylparaben to polyamide (Nylon) syringes, a simple linear relationship is followed at low concentrations and a Langmuir relationship at higher concentrations. The data presented by Rodell et al. (1964) on the interaction of sorbic acid with polyamide (Nylon 66) produced linear plots by either Langmuir equation or simple linear equation.

d. Diffusion equation—general

Diffusion is the process by which matter is transported from one part of a system to another as a result of random molecular motions under a concentration gradient. It is easily visualized by adding a drop of ink to a cup of water; the ink is gradually dissipated throughout the water. Absorption of drug substance by plastic or rubber is also controlled by a diffusion process. Diffusion can be defined by the following expression derived from Fick's first law of diffusion:

TABLE XII
Literature Values for Sorption Parameters Determined by Langmuir Equation

Solutes	Plastic	k_ℓ (liter/mole)	S_ℓ (moles/kg)	H (kcal/mole)	Reference
Chlorobutanol (38 °C)	Polyethylene	—	0.107	−0.06	Schoenwald and Belcastro (1969)
Chlorobutanol (38 °C)	Polyamide 66	—	0.61	−1.1	Ibid
Sorbic acid (25 °C)	Cellulose triacetate	294	0.182	—	Saski (1963)
Sorbic acid (25 °C)	Cellulose acetate	99	0.776	—	Ibid
Sorbic Acid (55 °C)	Polyamide 610	6.1	2.67	−9.77	Kapadia et al. (1964a)
Salicylic acid (41.5 °C)	Polyamide 66	—	0.85	−1.89	Kapadia et al. (1964b)
Salicylic acid (50 °C)	Polyamide 610	—	1.25	−3.39	Kapadia (1964a)
p-Hydroxybenzoic acid (50 °C)	Polyamide 610	53.6	0.837	—	Kapadia (1964a)
Benzoic acid (50 °C)	Polyamide 610	—	1.05	−3.19	Ibid
Methylparaben (50 °C)	Polyamide 610	—	1.22	−3.63	Ibid
Propylparaben (50 °C)	Polyamide 610	56.8	3.81	−2.60	Ibid
Phenol (37 °C)	Latex rubber	—	3.5	—	Wing (1955)
Insulin in 5% Dextrose (RT)	Polyvinyl chloride	0.059	14.5 units	—	Hirsch et al. (1977)
Insulin in Normal Saline (RT)	Polyvinyl chloride	0.052	21.9 units	—	Ibid

$$q = DA \int_0^t -(dc/dx)dt \qquad \text{(Eq. 7)}$$

where q is the amount of diffusing drug substance penetrating through a plastic piece with a surface area of A, in a finite time dt; dc/dx is the concentration gradient along the distance x from the origin, and D is the diffusion coefficient, which is assumed to be constant irrespective of the change in concentration.

The diffusion equation outlined above enables one to design an experiment for determining the diffusion coefficient, D. If one knows the mag-

nitude of the diffusion coefficient, it is possible to calculate the amount of drug diffusing at any given time, either in a solution or in any depth of a plastic.

In a typical experiment for monitoring the diffusion process, a strip of plastic is immersed in a drug solution and the amount of drug sorbed by the plastic piece is determined at intervals. This procedure differs from those employed to test the Freundlich and Langmuir equations. In the latter experiments, only equilibrium concentrations were determined.

There are many equations that can be employed to fit a sorption-time curve. These equations were originally derived for conductive heat flow. Derivation of these equations is complex, but most researchers in the pharmaceutical field need only choose an applicable equation from any comprehensive textbook, such as the one by Crank (1975). These equations were thoroughly reviewed for their applicability to diffusion in elastomers (van Amerongen, 1964). A general expression (van Amerongen, 1964; p. 1070) for the sorption-time relationship is

$$F = \frac{M_t}{M_\infty} = 1 - \left[\sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \exp\{-D(2n+1)^2\pi^2 t/4l^2\}\right]^i \quad \text{(Eq. 8)}$$

where fraction F, is the ratio of drug taken up at any time, M_t, to the amount of drug taken up at infinite time, M_∞, l is the thickness of the test piece, and integer $i = 1, 2$, or 3 is assigned when diffusion takes place in a sheet, a rod of square section, or a cube, respectively. This equation was derived for diffusion when only one side of the test piece was exposed to the drug solution. If sorption occurred from both sides, l is half the thickness of the test piece.

Pikal et al. (1977) employed this equation to assess the rate of nitroglycerin removal from a heat-sealed film.

e. Diffusion equation—constant drug concentration

It is obvious that Eq. (8) is quite complex. If one can assume that, at early stages of absorption, the amount of drug taken up by the plastic is minimal, the concentration of drug remaining is nearly constant. Then Eq. (9) can be used to describe sorption by a plane sheet of plastic:

$$F = (4l)(D/\pi)^{1/2}\, t^{1/2} \quad \text{(Eq. 9)}$$

F, D, and l are the same as defined in Eqs. (7) and (8).

Equation (9) dictates that the amount sorbed is a function of the square root of time. A linear sorption vs. $t^{1/2}$ plot would provide good evidence that diffusion in the plastic matrix is the rate-determining process. In practice, from a plot of F against $t^{1/2}$, D can be determined from the slope of the line obtained (Eq. 9).

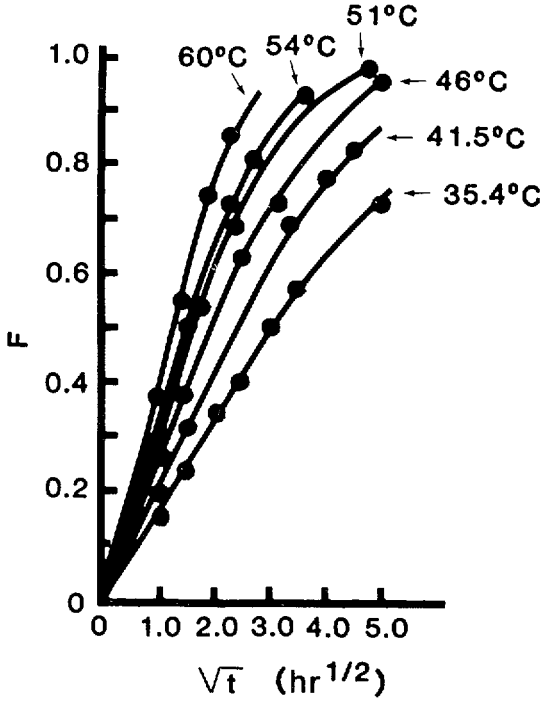


Figure 4—Fractional uptake, F, of salicylic acid by Nylon vs. square root of the time (in hours) at different temperatures [Source: Kapadia et al., 1964a,b].

The data presented by Kapadia et al. (1964ab) illustrate the F vs. $t^{1/2}$ linearity in the early stages of sorption (Fig. 4). Thus, initially the rate of sorption is relatively fast, but after a longer time of exposure the rate decreases. The data for sorption of benzyl alcohol and phenol by rubber closures are plotted in Fig. 5 (Rowles et al., 1971). A linear relationship of sorption vs. time$^{1/2}$ was observed, indicating that the diffusion process was operative. The line, however, produced a positive intercept instead of going through the origin. This observation can be interpreted as evidence of a rapid surface *ad*sorption followed by a slower *ab*sorption process.

In the next three subsections, discussion is focused only on the simplest configuration, plane sheet. Absorption by more complicated geometric configurations has also been reported. For instance, Anderson and Motzi (1982) presented mathematical equations for various geometric configurations, e.g., sheet, cylinder, and rectangular block, and found that the sorption of methylparaben is best fit by the cylinder model. Loss of vitamin A to plastic tubing was described by a convective diffusion model (Amidon

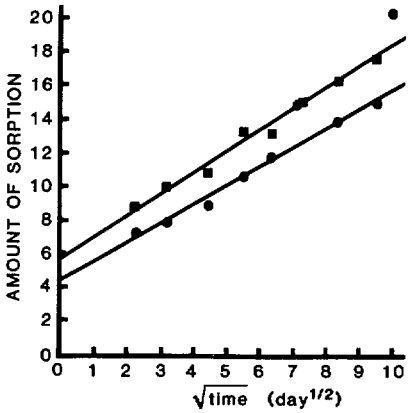


Figure 5—Sorption profiles of benzyl alcohol (circles) and phenol (squares) by rubber closures [Source: Rowles et al., 1971].

et al., 1981); when an effective tubing wall permeability is known, the amount of vitamin A lost to the tubing under any flow rate and tubing length can be estimated from this model.

f. Diffusion equation—varying drug concentration

If the extent of sorption is sizeable, the concentration of solute in the solution falls as solute enters the plastic. This situation contrasts with that assumed for Eq. (9), in which the concentration of drug remains constant. Drug concentration often declines when there is only a limited amount of drug. If the solution is well stirred, concentration will remain uniform throughout the solution. It is useful from an experimental point of view to have only a limited amount of solution, since the rate of solute uptake by the plastic can be deduced from the observed concentration changes in the solution, a procedure often simpler than to analyze the amount of solute taken up by the plastic. Typical illustrations of this situation for sterile products are injectable solutions of limited volume packaged in disposable syringes or in IV infusion bags.

The equation relating F, the fractional uptake, and time is:

$$F = \frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1+\alpha+\alpha^2 q_n{}^2} \exp(-Dq_n{}^2 t/l^2), \qquad \text{(Eq. 10)}$$

where M_t is the total amount of solute in the plastic at time t, M_∞ is the corresponding amount after infinite time and is the same as described previously. The half thickness on the plane sheet is used for l, if sorption occurred on both sides of the plastic strip (Yuen et al., 1979). The value of

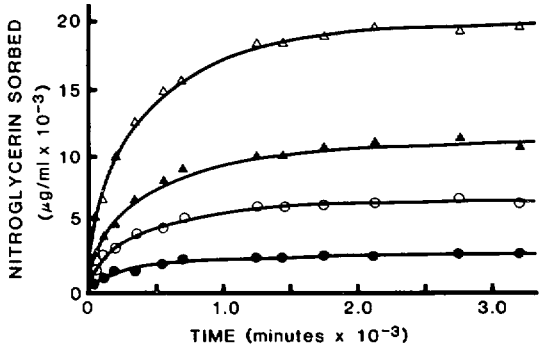


Figure 6—Relationship between concentration ($\mu g/cm^3$) of nitroglycerin absorbed by Viaflex® plastic and time from a solution initially at a concentration of 61 (closed circles), 143 (open circles), 267 (closed triangles), or 473 (open triangles) μg of nitroglycerin per ml at 30 °C. The symbols are experimental data and the lines are those generated by nonlinear least squares fitting, based on Eq. 10 [Source: Yuen et al., 1979].

α is the ratio of the final concentration, C_∞, to the total concentration drop in the aqueous solution (initial concentration, C_0, minus final concentration):

$$\alpha = \frac{C_\infty}{C_0 - C_\infty} \qquad \text{(Eq. 11)}$$

which can also be written:

$$\alpha = (1 - F_\infty)/F_\infty \qquad \text{(Eq. 12)}$$

The values of q_n are the nonzero positive roots of:

$$\tan q_n = -\alpha q_n \qquad \text{(Eq. 13)}$$

and can be obtained from literature data (Crank 1975, p 379). For example, at $F = 0.2$, $\alpha = 4.0$; q_n's are 1.72, 4.76, 7.89, etc., and at $F = 0.6$, $\alpha = 0.66$; q_n's are 2.17, 5.00, 8.04, etc.

In Fig. 6, the amount of nitroglycerin, M_t, sorbed by a strip of polyvinyl chloride sheet (from Viaflex bag) at time t, was fitted to Eq. (10), using a nonlinear least squares fitting technique (Yuen et al., 1979).

Equation (10) was also fitted by Roberts et al. (1979) to the sorption data for nitroglycerin and by Illum and Bundgaard (1982) to the sorption data for nitroglycerin, warfarin, and diazepam, all in polyvinyl chloride bags.

Diffusion coefficients determined by any one of the diffusion equations are compared in Table XIII.

TABLE XIII
Diffusion Coefficients and Activation Energy of Diffusion Determined by Sorption Kinetics

Compound/Sorbent	Diffusion Coefficient (cm^2/sec) $\times 10^9$	Reference
Nitroglycerin with PVC strips	2.4 (30 °C)	Yuen (1979)
	4.4 (35 °C)	
	8.3 (40 °C)	
	10.8 (45 °C)	
	E_d = 19.6 kcal/mole	
Nitroglycerin with PVC bags	2.8 (22 °C)	Roberts et al. (1980)
Nitroglycerin with polyethylene sheet	0.20 (25 °C)	Pikal et al. (1977)
Warfarin with PVC bag	1.1 (22 °C)	Illum and Bundgaard (1982)
Diazepam with PVC bag	1.2 (22 °C)	Illum and Bundgaard (1982)
Salicylic Acid with polyamide (Nylon 66) strips	0.897 (35.4° C)	Kapadia et al. (1964b)
	1.26 (41.5 °C)	
	2.08 (46 °C)	
	2.73 (51 °C)	
	3.86 (54 °C)	
	5.90 (60 °C)	
	E_d = 20.5 kcal/mole	
Sorbic acid with polyamide (Nylon 66)	2.62 (55 °C)	Rodell et al. (1964)
	2.85 (61 °C)	
	3.09 (67 °C)	
	E_d = 3.07 kcal/mole (at 0.125%)	
	3.53 (55 °C)	
	7.29 (61 °C)	
	14.6 (67 °C)	
	E_d = 26.2 kcal/mole (at 0.05%)	
Benzoic acid with polyamide (Nylon 610)	0.305 (45 °C)	Kapadia et al. (1964a)
	3.32 (65 °C)	
	E_d = 12.9 kcal/mole	
Methylparaben with polyamide (Nylon 610)	0.372 (45 °C)	Kapadia et al. (1964a)
	3.54 (67 °C)	
	E_d = 20.9 kcal/mole	
Propylparaben with polyamide (Nylon 610)	1.01 (45 °C)	Kapadia et al. (1964a)
	3.93 (65 °C)	
	E_d = 14.5 kcal/mole	

g. Diffusion equation—half-saturation time

As sorption progresses, it will reach a half-saturation point. This point is determined by following the sorption-time curve until the test piece is completely saturated. Derived from the general Eq. (8), the following equation provides a very simple means for calculating the diffusion coef-

TABLE XIV
Comparison of Diffusion Coefficients for Nitroglycerin calculated from Two Equations

Initial Concentration (μg/ml)	Amount Adsorbed at Equilibrium (μg/ml) $\times 10^{-3}$	$t_{1/2}$ (min)	Diffusion Coefficient, D, (cm^2/sec) $\times 10^9$ Calculated [a] from Eq. 10	Calculated from Eq. 14
61.1	2.40	180	1.75	1.90
143	5.88	210	2.01	1.63
266	11.3	200	2.06	1.71
470	19.9	175	2.22	1.95

[a] Yuen et al. (1979).

ficient from the half-saturation time, $t_{1/2}$:

$$D = 0.04939\, l^2/t_{1/2} \qquad \text{(Eq. 14)}$$

It is obvious from this equation that the diffusion coefficient has the dimensions of area per unit time (cm^2/sec).

Half-saturation times for sorption of nitroglycerin by PVC sheet were reported by Yuen et al. (1979). Diffusion coefficients calculated by use of Eq. (14) showed good agreement (Table XIV) with those calculated by use of Eq. (10) and nonlinear least squares fitting.

h. First-order equation

Another relatively simple equation could be derived to describe the kinetic data of sorption. If one were to take only the first term ($n = 0$) of the summation from Eq. (8), it would follow that:

$$F = \frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\exp[-\pi^2 Dt/4l^2] \qquad \text{(Eq. 15)}$$

which can be further simplified:

$$\log(1 - F) = -0.0908 + 1.07\,(D/l^2)t \qquad \text{(Eq. 16)}$$

By plotting $\log(1 - F)$ against time and measuring the slope of the line, the diffusion coefficient (D) can be calculated, if the thickness (l) of the plastic sheet is known, from the relationship of D = slope $\times\, l^2/1.07$.

Figure 7 illustrates the sorption of a dye, Orange II (sodium p-[2-hydroxy-1-naphthylazo] benzene sulfonate), to a polyamide (Nylon 66) sheet. With this example, it is timely to point out that a tremendous wealth of pertinent information has been generated by textile scientists who dealt with dyes that resemble drug substances or antimicrobial agents and with

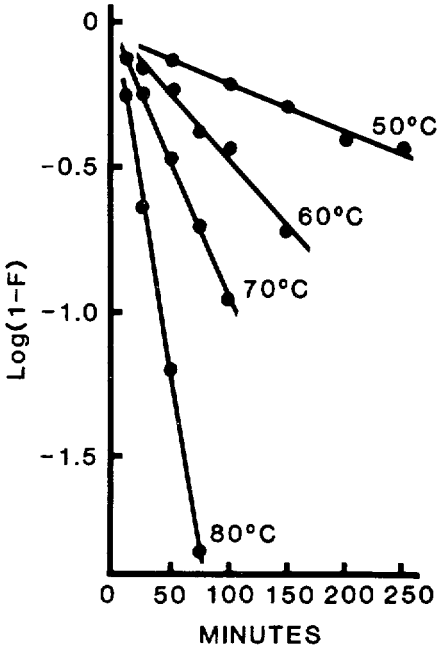


Figure 7—Sorption of Orange II from benzoic acid (5×10^{-2} M) solution at pH 5 by polyamide (Nylon 66) sheet, F is the fractional uptake [Source: Browne and Steele, 1956].

yarns (cellulose, polyamide) that resemble pharmaceutical packaging materials.

Sokoloski et al. (1980) studied the short-term loss of nitroglycerin from normal saline to polyvinyl chloride tubing. This loss was clearly the result of adsorption, because the test strip was immersed in the drug solution for no more than 40 min, and the amount of surface sorption was determined by a quick wash with ethyl acetate. Given these conditions, only the *ad*sorbed nitroglycerin could be accounted for. As shown in Fig. 8, the first-order plots, similar to those in Fig. 7, are linear. The rate constants for adsorption were determined from the slopes. It is interesting to observe that a first-order plot can fit both the *ad*sorption data and the diffusion-controlled absorption data.

i. Reversible first-order equation

A reversible first-order process is

$$A \underset{k_r}{\overset{k_f}{\rightleftarrows}} B \qquad \text{(Eq. 17)}$$

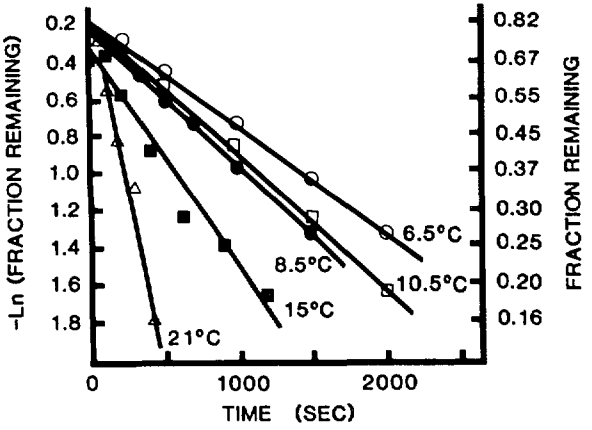


Figure 8—Sorption of nitroglycerin onto polyvinyl chloride tubing as expressed by a semilogarithmic relationship between fraction remaining to be sorbed and time at five different temperatures: 6.5 °C (open circles), 8.5° (closed circles), 10.5° (open squares), 15 °C (closed squares), and 21 °C (open triangles) [Source: Sokoloski et al., 1980].

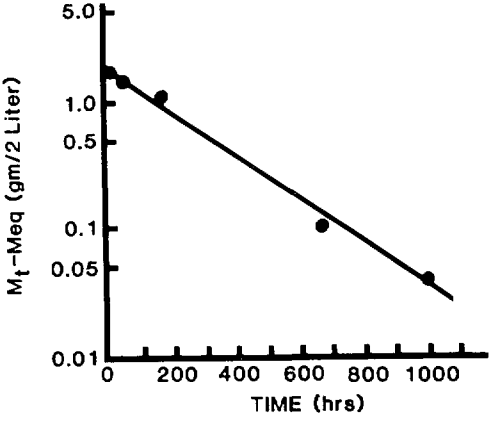


Figure 9—Relation between natural logarithm of amount remaining at time t less amount at equilibrium, as a function of time for nitroglycerin stored in vials with rubber closures at room temperature [Source: Sturek et al., 1978].

A semilog plot of the amount remaining at time "t" less the amount at equilibrium is a linear function of time following this relation:

$$\ln(M_t - M_\infty) = \ln(M_0 - M_\infty) - (k_f - k_r)t \qquad \text{(Eq. 18)}$$

where k_f and k_r are the rate constants for forward and reverse reactions, respectively. The slope equals the sum of k_f and k_r. Since this reversible process eventually reaches equilibrium:

$$K = \frac{k_f}{k_r} = \frac{M_0 - M_\infty}{M_\infty} \qquad \text{(Eq. 19)}$$

Both the forward and reverse rate constants can be evaluated once the slope of the line and the equilibrium constant (K) have been determined.

Sturek et al. (1978) employed Eq. (18) to relate time and the amount of nitroglycerin sorbed in a vial with a rubber closure (Fig. 9).

j. Bi-exponential equation

Malick et al. (1981) employed a compartmental model similar to the pharmacokinetic treatment of drug distribution in the human body to describe the sorption process of nitroglycerin in polyvinyl chloride bags. The loss of nitroglycerin from solution can be represented diagrammatically as follows:

$$\begin{array}{lcl} \text{nitroglycerin in} & \underset{k_2}{\overset{k_1}{\rightleftarrows}} \text{adsorbed} & \xrightarrow{k_3} \text{nitroglycerin} \\ \text{aqueous solution} & \text{nitroglycerin} & \text{dissolved in} \\ & \text{on plastic surface} & \text{plastic matrix} \end{array}$$

This model describes a rapid initial drop of the nitroglycerin concentration in the solution, at a rate of k_1, by adsorption to the PVC surface. The adsorbed molecule either diffuses into the plastic matrix at a rate of k_3, or partitions back to the solution at a rate of k_2.

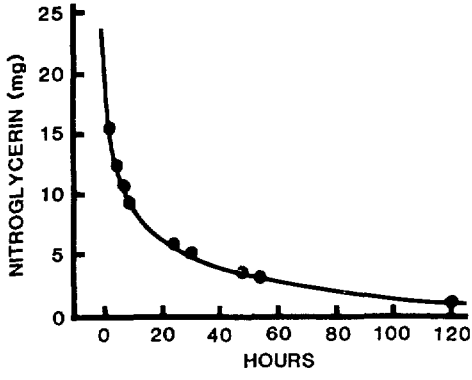


Figure 10—Amount of nitroglycerin in a plastic bag as a function of time. The symbols (closed circles) are experimental points. The solid line is the theoretically computed curve according to Eq. 20 [Source: Malick et al., 1981].

Through a steady-state approximation, the amount of nitroglycerin in the solution, A, can be expressed as:

$$A = \beta e^{-k_3 t} + (A_0 - \beta)e^{-k_1 t} \qquad \text{(Eq. 20)}$$

where

$$\beta = \frac{A_0}{\frac{k_3^2}{k_1 k_2} + \frac{k_1^2}{k_2} - \frac{2k_3}{k_2}} \qquad \text{(Eq. 21)}$$

and A_0 is the initial amount of nitroglycerin in the solution. Equation (20) indicates that the amount of nitroglycerin decreases in a bi-exponential manner.

Figure 10 illustrates the utility of Eq. (20) in fitting nitroglycerin sorption data.

3. Factors Influencing Sorption

The following seven subsections discuss literature reports pertinent to each of the factors that influences sorption. Generalizations about drugs and preservatives sorbed by plastic containers, plastic membrane filters, rubber closures, etc., are presented. Specific properties pertaining to each type of interaction, i.e., drug with plastic materials, preservatives with rubber closures, or adsorption by glass are discussed in the five subsequent sections, 4 through 8.

a. Effect of concentration

There are basically three types of concentration dependencies for a drug substance that interacts with a plastic material or rubber closure. Figure 11 illustrates these three types of sorption as curves generated from equilibrium experiments in which the amount of sorption was determined for various initial drug concentrations.

Curve A depicts leveling of percentage of drug sorbed at high drug concentration. Such behavior suggests that the sorbent (plastic) is comprised of a limited number of binding sites which become saturated at an increased drug concentration. This type of sorption process can be treated by a Langmuir equation (Eq. 6), as described in Section III.A.2.c. In addition to the investigators cited in Table XII, others have also observed this type of sorption pattern, but with insufficient data for calculating binding constants. Examples are the sorption of warfarin sodium, hydralazine HCl, and thiopental by polyvinyl chloride infusion bags (Kowaluk et al., 1981), butyric acid by polyamide (Autian, 1966), warfarin sodium by plastic infusion bag (Moorhatch and Chiou, 1974a), and of parabens and chloro-

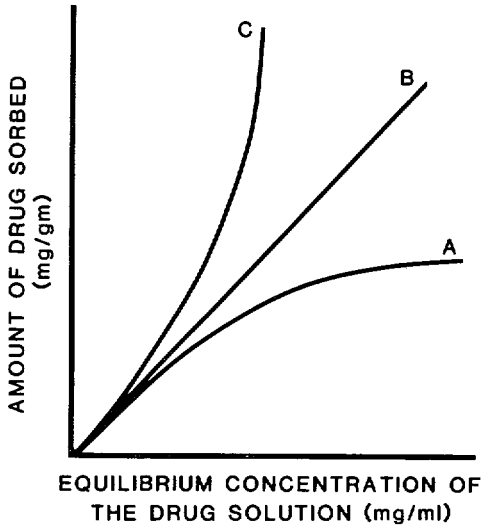


Figure 11—Typical equilibrium sorption patterns as a function of drug concentration.

butanol by polyamide syringes (Marcus et al., 1959; Schoenwald and Belcastro, 1969).

Curve B depicts the binding as a partitioning process that can be mathematically represented by a simple linear equation (Eq. 3), described earlier in Section III.A.2.b. This type of relationship was observed in the sorption of nitroglycerin by Roberts et al. (1980), vitamin A acetate and sodium methohexital by Moorhatch and Chiou (1974a) and isosorbide dinitrate by Cossum and Roberts (1981).

Curve C depicts an increase in the percentage of drug sorbed at high drug concentration. This type of sorption behavior was reported by Marcus et al. (1959) for phenol/polyamide, by Kowaluk et al. (1981) for clomethiazole/polyvinyl chloride, and by Nagabhushan et al. (1969) for methyl, ethyl, and propyl parabens and chlorocresol/polymethyl methacrylate. Autian (1966) suggested that, in some instances, these chemical agents acted as solvents for the plastic, causing an increase in polymer-chain flexibility through plasticization.

The concentration dependency of surfactant sorption is unique. Powell et al. (1969) reported a bell-shaped sorption pattern for benzalkonium chloride/polyamide, with maximum sorption occurring in the region of the critical micelle concentration. They theorized that below the critical micelle concentration, benzalkonium chloride was sorbed as single ions. As the

concentration of surfactant increased, dimers and aggregates of benzalkonium chloride were formed and these were, in turn, sorbed. Above the critical micelle concentration, micelles were being sorbed, leading to maximal sorption. A further increase in the concentration of benzalkonium chloride caused single molecules, aggregates, and micelles to be released to the solution. Thus, the amount of sorption decreased at concentrations higher than the critical micelle concentration.

b. Partition coefficient

Partition coefficient, K, is a measure of the relative affinity of a solute for aqueous and organic phases. The correlation of partition coefficient with drug absorption *in vivo* is well established in the literature. By intuition, one would anticipate that, regardless of the mechanism in operation, sorption of drug substances could also be directly related to the apparent partition coefficient, K_{app}, which was defined earlier in Eq. (3). Even for the sorption process that is in disagreement with Eq. (3), one may still determine the apparent partition coefficients, as long as one recognizes that K_{app} is a variable and dependent on the initial concentration and other parameters.

In general, drugs with high partition coefficients will exhibit rapid sorption with a greater extent of loss to a plastic material. Illum and Bundgaard (1982) correlated the initial rates of drug sorption with partition coefficients determined experimentally from a hexane/water or octanol/water system. The rate of sorption of the compounds from aqueous solution by polyvinyl chloride bags was related in rank order to their hexane/water partition coefficients. In the prediction of sorption behavior, however, the hexane/water partitioning system was more useful than the octanol/water system; hexane, being more lipophilic than octanol, seemed to be a better model for the polyvinyl chloride matrix.

Kowaluk et al. (1981) reported a similar observation. The percentage of drug lost during storage of an aqueous solution in polyvinyl chloride bags for 1 week did not correlate well with the apparent octanol/water partition coefficients. These investigators, however, attributed the poor correlation to other variables, such as the different degree of dissociation for ionizable compounds.

Sorption of drug begins with surface adsorption, followed by penetration through the microscopic spacings created by the movement of polymer chains in the plastic matrix. Until a better predictor is established, the partition coefficient remains the most useful parameter in predicting sorption behavior.

c. pH of the solution

A major factor influencing the sorption of acidic or basic drugs is the pH of the solution. It has been demonstrated repeatedly that the un-ionized

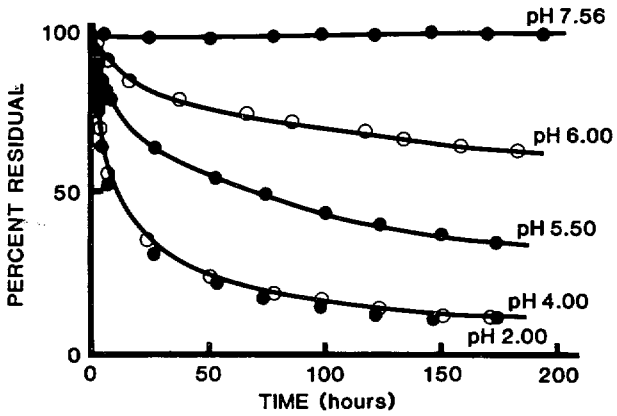


Figure 12—Effect of pH on the disappearance of warfarin sodium from various aqueous buffer solutions stored in polyvinyl chloride infusion bags (100 ml) for various times at room temperature [Source: Illum and Bundgaard, 1982].

drug species is the form that is lipophilic and, thus, most favorably sorbed by the plastic material. The extent of sorption is greatest in the pH range where an ionizable drug species exists predominantly in its un-ionized form. Sorption of a weak acid, e.g., warfarin, by polyvinyl chloride bags is illustrated in Fig. 12, in which both the rate and the extent of drug loss increase with a decrease in solution pH, i.e., with an increasing amount of un-ionized species. Sorption of a basic compound, benzocaine, by polyamide (Nylon 6) powder is illustrated in Fig. 13, in which the pH-sorption profile is superimposed on the drug dissociation curve calculated from the Henderson-Hasselbalch equation. The extent of sorption at pH 2.57, which is the pKa of benzocaine, was about half the maximum uptake that occurred at pH 6.

The sorption-pH relationship was also studied with other drug/plastic material combinations: butylparaben/polyethylene and butylparaben/polyvinyl chloride (Kakemi et al., 1971), sorbic acid/cellulose acetates (Saski, 1963), sorbic acid/polyamide (Autian and Shaikh, 1960) salicylic acid/polyamide (Nylon 66) (Kapadia et al., 1964b) butyric acid/polyamide (Nylon 66) (Berg et al., 1965), benzoic acid/polyamide 610 (Kapadia et al., 1964a and thimerosal/polyhydroxyethyl methacrylate (Richardson et al., 1975).

Sorption of protein onto a silicone-coated glass surface was an unusual case with respect to pH effect. The sorption patterns were comparable at pH 3, 7.2, and 9. Since the pH did not affect adsorption, it was surmised that adsorption was the result of hydrophobic bonding (Mizutani, 1981).

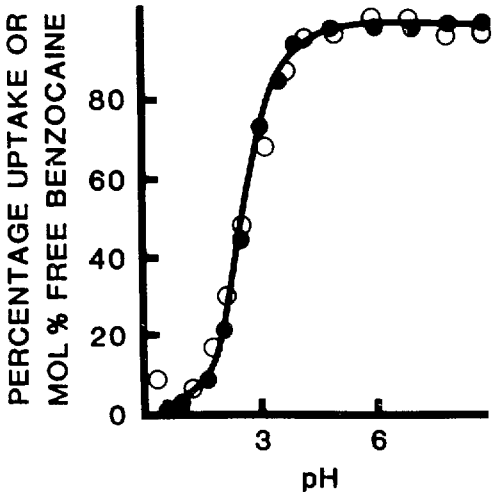


Figure 13—pH profile for the sorption of benzocaine by Nylon 6 powder from buffered solutions at 30° and ionic strength 0.5 M (open circles) and the corresponding drug dissociation curve (closed circles) [Source: Richardson and Meakin, 1974].

The pH effect is not just a tool to delineate the sorption mechanism. Significant loss of a drug substance can result from the introduction of some buffer components. Table XV shows that sorption of drugs by polyvinyl chloride was greater in a buffered solution than in an unbuffered one (Kowaluk et al., 1981). For weak basic drugs like those in Table XV, adjustment of the solution pH to 7.4 created only 1% un-ionized species, yet, the amount of sorption rose from less than 5% to between 50 and 90%.

TABLE XV
Loss of Drug from Buffered and Unbuffered Aqueous Solutions Stored in Polyvinyl Chloride Bags

Drug	pKa	% loss	
		Unbuffered	Buffered (pH 7.4)
Chlorpromazine HCl	9.3	5	86
Promazine HCl	9.2	0	48
Promethazine HCl	9.4	5	59
Thioridazine HCl	9.5	0	89
Trifluoperazine 2HCl	8.1	0	91

Source: Kowaluk et al. (1981).

d. Effect of excipients

As the polarity of the aqueous phase decreases with the addition of water-miscible solvents (such as ethanol, polyethylene glycol, etc.), the affinity of drug (undissociated species in the case of an ionizable compound) for the aqueous phase increases. Consequently, as the apparent partition coefficient decreases, there will be a reduction in the amount of sorption. Autian and Shaikh (1960) reported that as the water is replaced by glycerin or ethanol, the binding of sorbic acid to polyamide decreases. Kakemi et al. (1971) showed that inclusion of 30% propylene glycol in the formulation resulted in a decrease of adsorption of four parabens, benzalkonium chloride, and benzethonium chloride by sheets or granules of polyethylene, polypropylene, and polyvinyl chloride. Addition of 25% ethanol to the formulation reduced the sorption of phenol by polymethylmethacrylate (Nagabhushan et al., 1969). Reduction of diazepam sorption in polyvinyl chloride bags by the addition of 10% propylene glycol to the aqueous formulation was also reported (Illum and Bundgaard, 1982). The overall depressant effect of alcoholic solvents on sorption is illustrated by the effect of ethanol on the uptake of benzalkonium chloride by polyvinyl chloride bags (Fig. 14) (Guess et al., 1962).

The effect of solvent on the sorption of sorbic acid by cellulose acetate was atypical. Sorption was maximal in the presence of 10% ethanol, and fell to zero in the presence of 65% ethanol (Saski, 1963). No explanation was provided by the investigator.

When drugs or preservatives are solubilized by surfactants, the extent of sorption decreases. Various phenolic compounds have been shown to exhibit a smaller amount of sorption to polyethylene bottles in the presence of 2% polysorbate 80 (McCarthy, 1970a,b).

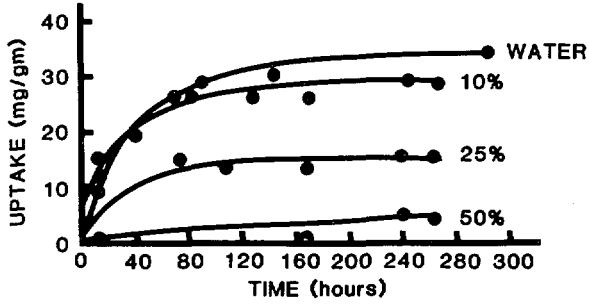


Figure 14—Effect of ethyl alcohol on uptake of benzalkonium chloride by polyvinyl chloride [Source: Guess et al., 1962].

Sodium chloride and dextrose solutions are the vehicles used most frequently for intravenous infusion. The effect of these two agents on sorption of drug substance to the infusion bag or tubing is complex and often inconsistent. Many investigators have reported different amounts of sorption from a variety of intravenous infusion vehicles (Parker and MacCara, 1980; Baaske et al., 1980; Weber et al., 1977). Unless a systematic approach is taken to analyze the mechanism involved, the cause of these differences may well be the result of artifacts. The only convincing report was offered by Illum and Bundgaard (1982) who attributed the difference in pH to the cause for a greater degree of sorption of warfarin to plastic strips from 5% dextrose (pH 4.5) than from normal saline (possibly, pH 6–7) observed by Moorhatch and Chiou (1974). It was explained that warfarin, an acidic compound, is more favorable absorbed as an un-ionized species in the dextrose solution which has a lower pH than as an ionized species in normal saline.

All components of a solution, including drug, solvent, and excipients, could be competing for the same binding sites in a plastic material. For example, binding sites for insulin can be occupied by other types of protein. The addition of gelatin or albumin to the insulin formulation was found to reduce insulin sorption (Reeve and Frank, 1956; Hill, 1959a,b).

Counter-ions could change the lipophilicity of an ion-pair, thus affecting sorption of the ionic species. For example, sorption of benzalkonium chloride was enhanced by the addition of 0.05% ammonium thiocyanate (Kakemi et al., 1971). Chloride anions caused a rapid, initial uptake of mercurial species by polyethylene bottles (Aspinall et al., 1980). In contrast, the presence of phosphate buffers in a solution of phenylmercuric acetate inhibited the sorption of a mercurial compound by polyethylene (Aspinall et al., 1980). Large amounts of sodium chloride (up to 6%) caused about a 60% increase in benzocaine sorption, an effect attributed to a "salting-out" phenomenon in the aqueous phase (Richardson and Meakin, 1974).

e. Effect of temperature

The effect of temperature on the equilibrium process is described by the van't Hoff equation:

$$\log \frac{K_1}{K_2} = \frac{H}{2.303R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \qquad \text{(Eq. 22)}$$

where H is the enthalpy of sorption and K_1 and K_2 are the equilibrium constants at the absolute temperatures of T_1 and T_2. For the sorption process, the equilibrium constants are the same as those partition coefficients described previously in Eq. (3). From the plot of $\log K_{app}$ against the reciprocal of the absolute temperature ($1/T$), the enthalpy of sorption can

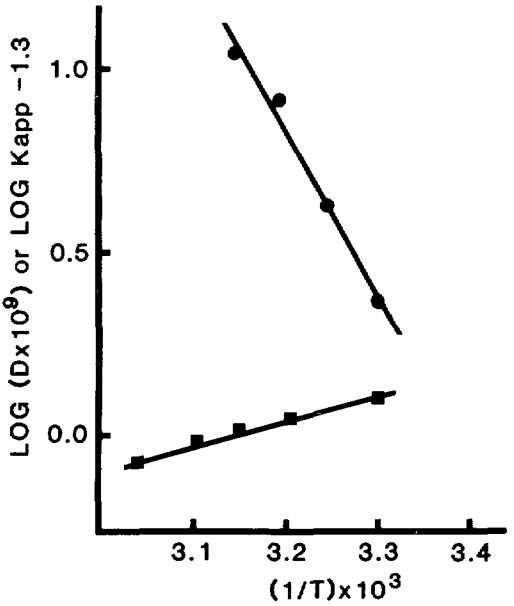


Figure 15—Comparison of temperature effects on sorption process. Key: circles, diffusion coefficients (D) of nitroglycerin in polyvinyl chloride; squares, equilibrium constants (K_{app}) of benzocaine with Nylon 6 powder [Sources: Yuen et al., 1979, Richardson and Meakin, 1974].

be determined from the slope. Figure 15 illustrates the sorption of benzocaine to polyamide (Nylon 6) powder. The enthalpy of sorption was calculated to be −2.9 kcal/mole. The small magnitude of the enthalpy of sorption is demonstrated by the fact that, as temperature increased from 30 °C to 56 °C, the value of K_{app} decreased from 25.3 to only 17.0.

The K_{app} value and enthalpy of sorption (H) are independent of drug concentration when the sorption process obeys a simple linear equation. For sorption processes that are best described by the Langmuir or Freundlich equations, the K_{app} value varies with drug concentration. Thus, the enthalpy of sorption for these Langmuir and Freundlich types of sorption becomes concentration dependent. Since these enthalpies are often small in value, ranging from 0 to −3 kcal/mole, the enthalpies often remain constant in the range of concentrations studied. Enthalpies reported in the literature or calculated from literature data are listed in Table XII.

The effect of temperature on kinetic (diffusion) process can be described as:

$$D = A \exp(-E_d/RT) \qquad \text{(Eq. 23)}$$

or

$$\log \frac{D_1}{D_2} = \frac{E_d}{2.303R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \qquad \text{(Eq. 24)}$$

where D_1 and D_2 are the diffusion coefficients at absolute temperatures of T_1 and T_2, E_d is the energy of activation for diffusion, and A is a frequency factor (or preexponential term). From the plot of log D vs. $1/T$ at various temperatures, the activation energy for diffusion can be determined. Figure 15 shows the plot of diffusion coefficients for nitroglycerin in polyvinyl chloride at various temperatures. The activation energy was found to be 19.6 kcal/mole. The activation energy of diffusion for other compounds is shown in Table XIII.

When the data in Fig. 15 are transcribed on a relative scale, it can be seen that the equilibrium process is much less sensitive to temperature change than is the diffusion process. Another point of contrast is that temperature has an opposite effect on the equilibrium and diffusion processes, viz, at higher temperatures, sorption occurs at a faster rate but to a lesser extent. It may be reasoned that there exists a weak interaction between a drug substance and a plastic material, or between an antimicrobial agent and a rubber closure. At higher temperatures, the increase in kinetic energy of both the solute molecules and the polymer molecules results in the breaking of these weak interactions, leading to a reduction in the amount of uptake. At high temperatures, therefore, the equilibrium constant is decreased. The kinetic energy, however, facilitates Brownian movement and thus accelerates the diffusion process. At high temperatures, therefore, the diffusion rate is increased.

In general, temperature has a more profound influence on the rate of sorption than on the equilibrium quantity. It is worthwhile mentioning here that, in comparing the sorption of different compounds, temperature effects can be compared only when all the systems are at equilibrium state or when all the compounds are in the process of diffusion. Otherwise, the observed temperature effects may lead to incorrect speculations about the mechanism involved. This is so because, after a given time interval, one compound may already have reached an equilibrium state, so that the effect of temperature on the percent loss reflects a low value for the heat of sorption; in contrast, another compound may still be in the process of diffusing, so that the effect of temperature on the percent loss reflects the activation energy of diffusion, thus yielding a higher value.

f. Structure of the polymeric sorbent

Only a few literature reports have been concerned with the effect of polymeric structure on the uptake of drugs. Autian (1963a,b) reviewed the information from the textile industry and attempted to apply that

knowledge to predicting the sorption behavior of drug substances. The pharmaceutical profession has contributed little to this area, presumably because it does not have control over or knowledge of either the manufacturing processes of or the composition of polymeric materials. Many reports from the pharmaceutical literature omit important information about the composition and structure of the polymeric materials used in the studies. It is, therefore, difficult to compare the data from one author with those from another because of the limited information available about plastic or rubber closures.

In a very general sense, one may anticipate a strong binding of drug substances by a hydrophilic plastic material, like cellulose (membrane filters) and polyamide (Nylon). The hydroxyl groups in the cellulose could easily form hydrogen bonds with drug substances. The positively and negatively charged centers in a polyamide material could attract drug species of opposite charge. Among such commonly used resins as polyvinyl chlorides, polyethylene, and polypropylene, the tendency to take up drug substances appears to decrease in that order, corresponding to a decreasing number of binding sites per molecule.

Plastics are very heterogeneous. Any segment of a plastic material may be composed of microscopic sections of crystalline and amorphous structure. It was well recognized that drug can penetrate only through the amorphous region, which is also rich in binding sites. Consequently, plastics with a high degree of crystallinity exhibit a low rate of sorption and a small amount of uptake. Crosslinking among polymer chains will result in reductions in the rate and amount of sorption. For example, Fischer and Neuwald (1971) observed only a 3–6% loss of phenylmercuric compound to high-density polyethylene, as compared with a 10–20% loss with low-density polyethylene; the former is more crystalline and crosslinked than the latter.

Plasticizers, which are often the primary culprit for drug sorption to plastic materials, have received little attention. Bray and Meakin (1975) demonstrated a linear correlation between benzocaine sorption and plasticizer (di-2-ethylhexyl phthalate) content in polyvinyl chloride (Fig. 16). Neuwald and Schmitzek (1968) observed a greater sorption of benzalkonium chloride, methylparaben, phenylmercuric nitrate, and chlorhexidine by plasticized polyvinyl chloride granules than by plasticizer-free granules. Inconsistencies in data for sorption by polyvinyl chloride may be attributable to the presence of different types and amounts of plasticizers, up to 50%, in polyvinyl chloride (McCarthy, 1970a,b; Guess et al., 1962).

g. Structure of the sorbate

The effect of different substituent groups in the sorbate molecule on the sorption process has been studied with a series of homologues (Table XVI).

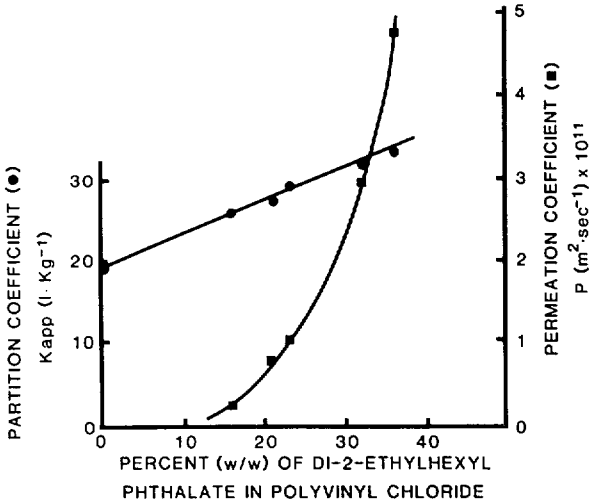


Figure 16—Effect of plasticizer concentration on sorption, as determined by partition coefficient (closed circles) and permeation, as determined by permeability coefficient (closed squares) of benzocaine in polyvinyl chloride [Source: Bray and Meakin, 1975].

In a study with phenolic preservatives (McCarthy, 1970), the addition of an electron-withdrawing group (e.g., halogens, carbonyl groups, nitro group) on the phenolic ring system was reported to cause an increase in the amount of sorption by the polyethylene container. Beyerlein et al. (1971) employed thermogravimetric analysis to determine the amounts of liquid substances sorbed by polyamide. Although the octanol/water partition coefficient increased as the series of homologues ascended from methanol to pentanol, the equilibrium sorption decreased, suggesting that partition coefficient alone could not explain the binding affinity. Perhaps the size of the molecule also plays a role in determining the extent of sorption. Similar to the finding by McCarthy (1970), Beyerlein et al. (1971) found that addition of an electron-withdrawing group to methanol to form phenylmethanol (benzyl alcohol) or to ethanol to form chloroethanol also resulted in a significant increase in sorption. It is known that electron-withdrawing groups increase the acidity of hydroxyl groups and, therefore, facilitate hydrogen bonding. A sorption study of benzalkonium homologues with polyhydroxyethylmethacrylate revealed an opposite trend (Davis and Watson, 1981). When the chain length was increased from C_{10} to C_{16}, the amount of sorption increased (Table XVI). Alcohol homologues and polymethyl methacrylate were found by Nagabhushan et al. (1969) to exhibit an interesting sorption

TABLE XVI
Structure–Sorption Relationship

Homologues	Sorption	Comment
Phenol	5%	Sorption occurred
3-Chloro-4-methyl-phenol[a]	12%	in polyethylene container
o-Phenyl-phenyl	74%	stored at 25 °C for
2,6-Dichloro-phenol	84%	12 weeks (McCarthy, 1970a,b
Methanol	83.3 mg/g	Equilibrium quantity
Ethanol	96.7 mg/g	of compounds
Propanol	85.9 mg/g	sorbed by polyamide
Butanol	24.4 mg/g	Beyerlein et al., 1971)
Ethanol	96.7 mg/g	
Propanol	85.9 mg/g	
Butanol	24.4 mg/g	
Pentanol	14.1 mg/g	
Phenylmethanol[b]	205.4 mg/g	
2-Chloroethanol	262.5 mg/g	
C_{10}-Benzalkonium chloride	0.8 mg/g	Amount of sorption by
C_{12}-Benzalkonium chloride	1.2 mg/g	polyhydroxylmethacrylate at
C_{14}-Benzalkonium chloride	3.2 mg/g	equilibrium concentration of 2%
C_{16}-Benzalkonium chloride	5.2 mg/g	(Davis and Watson, 1981)

[a] chlorocresol. [b] benzyl alcohol.

pattern (Fig. 17); as the molecular weight of the sorbate increased, affinity for the plastic material increased.

Given the conflicting results in the literature, it is difficult to predict sorption activity. It seems more appropriate, at this stage of knowledge, to study such activity, rather than try to predict it.

4. Drug-Plastic Interactions

a. General

Manufacturers of sterile products have encountered only limited drug-plastic interactions in the past, primarily because only ophthalmic, otic, and some nasal products were packaged in plastic bottles. Parenteral products packaged in plastic containers have previously been restricted primarily to nontherapeutic preparations, such as normal saline and dextrose solutions. During the '60s, the primary concern was the interaction between drugs and polyamide (Nylon) syringes. Autian and his co-workers pioneered extensive studies to delineate the mechanisms of drug-plastic

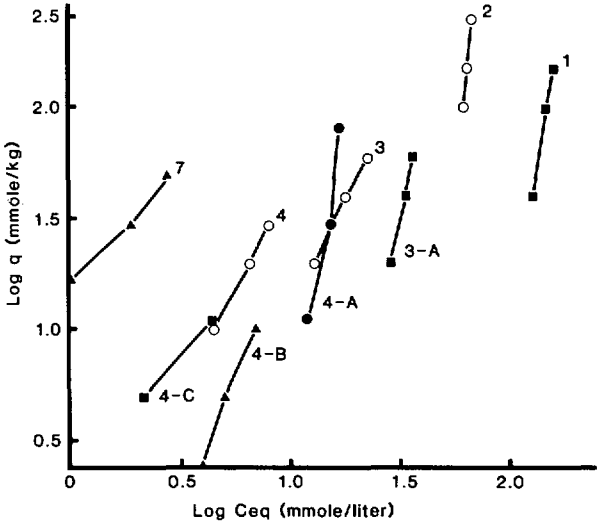


Figure 17—Structure—sorption relationship of alcohol homologues with polymethyl methacrylate at 30 °C. Key: 1 , methyl; 2, ethyl; 3, propyl; 3A, isopropyl; 4, butyl; 4A, S-butyl; 4B, i-butyl; 4C, t-butyl; 7, benzyl [Source: Nagabhushan et al., 1969].

interactions. In most of their studies, however, only model compounds, rather than parenteral drugs, were used.

Since the introduction of plastic bags for IV infusion in the early '70s, more and more drugs are administered through IV infusion sets that are made of various combinations of plastic items: polyvinyl chloride bags, polyethylene tubing, polypropylene syringes, etc. The literature contains many articles reporting the loss of drugs from the bags, tubing, etc. There have been more than 20 articles just on the sorption (or "availability" through IV sets) of nitroglycerin alone. Table XVII lists 116 drugs that have been studied with respect to sorption by plastic materials. For nitroglycerin, insulin, and diazepam, Table XVII includes only a partial listing of the references; these three compounds are discussed in greater detail in Sections III.A.4.b,c, and d. The following discussion is intended to highlight some major studies in the general area of drug-plastic interactions.

Filtration is an important process in the manufacturing of parenteral solutions. It is also used by hospital pharmacists for sterilization or clarification. Although the filtration set is not, strictly speaking, a packaging system, nevertheless physical and chemical interactions between drug and filter resemble those between drug and plastic container. Thus, studies on

TABLE XVII
Sorption of Drugs to Plastic Materials

Drug	Sorbent*	Observation	Reference
Aminophylline	Plastic syringes	Less than 5% loss (at 5 mg/ml after 18 hr)	Simmons and Allwood (1981)
Amoxicillin trihydrate	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Ampicillin trihydrate	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Apomorphine hydrochloride	PE device	Discolored after 1 month at 50 °C	Guess et al. (1965)
Ascorbic acid	PVC bags	No loss in 24 hr	Moorhatch and Chiou (1974a)
Atropine sulfate	PE & PVC	No sorption	Gotz (1980)
Benzocaine	Nylon 6 powder	Sorption isotherm presented	Richardson and Meakin (1974)
	PVC	Sorption constants increased linearly with plasticizer content	Bray and Meakin (1975)
Bleomycin sulfate	Inline cellulose ester filter	No loss at 50 U/50 ml	Butler et al. (1980)
Cefoxitin sodium	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Cephalothin sodium	3 membrane filters	No loss	Rusmin et al. (1977)
	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Chloramphenicol sodium succinate	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Chlormethiazole	500 ml I.V. infusion set	ca. 20% loss from 0.8% solution	Tsuei et al. (1980)
	Glass syringe infusion pump	No loss	Cossum and Roberts (1981)
Chlormethiazole edisylate	PVC bags	80% loss in 60 hr	Kowaluk et al. (1981)
Chlorpromazine hydrochloride	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Cimetidine	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Cloxacillin sodium	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Codeine hydrochloride	PE & PVC	No sorption	Gotz (1980)
Cyanocobalamin	PVC I.V. bags	No loss at 24 hr	Moorhatch and Chiou (1974a)
Dactinomycin	Inline cellulose ester filter	13% loss	Rusmin et al. (1977)
Dexamethasone	Inline cellulose ester filter	No loss	Rusmin et al. (1977)
Dexamethasone sodium phosphate	PVC bags	Insignificant loss	Kowaluk et al. (1981)

TABLE XVII (*continued*)

Drug	Sorbent*	Observation	Reference
Diazepam	PVC bags	60% loss from 40 μg/ml after 8 hr	Illum and Bundgaard (1982)
	PVC bags	32% loss in 1 week	Kowaluk et al. (1981)
Diethylstilbestrol diphosphate disodium	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Digitoxin	Nitrocellulose filter	58% loss from 3-ml filter	Chiou and Smith (1970)
	Inline cellulose ester filter	20% loss (at 0.2 mg/50 ml)	Butler et al. (1980)
Digoxin	Inline cellulose ester filter	No loss	Rusmin et al. (1977)
Dopamine	Plastic syringes	Less than 5% loss (at 10 mg/ml after 18 hr)	Simmons and Allwood (1981)
Dopamine hydrochloride	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Doxycyline	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Ephedrine hydrochloride	PE & PVC	No loss	Gotz (1980)
Ergonovine maleate	Inline cellulose ester filter	3–4% loss (at 0.2 mg/25 ml)	Butler et al. (1980)
Ethinyl estradiol	Nitrocellulose filter	38% loss from 3-ml filtrate	Chiou and Smith (1970)
Ethylmorphine hydrochloride	PE & PVC	No sorption	Gotz (1980)
Flucloxacillin sodium	PVC bags	Insignificant loss	Kowaluk et al. (1981)
5-Fluorouracil	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Folic acid	Inline cellulose ester filter	4–5% loss in the initial portion of 0.5 mg/liter	Butler et al. (1980)
Gentamicin sulfate	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Griseofulvin	Nitrocellulose filter	29% loss from 3-ml filtrate; adsorption isotherm presented	Chiou and Smith (1970)
Haloperidol	PVC bags	No loss	Gupta and Stewart (1982)
Heparin	Inline cellulose ester filter	No loss at 10,000 U/liter	Butler et al. (1980)
	PP syringes	8% loss in 3 weeks	Tunbridge et al. (1981)
	Plastic syringes	Less than 5% (from 1000 U/ml after 18 hr)	Simmons and Allwood (1981)
Hydralazine hydrochloride	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)

TABLE XVII (*continued*)

Drug	Sorbent*	Observation	Reference
Hydrocortisone	PE tubing	No adsorption	Levin et al. (1965)
	Plastic syringes	Less than 5% (from 8 mg/ml after 18 hr)	Simmons and Allwood (1981)
	Nitrocellulose filter	6% loss (from 3-ml filtrate)	Chiou and Smith (1970)
Hydrocortisone acetate	PVC bags	No loss (at 20 μg/ml after 8 hr)	Illum and Bundgaard (1982)
	Nitrocellulose filter	17% loss (from 3-ml filtrate)	Chiou and Smith (1970)
Hydrocortisone sodium succinate	PVC bags	No loss at 24 hr	Moorhatch and Chiou (1974a)
	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Insulin	Inline cellulose ester filter	77–100% loss in the initial portion of 40 U/liter	Butler et al. (1980)
	Plastic syringes	Less than 5% from 0.8 U/ml	Simmons and Allwood (1981)
Iopanoic acid	Nitrocellulose filter	6% loss from 3-ml filtrate	Chiou and Smith (1970)
Isoproterenol	Inline cellulose ester filter	No loss	Rusmin et al. (1977)
Isosorbide dinitrate	PVC bags and I.V. sets	About 30% loss	Cossum and Roberts (1981)
Kanamycin sulfate	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Levarterenol bitartrate	Inline cellulose ester filter	No loss from 4 mg/liter	Butler et al. (1980)
Lidocaine hydrochloride	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Lorazepam	I.V. tubing	No loss	Carpenter et al. (1981)
Medezepam	PVC bags	76% loss after 8 hr from 40 μg/ml	Illum and Bundgaard (1982)
Menadiol sodium	PVC I.V. bags	No loss at 24 hr	Moorhatch and Chiou (1974a)
Meperidine hydrochloride	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Mercaptomerin sodium	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
Merethoxylline procaine	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
Metaraminol bitartrate	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Methamphetamine hydrochloride	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
Methicillin sodium	PVC bags	Insignificant loss	Kowaluk et al. (1981)

TABLE XVII (*continued*)

Drug	Sorbent*	Observation	Reference
Methohexital sodium	PVC I.V. bags	8% loss at 24 hr	Moorhatch and Chiou (1974a)
Metronidazole	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Mithramycin	Inline cellulose ester filter	Lost 50–100% in the initial portion of 2.5 mg/liter	Butler et al. (1980)
Morphine hydrochloride	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Niacin	PVC I.V. bags	No loss at 24 hr	Moorhatch and Chiou (1974a)
Niacinamide	PVC I.V. bags	No loss at 24 hr	Moorhatch and Chiou (1974a)
Nitrazepam	PVC bags	15% loss (at 40 μg/ml after 8 hr)	Illum and Bundgaard (1982)
Nitroglycerin	PVC bags	54% loss (at 200 μg/ml after 8 hr)	Illum and Bundgaard (1982)
Nitroprusside sodium	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Ouabain	LDPE bottle	Sorption occurred	Neuwald (1965)
Oxazepam	PVC bags	22% loss (from 40 μg/ml after 8 hr)	Illum and Bundgaard (1982)
Oxytetracycline	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
Oxytocin	Inline cellulose ester filter	Up to 10% loss (at 25 U/100 ml)	Butler et al. (1980)
Pentobarbital sodium	PVC bags	No loss at 30 μg/ml after 8 hr	Illum and Bundgaard (1982)
	PVC I.V. bags	No loss at 24 hr	Moorhatch and Chiou (1974)
Phenobarbital sodium	Inline cellulose ester or polycarbonate filters	No loss	Rusmin et al. (1977)
	Nitrocellulose filter	6% loss from 3-ml filtrate	Chiou and Smith (1970)
Phenobarbital	Nitrocellulose filter	17% loss from 3-ml filtrate	Chiou and Smith (1970)
Phentolamine mesylate	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Phenylephrine	LDPE	Essentially no loss	Karig et al. (1973)
Phenytoin sodium	Cellulose ester filter	No loss	Rusmin et al. (1977)
	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Phytonadione	PE devices	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
Pilocarpine	LDPE bottle	Sorption	Neuwald (1965)

TABLE XVII (*continued*)

Drug	Sorbent*	Observation	Reference
Pilocarpine hydrochloride	PE & PVC	No sorption	Gotz (1980)
Practolol	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Prednisolone	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Procainamide hydrochloride	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Promazine hydrochloride	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Promethazine hydrochloride	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Propranolol hydrochloride	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Pyridoxine hydrochloride	PVC I.V. bags	1.8% loss at 24 hr	Moorhatch and Chiou (1974a)
Pyridoxine & thiamine hydrochlorides	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
Quinidine sulfate	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Quinine sulfate	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Reserpine	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
Retinol acetate	PVC bags	78% loss (from 200 ml at 3 μg/ml)	Chiou and Moorhatch (1973b)
	PVC I.V. bags	67% loss at 24 hr	Moorhatch and Chiou (1974a)
Riboflavin	PVC I.V. bags	No loss at 24 hr	Moorhatch and Chiou (1974a)
	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Scopolamine	LDPE bottle	Sorption occurred	Neuwald (1965)
Secobarbital sodium	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
Secretin	Catheter and syringe	45–55% loss	Miyata (1979)
Spironolactone	Nitrocellulose filter	99% loss from 3-ml filtrate	Chiou and Smith (1970)
Streptomycin sulfate	PE device	Discolored (after 1 month at 50 °C)	Guess et al. (1965)
Strophanthin	LDPE bottles	Sorption occurred	Neuwald (1965)
Sulfonamides	Polymethacrylate	20–60% sorption occurred	Lippold and Lippold (1974)
Testosterone	PE tubing	50% absorption occurred	Levin et al. (1965)
Thiamine hydrochloride	PVC I.V. bags	No loss in 24 hr	Moorhatch and Chiou (1974a)

TABLE XVII (*continued*)

Drug	Sorbent*	Observation	Reference
Thiopental sodium	PVC bags	25% loss (from 30 μg/ml after 8 hr)	Illum and Bundgaard (1982)
Thioridazine hydrochloride	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Tocopherol acetate	PVC I.V. bags	No loss in 24 hr	Moorhatch and Chiou (1974)
Tobramycin sulfate	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Trifluoperazine dihydrochloride	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Trimethoprim	PVC bags	Insignificant loss	Kowaluk et al. (1981)
Tubocurarine	PVC bags	No loss in 24 hr	Moorhatch and Chiou (1974a)
Vinblastine	Inline cellulose ester filter	Up to 2.5% loss at 10 mg/50 ml	Butler et al. (1980)
Vincristine sulfate	Inline cellulose ester filter	6–12% loss (at 1 mg/50 ml)	Butler et al. (1980)
Vitamin D	PVC I.V. bags	No loss in 24 hr	Moorhatch and Chiou (1974a)
Warfarin	Nitrocellulose filter	39% loss from 3-ml filtrate	Chiou and Smith (1970)
Warfarin sodium	Nitrocellulose filter	5% loss from 3-ml filtrate	Chiou and Smith (1970)
	PVC I.V. bags	12% loss in 24 hr	Moorhatch and Chiou (1974a)
	PVC bags	29% loss (from 30 μg/ml after 8 hr)	Illum and Bundgaard (1982)

* Abbreviations: LD = low density. PE = polyethylene. PP = polypropylene. PVC = polyvinyl chloride.

the interactions between drugs and filters are also included in Table XVII.

Guess et al. (1965) reported that a group of drug solutions discolored a polyethylene hypodermic device. The discoloration could not be removed by repeated washing of the plastic with distilled water, indicating, most likely, that some type of chemical reaction had taken place.

Moorhatch and Chiou (1974a) studied the interactions between drugs and strips of polyvinyl chloride, the plastic material used in Viaflex IV bags. Among the 17 drugs they studied, only vitamin A acetate, sodium warfarin, and sodium methohexital were found to be significantly sorbed. This lead caused the authors to study the effects of concentration, diluents, and temperature on sorption of these three drugs.

In one of the many impressive reports by Polack and his co-workers (Kowaluk et al., 1981), 46 injectable drug products, many of them requiring administration by intravenous infusion, were evaluated with respect to loss from aqueous solution after storage in polyvinyl chloride infusion bags for various lengths of time. Five of the drugs-chlormethiazole edisylate, diazepam, hydralazine hydrochloride, thiopental sodium, and warfarin sodium showed a substantial loss after one week (Kowaluk et al., 1981).

Sorption of drugs by PVC infusion bags was also investigated by Illum and Bundgaard (1982), who employed kinetic analysis for a group of benzodiazepines, warfarin, and nitroglycerin. They reported the effects of pH and the presence of propylene glycol on sorption and the correlation of sorption behavior with partition coefficients. The results suggested that polyvinyl chloride bags should not be used for these drugs. Additionally, the sorption of benzodiazepines, warfarin, nitroglycerin and thiopental sodium can be reduced by the use of polypropylene infusion bottles. The sorption of nitroglycerin was reduced to a minimum when polyolefin (Amann et al., 1980), polyethylene and polypropylene (Pikal et al., 1977; Mathot et al., 1980) were used. Similarly, insulin showed less sorption in polyolefin bags than in polyvinyl chloride bags (Hirsch et al., 1981).

In addition to the problems with syringes and bags discussed above, problems can also occur in IV tubing because, in the course of transport, the ratio of tubing surface area to fluid volume is large.

Through use of a volume-controlled infusion set (IVAC Volume Infusion Set), the concentration of chlormethiazole in the effluent was determined at various time intervals (Tsuei et al., 1980). Results are shown in Fig. 18. Before collecting samples for analysis, the infusion set was always primed with the running solution and three drops were let out. Curve A shows an initial drop to about 60% of the anticipated potency. Potency returned to about 80% after 60 min and was then maintained at that level. In curve B, when the solution was allowed to stand in the infusion set for 15 min prior to injection, the loss of chlormethiazole was considerably greater. The sample collected during the first minute of infusion contained only 40% of the original concentration. Perhaps binding sites in the infusion set were more occupied under the conditions for curve B than under those for Curve A, so that a steady level was reached more quickly in Curve B. Attainment of the steady level of chlormethiazole at 80% potency was attributed to loss from the infusion set to the atmosphere.

For an infusion of 0.02% nitroglycerin solution, the times required to regain the original concentration were 24, 15, and 6 hr for flow rates of 0.23, 0.52, and 0.75 ml/min, respectively (Roberts et al., 1979). Polyethylene, polyvinyl chloride, and Silastic® tubing were all incriminated in sorption

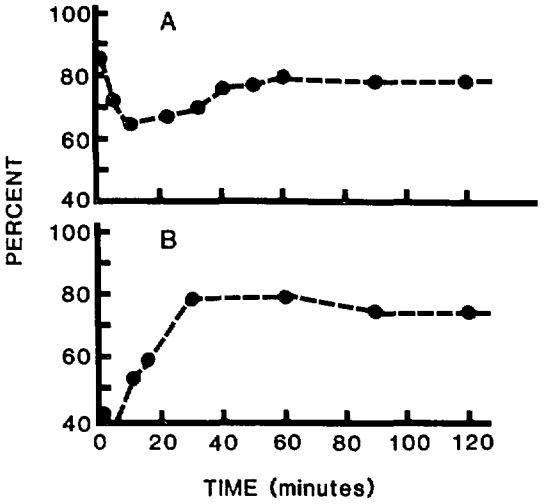


Figure 18—Sorption of chlormethiazole by IV infusion sets, represented by effluent concentration as percent of original concentration. *A*) Solution infused immediately; *B*) Solution allowed to stand in the set for 15 min [Source: Tsuei et al., 1980].

losses. As much as 15% of the nitroglycerin dose was lost during manufacturing (Boylan et al., 1978). Nitroglycerin loss to tubing was observed by Cossum et al., 1978, Baaske et al., 1980, and Jacobi et al., 1982. An insulin-plastic tubing interaction was also investigated by other workers (Weisenfeld et al., 1968; Petty and Cunningham, 1974; Peterson et al., 1976).

Although the general equation for the static sorption process (Eq. 8) is complex enough, a general equation for the dynamic sorption, requiring consideration of such additional variables as flow rate, tube diameter, and tube length, will be extremely complex. Mathematical equations for a convective diffusion model were derived to estimate the loss of drug to tubing. This model was found adequate to describe the reported 12% loss of retinol in polyvinyl chloride tubing (Amidon et al., 1981). However, hospital pharmacists still need a workable means to predict drug loss due to sorption by any infusion set. An ingenious nomogram was developed by scientists at the University of Michigan (Mason et al., 1981). This nomogram, plus a predictive dosing chart, permits calculation of the actual doses of diazepam delivered at various flow rates with different lengths of tubing.

The other components of an IV infusion set should not be overlooked, notably, the burette chamber and filter. A burette made of cellulose propionate (Buretrol) was reported to absorb a significant quantity of nitro-

glycerin (Roberts et al., 1980). In fact, the affinity of nitroglycerin for cellulose propionate is greater than that for polyvinyl chloride, as measured by partition coefficient, K_{app}. These same investigators also reported greater sorption of isosorbide dinitrate to a cellulose propionate burette (Buretrol) than to a polyvinyl chloride infusion bag. Of five administration sets evaluated by Whalen et al. (1979), sorption of insulin was greatest with a Buretrol set.

Many new designs of administration sets incorporate an inline filter to remove particulate matter and microbial contamination. The use of inline filters in the hospital has increased, and such filtration become another area of potential drug sorption. This problem is more serious when drug concentration is low, the filtration volume is small, or both conditions exist.

Chiou and Smith (1970) studied the sorption of 18 organic compounds by nitrocellulose membrane filters. The adsorption by the filters, a reversible process, ranged from 0 to almost 100% when 3 ml of test solution was filtered through a type MF (17.5-mm diameter) Millipore filter.

Drug sorption by filter sets made of stainless steel, cellulose ester, or polycarbonate was studied by Rusmin et al., 1977. Because of the small surface area and the low weight of the filters used, the amount sorbed proved to be insignificant from a therapeutic standpoint. The results of a subsequent study indicated that digitoxin, insulin, mithramycin, and vincristine sulfate each showed a measurable reduction in potency when filtered through an inline cellulose ester membrane (Butler et al., 1980). These 22-mm diameter membrane filters, which generally weigh 25 to 50 mg, have been reported to remove approximately 1–5 μg of drug for every milligram of filter material.

b. Insulin

Insulin is the first drug substance known to have lost potency by sorption. Adsorption of ^{131}I-insulin from dilute solutions to laboratory glassware was first reported in 1951 (Ferrebee et al., 1951). Adsorption was shown to be greatest at neutral pH and inhibited by the addition of albumin. In 1959, Hill found a significant adherence of radiolabeled insulin to siliconized glassware and to polyethylene reagent bottles. He reported a decrease in the adsorption of trace amounts of insulin after the addition of 5% gelatin. The sorption of insulin to intravenous infusion sets (glass bottle and polyvinyl chloride tubing) was investigated by Weisenfeld et al. (1968). The tubing was found to account for a large portion of the insulin adsorbed. The presence of 0.35% human serum albumin almost completely prevented the adsorption of insulin to glass bottles and markedly reduced the loss to polyvinyl chloride tubing. According to Petty and Cunningham (1974), the amount of insulin adsorption during rapid infusion was 52% of the loading

dose to the PVC bag and 27% to the tubing. Kraegen et al. (1975) reported a comparable result. In addition, their recovery studies showed that 0.5–3.5% of polygeline (the polymer of degraded gelatin) was as effective as human serum albumin in reducing insulin adsorption. Polygeline is superior to human serum albumin in ease of use and entails less risk of transmitting infection. On the other hand, Peterson et al. (1976), using a similar methodology, reported without any explanation only an 11% loss due to adsorption. From a study of effluent concentration, they recommended a 50 ml wash-out prior to administration to avoid any subpotent effluent in the first 100 ml. In a study using one-liter 5% dextrose solution containing 40 units of insulin, Hirsch et al. (1977) reported a 23–28% loss of insulin to polyvinyl chloride bags and administration sets when the flow rate was 100 ml/hr.

Comparing the adsorption loss of insulin to glass bottles and polyvinyl chloride bags, both Kraegen et al. (1975) and Weber et al. (1977) showed only 7% more adsorption of insulin to polyvinyl chloride bags than to glass bottles, and Whalen (1979) reported no difference. Likewise, Okamoto et al. (1979) reported a comparable extent of adsorption to both polypropylene and glass infusion containers.

In search of a means to reduce adsorption, Kerchner et al. (1980) demonstrated that addition of a small quantity of the patients' own blood to the insulin solution minimized the adsorption of insulin to polyvinyl chloride bags or to glass bottles. Two comprehensive reports showed sizeable variation in quantitative results concerning the availability of insulin from parenteral nutrient solutions (Weber et al., 1977) and from continuous low-dose infusions (Whalen et al., 1979), under simulated conditions of administration.

Since insulin is not a lipophilic substance, *ab*sorption to plastic material is not likely. This assumption is supported by the early data of Petty and Cunningham (1974), which showed that the equilibrium of sorption is reached instantaneously. Hirsch et al. (1977) presented a Langmuir *ad*sorption isotherm, Eq. (6), that substantiated this viewpoint.

c. Nitroglycerin

Nitroglycerin has been administered for the relief of angina pectoris since 1853. After 1975, considerable new interest in this drug was centered on its clinical use intravenously for the treatment of congestive heart failure, myocardial infarction, and in open-heart surgery. Until 1981, no intravenous nitroglycerin solution was commercially available; hospital pharmacists had always been called upon to prepare such a solution extemporaneously from an oral dosage form of nitroglycerin.

A rash of publications concerning the interaction of nitroglycerin with packaging components appeared in 1978, five within a 5-month period.

Ludwig and Ueda (1978) reported a continual and appreciable (30%) loss of nitroglycerin during the first 5 hr after the preparation of a 10 mg/ml solution with 5% dextrose. Their results, unlike most others, showed a comparable loss of nitroglycerin to both glass bottles and plastic bags. Sturek et al. (1978) showed a greater and faster rate of loss of nitroglycerin from vials stoppered with rubber closures than from nitroglycerin packaged in ampuls. In the same study, insulin loss within 2 days was 80% to PVC (Viaflex) bags, but only 15% to glass bottles. Cossum et al. (1978) showed a flow-rate-dependent loss of nitroglycerin from the plastic infusion set. Nitroglycerin content decreased rapidly within the first hour at all the flow rates used, but with fast flow rates, a subsequent small increase in nitroglycerin content occurred before a steady-state concentration (about 70% of original concentration) was reached. Very little loss was noted when the nitroglycerin solution was delivered from a glass syringe through a short length (80 cm) of polyethylene tubing. Crouthamel et al. (1979) and Boylan et al. (1978) also reported loss of nitroglycerin to PVC bags, intravenous administration sets, and Silastic® tubing.

McNiff et al. (1979) reported a satisfactory stability for at least 70 days of nitroglycerin stored in a glass container. Baaske et al. (1980) reported the sorption of nitroglycerin by intravenous filters, containers, and administration sets and recommended the use of polyolefin bottles. These bottles, like glass, may be employed in the preparation of nitroglycerin admixtures because, unlike polyvinyl chloride bags, they are nonabsorbing.

Jacobi et al. (1982) and Yliruusi et al. (1982), respectively, also demonstrated an absence of sorption of nitroglycerin by catheters and bags fabricated from polyethylene. The loss of nitroglycerin to a volumetric infusion pump was reported by St. Peter and Cochran (1982). Cossum and Roberts (1981) recommended the use of a glass syringe and polyethylene tubing to overcome the loss of nitroglycerin associated with administration sets.

A research effort at Ohio State University by Sokoloski and co-workers was directed at elucidating the sorption mechanisms of nitroglycerin. Sturek et al. (1978) began to describe the sorption of nitroglycerin by rubber closure as a reversible first-order process:

$$\text{Drug in solution} \rightleftharpoons \text{Drug in rubber closure}$$

Mathematical derivation of this process is described by Eqs. (17)–(19), and illustrated in Fig. 9. Then Yuen et al. (1979) studied the sorption of nitroglycerin by PVC strips and found that a linear relationship exists between the amount sorbed and the bulk concentration; they also determinated the half-saturation time to be approximately 200 min. From these results, they concluded that nitroglycerin is primarily *ab*sorbed by polyvinyl chloride

and that *ad*sorption could account for only a very minor quantity of the sorption loss. Finally, Sokoloski et al. (1980) reported rapid sorption of nitroglycerin to polyvinyl chloride tubing. Small segments of the tubing material were dipped into the nitroglycerin solution for brief periods of time and the amount adsorbed was extracted by a short-term ethyl acetate wash. By the adsorption process, the half-life for attaining equilibrium was found to be only 2.8 min. By fitting their data to the Polanyi theory, they concluded that adsorbed molecules formed multilayers, with the greatest density at the surface of the plastic material, decreasing inward.

Sorption of nitroglycerin by plastic material was first analyzed quantitatively by Pikal et al. (1977), who employed the diffusion equation, Eq. 8, to calculate the diffusion coefficient of nitroglycerin into thermoplastic material used in strip packaging for nitroglycerin tablets. Roberts et al. (1980) and Illum and Bundgaard (1982) used the same equation to describe nitroglycerin loss to polyvinyl chloride bags.

With both absorption and adsorption processes thoroughly analyzed, Malick et al. (1981) used a compartmental model similar to that first described by Roberts et al. (1979) and proposed a bi-exponential equation (Eq. 20 and Fig. 10). The disappearance profile of nitroglycerin, which has a high affinity for polyvinyl chloride, was consistent with a model that describes a rapid and significant initial uptake of solute from solution by the container wall, followed by a slower and essentially irreversible loss of solute to the atmosphere. A model depicting the loss of nitroglycerin during infusion therapy was provided by Amann and Baaske (1982).

d. Diazepam

Intravenous administration of diazepam has become one of the mainstays of therapy for convulsions and anxiety and of preoperative and postoperative anesthesia (Greenblatt and Shader, 1974). Lack of therapeutic response and low blood levels following intravenous infusion of diazepam from a glass container through plastic tubing prompted a recovery study. The effluent solution was discovered to have lost as much as 80% of the original concentration after 24 hr of storage, whereas solutions of diazepam kept in glass container for 24 hr retained nearly full potency (Mackichan et al., 1979). The sorption of diazepam was most rapid during the first five hours in polyvinyl chloride bags (Parker et al., 1979) and in plastic (cellulose propionate) burette chambers (Parker and MacCara, 1980). At the end of 24 hr, more than 60% of the diazepam had been lost to the PVC bags (Parker et al., 1979). The solutions that were stored in plastic burette chambers and then administered through plastic sets, lost more than 38% of potency after 4 hr; the loss occurred principally in the plastic chamber (Parker and MacCara, 1980). The results were in good agreement with those of Cloyd

et al. (1980). Mason et al. (1981) studied factors affecting diazepam infusion. They created a nomogram to allow an accurate prediction of sorption loss as a function of flow rate and tubing length. In addition to glass containers, which are generally acceptable, polyolefin (Mason et al., 1981) and polyethylene (Illum and Bundgaard, 1982) were also recommended to overcome the loss of diazepam to the administration set. Cossum and Roberts (1981) recommended the use of glass syringes and polyethylene tubing for infusion.

The kinetic data of sorption (Illum and Bundgaard, 1982) show a nice fit to the diffusion equations (Eqs. 7–10). The fraction of diazepam sorbed from normal saline solution by polyvinyl chloride infusion bags was found to be independent of initial solute concentrations over the range of 5–120 mg/liter. Both findings suggest that absorption, rather than adsorption, is the process primarily responsible for diazepam loss in PVC bags.

5. Drug-Rubber Closure Interactions

Although it is conceivable that sorption of drug to rubber closures could be just as common as sorption of drug to plastic material, only two reports deal with it. Rowles et al. (1971) studied sorption of 5% [^{14}C]thiamine hydrochloride to three different types of rubber closures—butyl, natural, and neoprene rubber. No definitive sorption patterns were observed. The amounts lost by sorption were low (mostly 2.5%). In 1978, Sturek et al. found that the loss of nitroglycerin from a solution packaged in vials stoppered with rubber closures was faster than that from ampuls. The loss of nitroglycerin to rubber closures was described as probably being a reversible first-order process (Eq. 18).

6. Sorption of Antimicrobial Agents by Plastics

a. General

Sorption of antimicrobial agents by plastic material can cause a reduction of preservative efficacy in a sterile product. Concern for adequate preservation is particularly critical for ophthalmic products packaged in plastic squeeze bottles. The introduction of contact lenses has resulted in a greater number of people having to use eye-care products on a daily basis. These contact lens solutions are subjected to severe and repetitive microbial insult during their use. Adequate antimicrobial efficiency in these products is of paramount importance.

Norton et al. (1974) evaluated the antimicrobial efficiency of 34 commercial contact lens solutions of unknown age by challenging them with four types of microorganisms. The results were quite alarming: of 14 solu-

tions used to soak and disinfect lenses, only four were able to inactivate all four test strains within 1 hr, and seven within 4 hr; six solutions permitted the growth of microorganisms after 24 hr of contact. Of the remaining 20 solutions used for cleaning and wetting of lenses, 13 failed to inhibit all four strains after 24 hr of contact. The significance of the failure rate by microbial challenge test for these products can not be overemphasized.

Study of preservative-plastic interactions began in the late 1950's when there was an increase in the use of plastic packaging systems for pharmaceuticals. All the relevant reports on sorption of antimicrobials by plastics are listed in Table XVIII. (Sorption of antimicrobial agents by rubber closures is discussed in Section III.A.7). Since preservatives are rarely used in an intravenous admixture program, sorption of preservatives to infusion bags and tubing has received only limited attention. The reports cited in Table XVIII appear to be concerned primarily with ophthalmic products, except for one that reported the sorption of methyl- and propylparaben by polyvinyl chloride intravenous bag (Gupta et al., 1982). The remaining portions of this section offer the highlights of some important studies and are followed by separate sections that contain detailed discussions of the reports on sorption of benzalkonium chloride and phenylmercuric compounds. In all these sections, the terms preservative and antimicrobial agent are used interchangeably.

In an attempt to delineate the sorption process in plastic syringes, Marcus et al. (1959) studied the interaction of six bacteriostatic agents (parahydroxybenzoic acid, methylparaben, propylparaben, phenol, sorbic acid, and 4-chloro-3-methylphenol) with three types of plastic syringes (polyamide, polyethylene, and polystyrene). Only polyamide (nylon) was found to bind these agents to various degrees, ranging from 47 to 85% after 1 week at 30 °C. Further studies concerning sorbic acid with polyamide attributed the interaction to hydrogen bonding at the amide linkage (Rodell et al., 1964). The rate-determining step in sorption of sorbic acid is a diffusion process in the polyamide matrix (Rodell et al., 1965).

In contrast, interaction by hydrophobic force was emphasized by Kakemi et al. (1971). In their extensive work, the interaction of seven preservatives (methyl-, ethyl-, propyl-, butyl-, and benzylparaben, benzalkonium chloride, and benzethonium chloride) with plastic materials (polycarbonate, polystyrene, two types of polypropylene and polymethacrylate, and three types of polyethylene and polyvinyl chloride) was studied. Sorption was observed to increase from methyl (C_1) to butyl (C_4) paraben in the cases of polypropylene and polyvinyl chloride. Methylparaben exhibited an unusually high amount of sorption by polycarbonate (91 μg/g of plastic) as compared with ethylparaben (0), propylparaben (0.14 μg), and butyl-

TABLE XVIII
Interaction of Antimicrobial Agents with Polymeric Materials Used in the Packaging of Sterile Products

Antimicrobial Agent	Polymeric Material*	Results	Reference
Benzalkonium chloride	PE bottles	6% loss in 4 months at 50 °C	Autian (1968)
	MDPE bottles	$T_{90\%}$ = 15 weeks at 20 °C	McCarthy (1970a)
	HDPE sheet	28.6% loss in 4 days at 40 °C	Kakemi et al. (1971)
	PE bottles, granules	Minimal loss from bottle; adsorption observed with granules	Richardson et al. (1977)
	PP bottles	30% loss in 5 months at 50 °C	Autian (1968)
	PP sheet	9% loss in 4 days at 40 °C	Kakemi et al. (1971)
	PP bottles, granules	Minimal loss from bottle; strong adsorption with granules	Richardson et al. (1977)
	PVC sheet	Equilibrium sorption achieved in 3 days at 50 °C	Guess et al. (1962)
	PVC bottles	No detectable loss in 12 weeks at 20 °C	McCarthy (1970a)
	PVC bottles	60–68% loss in 30 min at 100 °C	Kakemi et al. (1971)
	Nylon sheet	Equilibrium sorption isotherms at 40–70 °C	Powell et al. (1969)
	Polycarbonate sheet	14.7% loss in 4 days at 40 °C	Kakemi et al. (1971)
	Cellulose membrane	4.5–9% adsorption with 10 ml filtrate	Van Ooteghem and Herbots (1968)
	Polyhydroxyethyl methacrylate	Sorption isotherm for C_{10}–C_{16}	Davis (1981)
Benzethonium chloride	HDPE sheet	4.9% loss in 4 days at 40 °C	Kakemi et al. (1971)
	PP sheet	12.6% loss in 4 days at 40 °C	Kakemi et al. (1971)
	PVC bottles	35% loss in 30 min at 100 °C	Kakemi et al. (1971)
Benzoic acid	PE bottles	9% loss in 12 weeks at 25 °C	McCarthy (1970b)
	PVC bottles	No detectable loss in 12 weeks at 25 °C	McCarthy (1970b)
	Nylon	Freundlich isotherm presented	Browne and Steele (1956)

TABLE XVIII (continued)

Antimicrobial Agent	Polymeric Material*	Results	Reference
Benzyl alcohol	PE bottles	88% loss in 4 months at 50 °C	Autian (1968)
	MDPE bottles	$T_{90\%}$ = 3 weeks at 20 °C	McCarthy (1970a)
	PP bottles	30% loss in 4 months at 50 °C	Autian (1968)
	PVC bottles	2% loss in 12 weeks at 20 °C	McCarthy (1970a)
Chlorobutanol	PE strips	Langmuir adsorption, $T_{90\%}$ about 200 hr	Schoenwald and Belcastro (1969)
	PE bottles, granules	Significant loss to sorption	Richardson et al. (1977)
	PE bottles	$T_{90\%}$ = 1 ~ 2 weeks at 45°C	Friesen and Plein (1971)
	PP bottles, granules	Significant loss to sorption	Richardson et al. (1977)
	Nylon 66 strips	Langmuir adsorption, $T_{90\%} \simeq$ 45 hr at 38 °C	Schoenwald and Belcastro (1969)
	Plastic bottles	about 50% loss from ophthalmic solutions.	Blackburn et al. (1978)
Chlorocresol	MDPE bottles	$T_{90\%}$ = 1 week at 20 °C	McCarthy (1970a)
	PE granules	20% loss in 1 month	Sina et al. (1973)
	PE bottles	50% loss in 1 month	Youssef et al. (1973)
	PVC bottles	10% loss in 12 weeks	McCarthy (1970a)
	PVC granules	40% loss in 1 month at 34 °C	Sina et al. (1973)
	Polymethyl methacrylate	Sorption isotherm presented	Nagabhushan et al. (1969)
	Vinyl lining	Significant loss	McLaughlin (1972)
Chlorhexidine diacetate	MDPE bottles	$T_{90\%}$ = 15 weeks at 20 °C	McCarthy (1970a)
	PVC bottles	No detectable loss in 12 weeks at 20 °C	McCarthy (1970a)
Chlorhexidine gluconate	PE bottles, granules	Minimal loss and adsorption	Richardson et al. (1977)
	PE bottle	10% loss in 6 months	McTaggart (1979)
	PP bottle	4% loss in 6 months	McTaggart (1979)
	PP bottles, granules	Minimal loss	Richardson et al. (1977)
	Cellulose membrane	1.1–7.6% adsorption with 10 ml filtrate	Van Ooteghem and Herbots (1968)
Chloroxylenol	PE bottles	No detectable sorption, but permeated through the bottle during autoclaving	Goss et al. (1968)
Methylparaben	PE bottles	20% loss in 4 months at 50 °C	Autian (1968)

TABLE XVIII (continued)

Antimicrobial Agent	Polymeric Material*	Results	Reference
	PE bottles	No detectable loss in 12 weeks at 25 °C	McCarthy (1970b)
	HDPE sheet	0.6% loss in 4 days at 40 °C	Kakemi et al. (1971)
	PE bottles	10% loss in 1 month	Youssef et al. (1973)
	PE granules	30% loss in 1 months at 34 °C	Sina et al. (1973)
	PP bottles	22% loss in 4 months at 50 °C	Autian (1968)
	PP sheet	94% loss in 4 days at 40 °C	Kakemi et al. (1971)
	PVC bags	45% loss in 38 days at 24 °C	Gupta and Stewart (1982)
	PVC bottles	2% loss in 12 weeks at 25 °C	McCarthy (1970b)
	PVC bottles	3–8% loss in 30 min at 100 °C	Kakemi et al. (1971)
	PVC granules	70% loss in 1 month at 34 °C	Sina et al. (1973)
	Nylon syringes	Sorption isotherm presented, 50% sorption in 48 hr at 30 °C	Marcus et al. (1959)
	Nylon 6 membrane	Sorption isotherm presented	Patel and Nagabhushan (1970)
	Polystyrene sheet	No loss in 4 days at 40 °C	Kakemi et al. (1971)
	Polycarbonate sheet	4.8% loss in 4 days at 40 °C	Kakemi et al. (1971)
	Polymethyl methacrylate	Sorption isotherm presented	Nagabhushan et al. (1969)
	Polymethacrylate	1% loss in 4 days at 40 °C	Kakemi et al. (1971)
Propylparaben	PE bottles	77% loss in 4 months at 50 °C	Autian (1968)
	HDPE sheet	1.5% loss in 4 days at 40 °C	Kakemi et al. (1971)
	PP bottles	32% loss in 4 months at 50 °C	Autian (1968)
	PP sheet	2.4% loss in 4 days at 40 °C	Kakemi et al. (1971)
	PVC bags	87% loss in 34 days at 24 °C	Gupta and Stewart (1982)
	PVC bottles	12–15% loss in 30 min at 100 °C	Kakemi et al. (1971)

TABLE XVIII (continued)

Antimicrobial Agent	Polymeric Material*	Results	Reference
	Nylon syringe	Sorption isotherm presented, 15% sorption in 48 hr at 30 °C	Marcus et al. (1959)
	Nylon 6 membrane	Sorption isotherm presented	Patel and Nagabhushan (1970)
	Polycarbonate sheet	1.4% loss in 4 days at 40 °C	Kakemi et al. (1971)
	Polymethyl methacrylate	Sorption isotherm presented	Nagabhushan et al. (1969)
Butylparaben	HDPE sheet	6.6% loss in 4 days at 40 °C	Kakemi et al. (1971)
	PP sheet	2.4% loss in 4 days at 40 °C	Kakemi et al. (1971)
	Polycarbonate sheet	7.8% loss in 4 days at 40 °C	Kakemi et al. (1971)
Phenol	PE granules	2% loss in 1 months at 34 °C	Sina et al. (1973)
	PE bottles	No detectable loss in 12 weeks at 25 °C	McCarthy (1970b)
	PE bottles	70% loss in 4 months at 50 °C	Autian (1968)
	PE bottles	40% loss in 1 month	Youssef et al. (1973)
	PP bottles	19% loss in 4 months at 50 °C	Autian (1968)
Phenol	PVC bottles	No detectable loss in 12 weeks at 25 °C	McCarthy (1970b)
	PVC granules	40% loss in 1 month at 34 °C	Sina et al. (1973)
	Nylon granules	Freundlich isotherm presented	Browne and Steele (1956)
	Nylon syringes	Sorption isotherm presented, 45% sorption in 48 hr at 30 °C	Marcus et al. (1959)
	Polymethyl methacrylate	Sorption isotherm presented	Nagabhushan et al. (1969)
Phenoxyethanol	MDPE bottles	$T_{90\%}$ = 12 weeks at 20 °C	McCarthy (1970a)
	PVC bottles	2% loss in 12 weeks at 20 °C	McCarthy (1970a)
Phenylethanol	PE bottles	75% loss in 1 month at 50 °C	Autian (1968)
	PP bottles	44% loss in 4 months at 50 °C	Autian (1968)

TABLE XVIII (continued)

Antimicrobial Agent	Polymeric Material*	Results	Reference
	Plastic drip with attachment	20–30% sorption in 4 months	Christensen and Dauv (1969)
Phenylmercuric acetate	PE bottles	34% loss in 12 weeks at 25 °C	Lachman et al. (1964)
	LDPE bottles	60% loss in 100 days	Aspinall et al. (1980)
Phenylmercuric borate	PVC bags	12.5% loss in 10 weeks at 20 °C	Van Houta and Leupin (1969)
	Nylon	18% in 10 weeks at 50 °C	Von Houta and Leupin (1969)
	Cellulose membrane filter	5.2–16% adsorption with 10-ml filtrate	Van Ooteghem and Herbots (1968)
Phenylmercuric nitrate	PE bottles	2% loss in 12 weeks at 25 °C	McCarthy (1970b)
	PE bottles	20% loss in 1 month	Youssef et al. (1973)
	PE granules	38% loss in 1 month at 34 °C	Sina et al. (1973)
	PVC bottles	No detectable loss in 12 weeks at 25 °C	McCarthy (1970b)
	PVC granules	88% loss in 1 month at 34 °C	Sina et al. (1973)
	Nylon tip	Significant sorption	Christensen and Dauv (1969)
Phenylmercuric compounds (acetate, borate, nitrate)	PE bottles	8–79% labeled amount loss	Eriksson (1967)
	LDPE	10–20% loss in 3 months at 22 °C	Fischer and Neuwald (1971)
	HDPE bottles	3–6% loss in 3 months at 22 °C	Fischer and Neuwald (1971)
	PP bottles	5% loss in 3 months at 22 °C	Fischer and Neuwald (1971)
	PVC bottles	2% loss in 3 months at 22 °C	Fischer and Neuwald (1971)
	Nylon	2% loss in 3 months at 22 °C	Fischer and Neuwald (1971)
Sorbic acid	MDPE bottles	$T_{90\%}$ = 14 weeks at 20 °C	McCarthy (1970a)
	Nylon syringes	Sorption isotherm presented, 27% sorption in 48 hr at 30 °C	Marcus et al. (1959)
	Nylon sheet	Sorption mechanism delineated	Rodell et al. (1964)
	Cellulose acetate	Sorption of 40 mg/g in 10 days	Saski (1963)

TABLE XVIII (continued)

Antimicrobial Agent	Polymeric Material*	Results	Reference
	Cellulose triacetate	Sorption of 15 mg/g in 10 days	Saski (1963)
	Polymethyl methacrylate	Sorption isotherm presented	Nagabhushan et al. (1969)
Thimerosal	PE bottles, granules	Some loss to sorption	Richardson et al. (1977)
	PE bottles	10% loss in 6 months	McTaggart (1979)
	PP bottles	4% loss in 6 months	McTaggart (1979)
	PP bottles, granules	Some loss to sorption	Richardson et al. (1977)

* Abbreviations: HD = high density; LD = low density; MD = medium density; PE = polyethylene; PP = polypropylene; PVC = polyvinyl chloride. $T_{90\%}$ is the time predicted for 10% loss of sorbate from solution.

paraben (1.37 μg). This trend suggested that a mechanism of interaction other than hydrophobic binding might be operative.

McCarthy (1970a) investigated the interaction of the preservatives benzyl alcohol, chlorocresol, phenoxyethanol, chlorhexidine diacetate, propylene phenoxyethanol, chlorophenoxyethanol, and benzalkonium chloride with containers fabricated from polyethylene, polyvinyl chloride, and glass. Polyethylene containers seemed to be unsuitable for aromatic alcohol and phenolic preservatives, particularly chlorocresol. In an extension of the same study with ten additional antimicrobial agents, McCarthy (1970b) reported that polyethylene was unsatisfactory for use with substituted phenols and phenylmercuric nitrate. In a study by Fisher and Neuwald (1971), sorption of phenylmercuric salts, thimerosal, and three other organic mercurial preservatives was evaluated with three types of polyethylene, polypropylene, two types of polyvinyl chloride, and polyamide. Small losses (<10%) of preservative occurred after heat sterilization, whereas considerable loss (20–40%) was detected after storage for 3 months.

Solubilization with a nonionic surfactant, such as 2% polyoxyethylene sorbitan monooleate, was able to reduce sorption of antimicrobial agents; however, depletion of free preservative from the aqueous phase by micelle formation rendered the solution inadequately preserved (McCarthy, 1972).

As a sequel to the report on contact lens solutions discussed earlier (Norton et al., 1974), workers at the University of Bath studied the mechanisms of interaction between chlorhexidine gluconate, thimerosal, benzalkonium chloride, and chlorobutanol with polypropylene and polyethylene (Richardson et al., 1979). The results indicated that chlorhexidine gluconate

and benzalkonium chloride showed an initial loss from solution, but no further decrease thereafter. This observation suggested that these preservatives interact with the container material by surface adsorption only. Their loss from solution reached equilibrium when binding sites on the surface were occupied. Therefore, it is unlikely that the concentration of benzalkonium chloride and chlorhexidine gluconate would be reduced to an extent that impaired antimicrobial potency of the product. On the other hand, thimerosal and chlorobutanol showed a continuous loss from solution, suggesting the absorption of antimicrobial agents into the polymer. It is possible that both thimerosal and chlorobutanol may be removed from solution by plastic containers to an extent that would markedly reduce their antimicrobial efficiency. This fact is of particular importance for contact lens solutions, which often contain a much lower concentration of preservative than other ophthalmic preparations in order to reduce their propensity for causing eye irritation; thus, any reduction in the preservative concentration might have a profound effect on the power of the products to prevent "in use" contamination.

Several reviews have discussed the interaction of preservatives and plastics (Armstrong, 1974; Coates, 1973; McTaggart, 1980; Polack, 1967a). Of these, Armstrong (1974) discussed the uptake of preservatives according to the type of polymers involved. None of these reviews has made an in-depth comparison of the available data, or provided a thorough discussion of each type of preservative.

b. Benzalkonium chloride

Benzalkonium chloride is the preservative most frequently used for ophthalmic products. It is a mixture of alkyldimethylbenzylammonium chlorides, in which the alkyls ranges from C_8H_{17} to $C_{18}H_{37}$. A concentration of 0.02% (w/v) is rapidly germicidal against many pathogenic, nonsporulating bacteria and fungi. Its activity may be reduced in the presence of certain metallic ions, but potentiated in the presence of a chelating agent like disodium edetate.

Large quantities of benzalkonium chloride were removed by polyvinyl chloride sheet when 20 g of the plastic were soaked in 150 ml of solution (Guess et al., 1962). Although the absolute amount of sorption increased at higher concentrations, there was, in fact, less sorption expressed in percent uptake, e.g., after 5 days at 50 °C, a 50% uptake from a 0.064% solution and only a 14% uptake from a 0.32% solution. Because benzalkonium chloride is often used as a dilute solution, such as the disinfectant solution used in the sterile room, a substantial amount of benzalkonium chloride could be removed from a solution in contact with PVC material, thereby reducing its effective bactericidal or bacteriostatic activity. The effect of

pH on sorption of benzalkonium chloride by polyvinyl chloride is complex, but sorption was minimal in the range of pH 3–5. Uptake by polyvinyl chloride was reportedly reduced in a solution containing 10–25% of alcoholic solvents (such as ethanol, propylene glycol, glycerol or polyethylene glycol 400) (Guess et al., 1962). Sorption equilibrium was generally achieved in 120 hr or longer. Because surface adsorption is a rapid process, and in view of the large quantity of the agent taken up (about 4 mg/g of plastic), the authors concluded that both absorption and surface adsorption, were occurring, implying penetration of the plastic material. They further surmised that since there was no potential mechanism of interaction between the nonpolar polyvinyl chloride and the polar benzalkonium chloride, the preservative must have been interacting with one or more of the additives in polyvinyl chloride. Contradictory results were reported by McCarthy (1970a), who studied the sorption of benzalkonium chloride (at 0.1% and 1%) in a rigid polyvinyl chloride container up to 12 weeks at 20 °C and found no detectable loss. The disparity of results in these two investigations (Guess et al., 1962; McCarthy, 1970a) could easily be attributed to variation in composition of plastic, since polyvinyl chloride generally contains up to 40% plasticizer. Kakemi et al. (1971) reported an uptake of benzalkonium chloride by polyvinyl chloride bottles and bags during a 30-min heat sterilization process (100 °C) that ranged from 0.046 to 0.108 mg/g of plastic. This quantity certainly reflects only adsorption.

A unique property of benzalkonium chloride that is not shared by other preservatives is its surface activity. Its critical micelle concentration is approximately 80 mg/100 ml. Maximal sorption to polyamide was observed in the region of critical micelle concentration. It was proposed that the hydrophobic moiety of the benzalkonium cation interacted with nonspecific sites along the hydrocarbon section of the polyamide (Powell et al., 1969).

Sorption to polyethylene and polypropylene was examined by several investigators (Kakemi et al., 1971; Autian, 1968, Richardson et al., 1977, 1979; McCarthy, 1970a). Benzalkonium chloride is believed to interact with plastic by a surface adsorption process that is most prominent with cationic agents (Richardson et al., 1977). This interaction is reflected in the large loss (70–80%) of benzalkonium chloride from a simple aqueous solution in contact with polypropylene powder, which has a large surface area, compared with that of polyethylene granules, where only about 30% of the agent was removed (Richardson et al., 1977, 1979).

With polypropylene bottles, Autian (1968) reported 30% sorption when a 0.01% solution of benzalkonium chloride was stored at 50 °C for 5 months. Less sorption to polyethylene bottles was observed by Autian (1968) and by McCarthy (1970b). Conversely, more sorption by polyethylene than by

polypropylene was reported by Kakemi et al. (1971). During 30 min of a heat sterilization process at 100 °C, 0.013 mg/g of benzalkonium chloride was adsorbed by high-density polyethylene compared with only 0.003 mg/g adsorbed by polypropylene. There was also more loss in polyethylene bottles than in polypropylene bottles during a 4-day storage at 40 °C.

The effect of the alkyl chain length of benzalkonium chloride on sorption behavior was illustrated by Davis and Watson (1981), who studied the sorption of benzalkonium chloride with an alkyl chain length ranging from C_{10} to C_{16} to polyhydroxyethyl methacrylate, a polymeric material for soft contact lenses. As much as a sixfold increase in the amount of sorption occurred as the alkyl chain length increased.

The effects of counter-ions on sorption were also evaluated (Kakemi et al., 1977). Adsorption of benzalkonium cation was greatly enhanced in the presence of ammonium thiocyanate.

c. Phenylmercuric compounds

Most ophthalmic products and one injectable product (Estradurin) in the United States are known to contain phenylmercuric compounds as preservatives. All three salts, acetate, borate, and nitrate, have been studied. These salts differ chiefly in solubility, the nitrate being relatively insoluble, whereas the acetate and borate are more soluble. The presence of excessive chloride will cause precipitation of phenylmercuric chloride. According to the British Pharmacopoeia, phenylmercuric nitrate is bacteriostatic at a concentration of 0.001% and bactericidal at 0.002%.

Lachman (1964) reported sorption of phenylmercuric acetate by polyethylene containers. The loss through sorption in 12 weeks was as much as 33.7% at 25 °C and to 70% at 40 °C. Eriksson (1967) examined the mercurial content of 20 eyedrop preparations and nasal sprays packaged as aqueous solution in polyethylene containers after storage ranging from 4 to 24 months. All but one contained less than 80% of the label amount. The extent of loss was time dependent.

Von Houta and Leupin (1969) stored 0.1% phenylmercuric borate solution in different plastic containers for 10 weeks at 20 °C. No sorption was found with high- and low-density polyethylene, polypropylene, or hard polyvinyl chloride, but a 12.5% loss occurred with soft polyvinyl chloride. Christensen and Dauv (1969) determined the content of phenylmercuric nitrate in eyedrops stored in three types of glass bottles with a plastic drip attachment. When the packages were kept in an inverted position, so that the product was in contact with the plastic drip attachment, loss of phenylmercuric nitrate was total in two types and only 50% on the third. Rubber bulb, nylon tip, and polyamide screw cap were all considered responsible for removal of phenylmercuric nitrate from the solution.

Most sorption studies have been conducted with a simple preservative

solution not containing either an active component or other excipients, presumably because most researchers were not able to assay the preservative in the presence of interfering substances. Aspinall et al. (1980) overcame this difficulty by employing ^{203}Hg-phenylmercuric acetate for a sorption study of phenylmercuric acetate in the presence of lachesine chloride, atropine sulfate, and chloramphenicol. When these ophthalmic preparations were stored in a polyethylene container at ambient temperature for 100 days, reductions in preservative content ranged from 40 to 90%. Unlike other investigators who assayed the content of phenylmercuric salts in aqueous solution, Aspinall used the radiochemical tracer to observe the distribution of mercury throughout the package. In the presence of lachesine, a significantly lesser amount of mercury was retained by the polyethylene bottles below the meniscus, as compared with that from bottles with phenylmercuric acetate alone. They also found that 20% of the total radioactivity was completely lost from the system. Since phenylmercuric acetate melts at about 180 °C, it is unlikely that it could vaporize from the bottle surface. However, the phenylmercuric compound is known to degrade to mercuric ions and metallic mercury on standing; perhaps, vaporization of metallic mercury contributed to the loss of phenylmercuric compound to the atmosphere.

It is generally futile to try to reproduce sorption data generated by another laboratory, or to compare one's own data with them. The plastic material marketed by a different manufacturer, although of identical generic name, could, and generally does, behave quite differently. Additives in the plastic material play a major role in sorption phenomena, yet one rarely finds a report providing quantitative information on the additives. A step in the right direction was taken by Fisher and Neuwald (1971), who showed the composition and physical properties of a variety of plastic containers used in their study. Three phenylmercuric salts, studied side by side, behaved similarly. During the heat sterilization, an unusually high sorption rate (22% loss) occurred in a polyvinyl chloride container. This loss was attributed to the interaction of the preservatives with the stabilizer in the plastic material, di-n-octyl tin. Three months' storage of phenylmercuric salts resulted in a significant loss in two of the three polyethylene bottles studied and in minimal loss in an additive-free polyamide bottle.

7. Sorption Of Antimicrobial Agents By Rubber Closures

a. General

Rubber closures are used extensively to seal a variety of injectable solutions in vials, disposable syringes, or IV administration sets. Ophthalmic

products often use rubber bulbs. Loss of preservatives by sorption could be detrimental to product integrity, especially in a multi-dose injection vial.

Preservative is an essential component in a multi-dose injection product and its loss could result in microbial contamination. It has long been known that injectable solutions in rubber-closed containers lose substantial quantities of their bacteriostatic phenolic preservative. As early as 1923, Masucci and Moffat (1923) reported the loss of 50–70% of cresol and 20–40% of phenol from solutions stored in rubber-capped vials for 18 months at room temperature.

Absorption of preservatives by rubber closures was first studied systematically by Wing (1955, 1956a,b), then by Royce and Sykes (1957). The primary mechanism of absorption is interfacial partitioning of preservatives between rubber closure and injection vehicle. Because one of the phases is a pseudosolid, the time to reach equilibrium is long and is dependent on the rate of diffusion of the substance moving into the rubber. In the case of phenol and rubber (Wing, 1955), equilibrium was reached in 6 weeks at 2 °C and in 3 days at 37 °C. Royce and Sykes (1957) studied uptake of phenolic compounds by rubber and found that pseudoequilibra were reached after four successive heat treatments at 100 °C for 30 min each. Upon further treatment for a prolonged period of time, more absorption occurred. Two explanations were offered: (*1*) the bacteriostat was absorbed onto the surface layers of rubber and gave an impression of rapid saturation during initial treatment, but it subsequently diffused into deeper layers, thus freeing the surface layers to absorb more; and (*2*) preservatives were lost to the atmosphere by the normal process of volatilization. These views were supported by the data of Yanchick and Sperandio (1969) showing that absorption was rapid at the beginning and continued for as long as 8 weeks. By use of an air-scrubbing tower technique, Rowles et al. (1971) confirmed that preservatives were lost through rubber closures by volatilization.

The amount of preservative taken up by rubber closures was proportional to the partition coefficient [See Section III.A.3.b]. In general, compounds with a high oil/water partition coefficient showed greater loss than did compounds with a low partition coefficient. Table XIX summarizes the partition coefficients for various preservatives from several studies. It is apparent that benzyl alcohol has the lowest partition coefficient and is, therefore, the preservative least susceptible to uptake by rubber closures.

Rubber closures are available in a wide variety of compositions. For gross comparisons, one may assume the tendency for sorption to be, in descending order, neoprene, natural rubber, butyl rubber, and silicone rubber.

TABLE XIX
Partition Coefficients (Closures/Water) of Preservatives Between Rubber Closures and Aqueous Injections

	Natural Rubber	Silicone Rubber	Neoprene
Benzyl alcohol	0.53[a], 0.63[b]	—	1.66[e]
Phenol	1[a], 1.87[b]	0.31[b]	—
Cresol	1.5[a]	—	—
Phenylethanol	1.72[e]	—	4.23[e]
Methylparaben	1.36[e], 0.33[f], 1.932[g]	0.311[g]	7.27[e]
Propylparaben	1.4–20[f]	—	—
Chlorobutanol	12–27[a], 9.8[e]	—	14.5[e]
Chlorocresol	17[a], 24[b]	6.4[c]	—
Dichlorobenzyl alcohol	27[f]	—	—
Phenylmercuric chloride	57[a]	—	—
Chinosol	37–72[d]	11.5[d]	—

[a] Royce and Sykes, 1957; 25 °C. [b] Wing, 1955; 37 °C. [c] Wing, 1965a,b; 37 °C. [d] Landi and Held, 1965; 25 °C. [e] Lachman et al., 1963b; 25 °C. [f] Sykes, 1958. [g] Anderson and Motzi, 1982.

Lachman et al. (1963a,b) reported that among butyl, neoprene, and natural rubber closures, butyl rubber exhibits the least sorbing tendencies toward benzyl alcohol and methylparaben, whereas sorption of methylparaben by neoprene rubber is greater than by natural rubber, and the extent of sorption of benzyl alcohol is equal for neoprene and natural rubber. In solutions of ^{14}C-labeled benzyl alcohol and phenol, butyl rubber closures sorbed a substantially smaller amount of preservatives than did natural or neoprene rubber (Rowles et al., 1971). The low sorption and inert nature of silicone rubber are illustrated by the results of a chinosol sorption study; after a 2-day exposure of chinosol solution to various rubber closures, the solution in contact with silicone rubber retained 53% potency, whereas all others retained 3–4% potency or none at all (Landi and Held, 1965). Wing (1956) also showed that the oil/water partition coefficient of chlorocresol is 6.4 for silicone rubber, but ranges from 14 to 40 for all other rubber stoppers.

Factors affecting sorption of preservatives by rubber closures may be summarized as follows:

1) Temperature: An increase in temperature can decrease the partition coefficient and increase the sorption rate (Wing, 1955). Since it takes a long time to reach equilibrium, loss of preservative at a higher temperature may be faster and greater.
2) Concentration: An increase of preservative concentration can reduce the partition coefficient, presumably because of a limited number of

adsorption sites available in the rubber closures. Nevertheless, uptake is greater from solutions of higher concentration, e.g., 5.8, 11.1, 21.3, and 40.4 mg of phenol were absorbed by each gram of rubber closure after its exposure to 0.5, 1, 2, and 4% concentrations of phenol solution (Wing, 1955).

3) Position: Lachman (1963b) reported that the amount of benzyl alcohol and methylparaben lost from solutions was not significantly influenced by whether the vials were stored upright or inverted. Yanchick and Sperandio (1969), however, reported slightly greater absorption in inverted vials than in upright ones, with the disparity greater at higher temperatures.

4) Rubber composition: The effect of chemical composition of the rubber mix on sorptions was studied by Wiener (1955) on thimerosal, by Wing (1955) on phenol and chlorocresol, and by Landi and Held (1965) on chinosol. Only a limited, generalized conclusion can be drawn from these studies: the amount of zinc oxide or sulfur contained in rubber has only a minor effect on absorption of preservatives.

Many methods have been proposed to curtail sorption of preservatives. Although an obvious approach is to seal the rubber surface with a thin coating, this method has not been very successful because of other complicating factors, such as resistance of the seal to needle puncture, the possibility of needle blockage, and the shedding of particles by needle puncture. Royce and Sykes (1957) found that paraffin, paint, and sputtered metal were unsatisfactory as coating materials. A Teflon® lining on polyurethane or natural rubber was reported to be effective in retarding sorption of *p*-chlorophenylethyl alcohol (Lachman et al., 1966). Kinetic data were presented by a vendor to promote the advantage of Teflon lining on natural rubber in reducing sorption of benzyl alcohol, methylparaben, phenol, and chlorobutanol (Adams, 1978). On the other hand, an epoxy lining on neoprene or natural rubber was found to be ineffective (Lachman et al., 1964).

Despite criticism by Royce and Sykes (1957), the British Pharmaceutical Codex (1953–1973) specifies that before use, rubber closures should be autoclaved for at least 30 min in an aqueous solution of a bacteriostat, followed by soaking in the same solution of the bacteriostat for at least 7 days. This treatment is designed to pre-equilibrate the closure/preservation sorption process.

b. Benzyl alcohol

Benzyl alcohol, at a concentration of 0.5–2%, is commonly used as a preservative in parenteral products. It has rapid bactericidal action against several microorganisms at concentrations of 1–3%. Lachman et al. (1962)

TABLE XX
Comparative Sorption Rates of Benzyl Alcohol

Closures	$T_{90\%}$ [a] (in days)	Conditions	Reference
Rubber	30	2-ml cartridge, at 25 °C	Royce & Sykes (1957)
Butyl	30	2.5-Gm rubber cubes in 10-ml solution, room temperature	Lachman et al. (1963b)
Butadiene-acrylonitrile	5	Ibid	Ibid
Natural Rubber	55	Rubber closure, 10-ml solution, room temperature	Lachman et al. (1963b)
Natural Rubber	70	20 mm closure, 5-ml solution, 10 °C	Yanchick and Sperandio (1969)
	14	Ibid 25 °C	
	7	Ibid 45 °C	
	5	Ibid 60 °C	
Neoprene rubber	35	20 mm closure 5 ml solution, 10 °C	Yanchick and Sperandio (1969)
	14	Ibid 20 °C	
	7	Ibid 45 °C	
	3	Ibid 60 °C	
Natural rubber (Company A)	30	25 °C, 50-mm closure, 5-ml solution	Rowles et al. (1971)
	10	Ibid with thiamine	
	30	Ibid with phenol	
	30	Ibid with 0.9% NaCl	
Natural rubber (Company B)	20	25 °C, 20-mm closure, 5 ml-soln	Rowles et al. (1971)
	5	Ibid with thiamine	
	20	Ibid with phenol	
	10	Ibid with 0.9% NaCl	

[a] $T_{90\%}$ is the time predicted for 10% loss of benzyl alcohol from the solution.

determined that the lowest concentrations of benzyl alcohol required to destroy *Staphylococcus aureus* and *Escherichia coli* in 15 min or less are 0.9% and 0.8%, respectively. As described in Section III.A.7.b, benzyl alcohol

is the preservative with the least potential for sorption by rubber closures because of its low partition coefficient (see Table XIX).

Sorption rates of benzyl alcohol are compiled in Table XX. The varied conditions employed make comparison of results difficult. Workers from Purdue University (Yanchick and Sperandio 1969; Rowles et al., 1971) provided the most in-depth analysis of the sorption of benzyl alcohol. They concluded that: *1*) butyl rubber closures are superior to natural or neoprene rubber closures in lack of sorption; in most cases, total loss was less than 10% throughout the studies; *2*) rate of sorption was directly affected by temperature and the position in which the rubber closure-stoppered vials were stored; *3*) natural rubber accounted for the greatest loss of benzyl alcohol as the temperature increased. Whereas butyl rubber was least affected by temperature; and *4*) repeated puncturing of the closure did not cause any significant variation in sorption rate.

c. Phenol

Sorption of phenol had been noted briefly as early as 1937 by McGuire and Falk, and in 1953 by Burrell. Using rubber tubing to simulate the closure, Wing (1955) determined the amount of sorption as a function of phenol concentration. He found that sorption is a reversible process and proceeds to a state of equilibrium, no matter whether rubber is removing phenol from a phenol solution or releasing phenol to water. The partition coefficients were determined for closures with a variety of compositions (Wing, 1955). The results did not show any consistent agreement between phenol absorption and content of rubber in the rubber mix. The physical state of the rubber mix might account for differences in phenol absorption among the various samples.

Using [^{14}C]phenol, Rowles et al. (1971) studied the rate at which it was sorbed by butyl, natural and neoprene closures made by three companies. Approximately 1–4% was lost to butyl rubber and 20–25% to neoprene or natural rubber after 3 months' storage at 25 °C. Royce and Sykes (1957) studied the effect of treating rubber closures with bacteriostatic solutions and of sealing the closures with paraffin wax. Metal overseals were found to cause some reduction in loss of phenol, but the results were variable and seemed to depend on the rimming procedure. Paraffin coating was successful, but tended to cause needle blockage.

d. Chlorobutanol

Sorption of chlorobutanol was discussed at great length by Lachman et al. (1962). In 10-ml vials of 0.5% cholorobutanol solution, approximately 20–50% of chlorobutanol was lost in a 12-week period at 40 °C. Most of the loss occurred during the first 2 weeks of storage. This phenomenom can be ascribed to the development of an apparent equilibrium state between the

concentration in solution and that in the rubber closure. Among the three kinds of rubber closures tested, neoprene rubber caused greatest loss, natural, and butyl rubber closures exhibited lesser degrees of sorption.

e. Parabens

Lachman et al. (1963b) reported loss of methylparaben from a 10-ml vial of 0.2% solution; after 12 weeks of storage at 60 °C, the loss was 0, 5% and 11% for butyl, natural rubber, and neoprene, respectively.

f. Mercuric compounds

Using turbidity measurements in serially diluted serum broth, Wiener (1955) studied the bacteriostatic action of thimerosal in the presence of a variety of rubber pieces. A red rubber closure reduced the activity of thimerosal by a factor of 50. Birner and Garnet (1964) determined the loss of thimerosal in vaccines stored in bottles stoppered with rubber closures. In 1-ml vials after 6 months' storage at 6 °C, more than 70% of the 100 ppm thimerosal solution had been taken up by rubber closures, whereas in 5-ml or 10-ml vials only about 5% had been taken up.

Phenylmercuric compounds, nitrate, acetate, or chloride, exhibit high oil/water partition coefficients. Predictably, a significant uptake by rubber closures can occur, i.e., more than 80% uptake occurs within 3 days, as analyzed by microbiological assay (Royce and Sykes, 1957). Using a radiochemical method, Ingversen and Anderson (1968) demonstrated a significant sorption of ^{203}Hg-phenylmercuric acetate by rubber closures as well as onto glass surfaces. A significant loss of thimerosal occurred from ophthalmic solutions in contact with a rubber-tipped eye dropper (Tsuji et al., 1964). After storage at 37 °C for 30 days, less than 10% of the original thimerosal concentration was retained in the bulk ophthalmic solution.

8. Adsorption onto Glass Surfaces

a. General

Glass is considered the most inert primary packaging material for pharmaceutical products. Because of its impervious nature, surface adsorption is the only plausible mechanism for interaction. In general, surface adsorption reaches equilibrium rapidly and the glass surface removes only a limited amount of adsorbate. Historically, glass adsorption has not been of concern to hospital pharmacists or pharmaceutical scientists in the manufacturing area, except in the case of insulin. Among recent trends that warrant a closer look at the problem of glass adsorption is the increasing use of intravenous infusion for administration of drugs, i.e., drugs are often diluted in a large glass infusion bottle. The decrease in concentration and the increase in glass surface both enhance the degree of adsorption that can occur. Second trend is the increasing purity of biochemical substances,

exemplified by high-titer, pure monoclonal antibodies that can now be given in a very low dose that still possesses the desired therapeutic activities. Adsorption problems are more readily encountered in the low-dose products. The literature on glass adsorption is scanty. For purposes of discussion, we have divided the literature into biologicals, such as insulin and other protein substances, and non-biologicals, such as alkaloids and synthetic chemicals.

b. Biological compounds

Insulin is the most widely studied drug substance with respect to glass surface adsorption. Adsorption of ^{131}I-insulin from dilute solutions to laboratory glassware was first reported in 1951 (Ferrebee et al., 1951). This observation was confirmed with noniodinated insulin (Hill, 1959a,b; Wiseman and Baltz, 1961), a large proportion of which was also found to be adsorbed to glass. The adsorption was, however, shown to be reversible (Hill, 1959a,b). Because of evidence that insulin binds to paper, polyethylene, polyvinyl chloride, and siliconized Pyrex glassware, its adsorption is considered to be a nonspecific surface phenomenon (Weisenfeld et al. 1968).

According to Petty and Cunningham (1974), adsorption of insulin to glass surfaces was rapid, equilibrium was attained in 15 sec. On the other hand, Weisenfeld et al. (1968) demonstrated a gradual increase in the amount of adsorption over a 2-hr period (Fig. 19).

Several studies have examined the percent recovery of insulin passed through a simulated infusion system consisting of a glass bottle and plastic tubing (Weisenfeld et al., 1968; Petty and Cunningham, 1974; Weber et al., 1977; Okamoto et al., 1979). The specific amount of insulin removed by the glass surface in the presence of other excipients is summarized in Table XXI. The data indicate that glucose appears to reduce the extent of insulin adsorption to glass, although increased adsorption were reported by Okamoto (1979). However, in a recent comprehensive study, Mitrano and Newton (1982) found that adsorption of insulin to glass was greater in glucose solution than in normal saline (Fig. 20). The authors attributed this disparity to the difference in pH of the two intravenous infusion solutions. In glucose solution (pH 4.3), insulin exists predominantly as a cationic species that can be strongly attracted to the anionic glass surface. In normal saline (pH 6.0), insulin is much less cationic, since the isoelectric point for insulin is between 5.3 and 5.5. They also demonstrated that, in glucose solution, progressively increasing the concentration of potassium chloride caused a significant nonlinear decrease in percent of insulin adhering to the glass, whereas the magnitude of this effect in normal saline was not sizeable (Fig. 21). The effect of potassium chloride on insulin adsorption

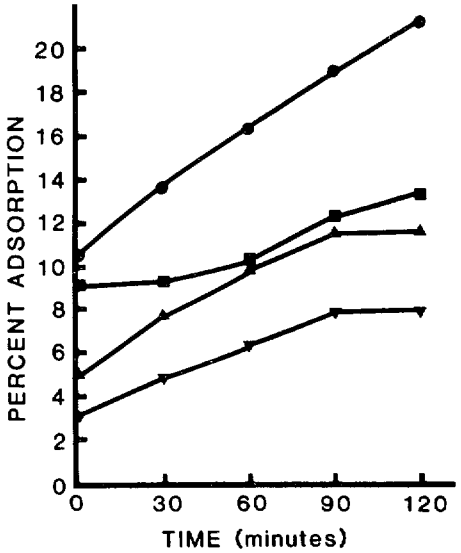


Figure 19—Effect of insulin concentration on adsorption by glass bottles. Key: (concentration in units per 500 ml)—circles, 5; squares, 10; triangles, 20; inverted triangles, 40 [Source: Weisenfeld et al., 1968].

was explained on the basis of changes in ionic strength: at a high concentration of potassium chloride, the great ionic strength produced shielding between the negatively charged anionic glass surface and the positively charged insulin molecules, thus reducing the electrostatic attraction.

TABLE XXI
Comparison of Literature Values of Insulin Recovered from Solutions Stored in Glass Bottles

Concentration (Units/500 ml)	Recovery of Insulin (in %)			
	Okamoto	Weisenfeld	Petty	Mitrano
5	62[a]	21[b]	—	—
10[e]	—	13.3[b]	—	30[a], 8[b]
15	—	—	55[c], 35[d]	—
20	40[a], 32[b]	11.5[b]	—	—
25	—	—	—	45[a], 14[b]
40	18[a]	8[b]	—	—

[a] In 5% glucose; [b] in saline; [c] in lactated Ringer's solution; [d] in lactated Ringer's and 5% dextrose solutions; [e] 10 units/500 ml (equals 0.8 μg/ml).

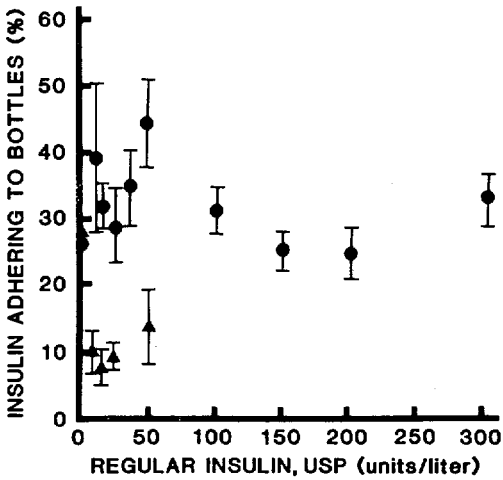


Figure 20—Relationship between concentration of regular insulin and fraction of insulin adhering to 200 ml bottles (211 cm^2 surface) from 50 ml admixtures in 5% dextrose (circles) and 0.9% sodium chloride (triangles) injections containing 0.2 μl ^{125}I-insulin/ml [Source: Mitrano and Newton, 1982].

As discussed earlier in the section on "Drug-Plastic Interactions," (Section III.A.4.b) the adsorption of insulin to a glass surface can be in-

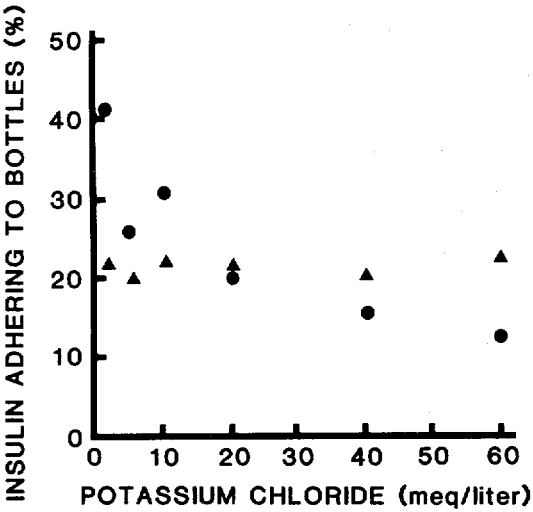


Figure 21—The effect of potassium chloride on adsorption of ^{125}I-insulin to glass bottles, from 5% dextrose injection (circles) and from 0.9% sodium chloride injection (triangles) [Source: Mitrano and Newton, 1982].

hibited by 5% gelatin (Hill, 1959a,b), human serum albumin (Wiseman and Baltz 1961; Petty and Cunningham, 1974), plasmanate (Petty and Cunningham, 1974), casein hydrolysate (Weber et al., 1977) and 3.5% polygeline (Kraegen et al., 1975).

When the adsorption of bovine serum albumin on pulverized Pyrex glass was analyzed for the effects of pH and protein concentration (Bull, 1956), adsorption was faster at low pH. Volumetric glassware with a surface of less than 1 cm^2 per ml could adsorb no more than 1% of ^{131}I-albumin at 10 $\mu g/ml$ and no more than 5% at 1 $\mu g/ml$ (Reeve and Frank, 1956). Anik et al. (1982) reported adsorption of D-Nal(2)^6 leuteinizing hormone releasing hormone, a decapeptide, onto glass surfaces. Tunbridge et al., (1981) found evidence that heparin was probably adsorbed on glass.

Using porous glass beads (100-μ beads with a controlled pore diameter at 240 Å and a surface area of 97 m^2/g), Mizutani studied the adsorption of bovine serum albumin, lysozyme, chymotrypsin, peroxidase, phosphatase, catalase, insulin, globulin and hemoglobulin (Mizutani and Mizutani, 1978; Mizutani 1980a,b, 1981). The amount of insulin adsorbed to 1 g of porous glass beads ranged from 5.5 to 5.9 mg; thus, 0.3 μg (ca. 0.01 unit) of insulin might be adsorbed on 51 cm^2 of the surface of a 20-ml glass vial. The major force for adsorption of proteins onto a glass surface may be ionic bonding between amines in the protein molecules and terminal silanol groups on the glass surfaces (Mizutani and Mizutani, 1978). Intermolecular hydrogen bonding may also contribute to the attraction between protein and glass. Studying the interaction of the same group of compounds with silicone-coated glass, Mizutani (1981) hypothesized that adsorption to silicone-coated glass is a hydrophobic interaction because it was independent of pH, it was greater for compounds with more aliphatic content, and detergent was required to elute the adsorbate from the glass column. Adsorption of secretin (Ogino et al., 1979) and of albumin (Brash and Uniyal, 1979) to silicone-coated glass has also been reported.

Silicone coating of glass surfaces is often used to prevent the adsorption of hydrophilic substances such as protein, peptides, and water-soluble drugs, despite the fact that no report substantiates the inability of such coated surfaces to adsorb material. In fact, secretin was shown to be adsorbed preferentially onto silicone-coated glass beads, as compared with noncoated beads (Ogino et al., 1979). Figure 22 illustrates that the amount of secretin adsorbed onto 5 mg of coated beads was approximately equal to the amount adsorbed onto 100 mg of noncoated beads. The addition of albumin, however, effectively inhibited adsorption, as evidenced by complete recovery of secretin activity.

Protein in the adsorbed state must be denatured, at least in part. For horseradish perioxidase, phosphatase, and catalase, 97, 88, and 63% of the

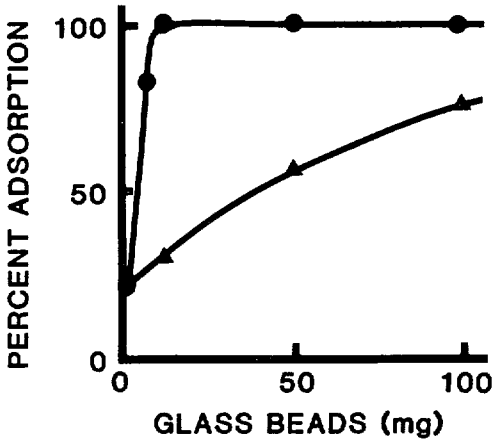


Figure 22—Adsorption of secretin on noncoated (triangles) and silicone-coated (circles) glass beads [Source: Ogino et al., 1979].

activity was recovered after adsorption onto a controlled-pore glass surfaces for 1 week. Insulin, however, was not inactivated by adsorption for 3 months (Mizutani, 1980a).

c. Non-biological compounds

Mizutani and Mizutani (1978) also investigated the adsorption of non-biological compounds. The amounts adsorbed on 1 g of controlled-pore-size glass are shown in Table XXII. The adsorption of such basic drugs as epi-

TABLE XXII

Adsorption of Biological and Nonbiological Drugs to Glass Surfaces[a]

	Amount of Drug (mg) and Vehicle			
Drug	Water	Tris(hydroxymethyl)-aminomethane hydrochloride	Saline	Glycerin, isotonic solution
Epinephrine	2.00	0.03	0.03	—
Atropine sulfate	1.70	0.70	0.05	—
Physostigmine salicylate	1.54	0.86	0.08	—
Insulin	5.46[b]	—	—	5.95[b]
Barbital	0	0.10	0	—
Aspirin	0	0.03	0	—
Sulfamethoxazole	0	0	0	—
Acetylcholine chloride	0.35	0	0	—
Ascorbic acid	0	0.01	0.03	—

[a] Per gram of controlled pore size glass. [b] Measured at pH 2.6.
Source: Mizutani and Mizutani (1978).

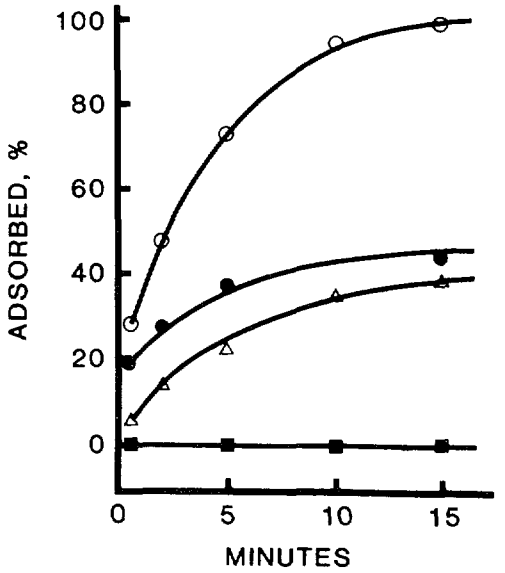


Figure 23—Effect of organic cosolvents on adsorption of methotrexate onto glass syringes. Key: open circles, methotrexate in methanol, 0.1 μg/ml; closed circles, methotrexate in methanol, 10 μg/ml; open triangles, methotrexate in 80% ethanol, 10 μg/ml; and closed squares, methotrexate in water, 0.1 μg/ml [Source: Chen and Chiou, 1982].

nephrine and atropine to the inner surface (50 cm^2) of a 20-ml glass vial was estimated as 0.1 μg. Adsorption of neutral and acidic drugs was even less.

An experimental antimalarial, a quinolinol-secondary amine compound was found to be adsorbed onto glassware (Thakker et al., 1979). Low concentrations were usually employed because of its limited solubility. At 0.11 μg/ml in a water-methanol mixture, the compound had only 36% of drug remained after 10 hr of agitation. Adsorption was effectively reduced by earlier coating of glassware with either methacrylate or silicone.

As discussed in Section III.A.3.d, organic cosolvents frequently reduced drug sorption to a container surface. Chen and Chiou (1982) reported the unusual observation that adsorption of methotrexate onto glassware and syringes was enhanced in the presence of methanol or ethanol (Fig. 23).

B. Leaching

1. General

Leaching describes the phenomenon of a substance migrating from a packaging material into a drug or biological product in intimate contact. Examples are diffusion of plasticizers from a PVC bag into a large-volume intravenous solution, extraction of zinc salt from a rubber closure into a small-volume injectable and corrosion of a glass surface. Substances that require a solvent to facilitate leaching are often referred to as extractables or extractives. Some authors have used the word "migration" to express the leaching of plasticizer.

Sorption has been discussed in great length in Section III.A. Put in perspective, leaching can be considered as the reverse of the process of sorption. The terms desorption and leaching have been used interchangeably by many researchers. In a more rigorous sense, however, desorption describes the migration of an exogenous substance, such as a preservative or a drug substance that is not originally present in the packaging components. Leaching is more properly applied to the migration of an endogenous substance, such as filler, activator, or plasticizer, out of the packaging components.

The obvious detrimental effects of leaching on pharmaceutical products are discoloration, precipitation, change in pH, and contamination. Other effects, such as increased toxicity or instability of a drug substance as a result of leaching, may not be easily detected. In studies of leaching phenomena, a few reports have examined the kinetics of metals leaching out of rubber closures (Reznek, 1953a,b; Boyett and Avis, 1975; Milano et al., 1982). On the other hand, several reports have investigated the leaching of plasticizer from plastic bags in a qualitative manner (Jaeger and Rubin, 1970). During the investigation of the sorption phenomena, desorption of a few drug substances was also conveniently studied (Yuen et al., 1979; Guess et al., 1962; Kakemi et al., 1971).

2. Mathematical Models

a. Square-root-of-time equation

The process of leaching can often be fitted to the square-root-of-time equation first developed by Higuchi (1960) to describe release of drug substances from ointment formulations. Employing dilute solutions of hydrochloric acid at pH 1.9, Boyett and Avis (1975) determined the amount of leachable zinc from rubber closures and found that the total quantity of zinc components leaching into the medium was directly proportional to the square root of time.

The equation describing this leaching process is:

$$Q = [D_m C_s (2C_m - C_s)t]^{1/2} \qquad \text{(Eq. 25)}$$

where Q (mg/cm^2) is the amount of zinc released from a unit surface area of rubber closure exposed to a pH 1.9 solution; D_m (cm^2/sec) is the effective diffusion coefficient in the rubber matrix; C_s (mg/ml) is the solubility of zinc in the solution; and C_m (mg/cm^3) is the concentration of zinc in the rubber matrix.

Equation (25) can be reduced to the following:

$$Q = \mathrm{K}t^{1/2} \qquad \text{(Eq. 26)}$$

where $\mathrm{K} = [D_m C_s (2C_m - C_s)]^{1/2}$. For this equation, K has been called the diffusion rate constant. It is obvious from this equation that the amount of substance leaching from a defined system is directly proportional to the square root of time. As an example, Fig. 24 shows a linear plot of zinc extraction from butyl rubber closures.

In several other studies, the kinetics of leaching could be described by Eq. (26). Milano et al. (1982) showed linear plots of the amount of aluminum extracted vs. the square root of time when an anesthetic solution was stored in vials sealed with a chlorobutyl rubber closure. Results obtained by Reznek (1953ab) indicated that the amount of zinc extracted from rubber

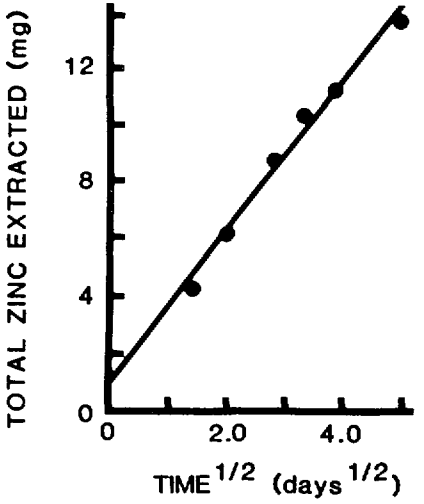


Figure 24—Extraction profile of zinc from butyl rubber closures in a buffer solution, at pH 1.9, plotted according to the diffusion mathematical model (Eq. 26) [Source: Boyett and Avis, 1975].

by 0.1 N HCl, during a storage period of 2–56 days, agreed with Eq. (26). Inchiosa (1965) reported increased ultraviolet absorbance for water stored in two brands of disposable syringe. The increase in absorbance was linearly related to the square root of time.

b. First-order equation

It is known that only a dissolved substance can migrate within a rubber or plastic matrix. A solid substance must first be dissolved in the matrix before migration can take place. Since leachable components are mostly insoluble or only slowly dissolved substances, the rate of leaching may depend on the rate of dissolution. Boyett and Avis (1975) proposed a first-order kinetic model to describe the dissolution-controlled leaching process:

$$Q_0 - Q_t = Q_0 \exp^{-kt} \qquad \text{(Eq. 27)}$$

or

$$\log[1 - (Q_t/Q_0)] = -kt \qquad \text{(Eq. 28)}$$

where Q_0 is the extractable amount of the leaching substance in rubber at time zero, Q_t is the amount of leaching substance extracted at time t, and k is the rate constant. A semilogarithmic plot of the unextracted fraction, $1 - (Q_t/Q_0)$, vs. time yields a first-order rate constant of extraction for a given set of experimental conditions. This type of relationship was first observed by Schwartz et al. (1968), who studied the release of drug into aqueous medium from wax matrices. Figure 25 shows the linearity of a semilogarithmic plot for zinc components leaching out of a butyl rubber closure to a pH 1.9 solution. One should be cautioned that Q_0 is not the total zinc content of the rubber matrix; rather, it is the extractable portion of the total zinc. For instance, the rubber closure used in Fig. 25 contained a total of 70 mg of zinc, of which only 5.41 mg (Q_0), representing 7.7% of the total zinc, was found to be extractable.

c. Log-log equation

Milano et al. (1982) proposed that extraction of soluble aluminum from chlorobutyl rubber involved a process similar to sorption of water, but proceeding in the opposite direction. The equation that defines water sorption was first proposed by Milosovich and Mattocks (1956) as:

$$W = kt^n \qquad \text{(Eq. 29)}$$

where W is the weight of water sorbed at time t; k and n are constants influenced by temperature, composition, and physical properties of the rubber closure and the vapor pressure of the solution. The equation describing the leaching of soluble, substances is:

$$Q = kt^n \qquad \text{(Eq. 30)}$$

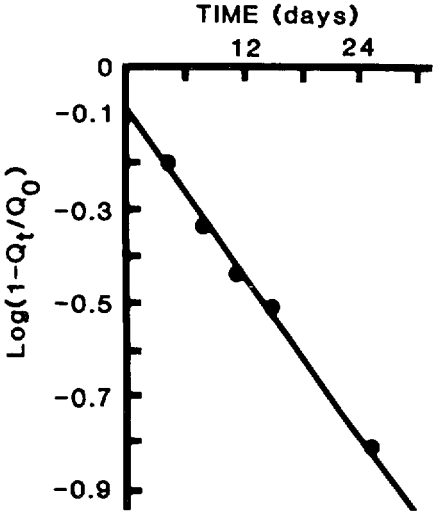


Figure 25—Extraction profile of zinc from butyl rubber closures in a buffer solution at pH 1.9, plotted according to first-order kinetics (Eq. 28) [Source: Boyett and Avis, 1975].

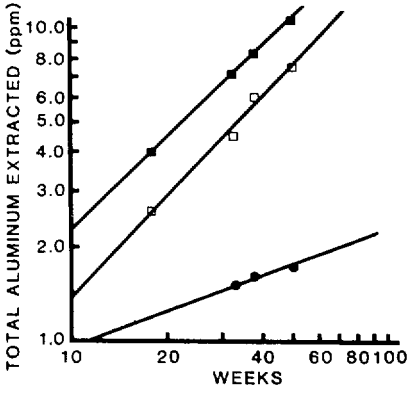


Figure 26—Aluminum extraction from three lots of chlorobutyl rubber closures at room temperature, plotted according to the mathematical model for leaching (Eq. 31). Key: Closed circles, closure contained 0.5% to 1% soluble aluminum; open squares, 1–2.5%; closed squares, greater than 2.5% [Source: Milano et al., 1982].

where Q is the concentration of the substance leached out; k and n are constants. Equation (30) can be expressed in its expanded form:

$$\log Q = \log k + n \log t \qquad \text{(Eq. 31)}$$

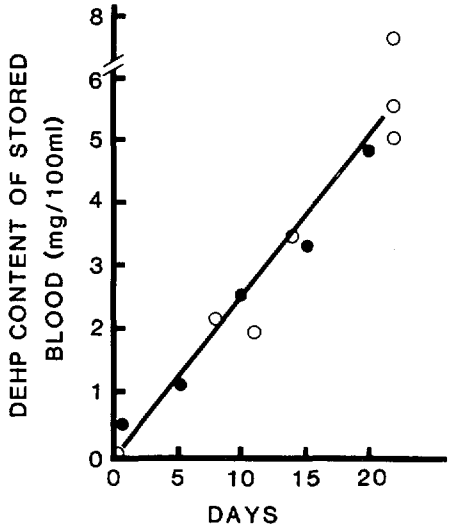


Figure 27—Di-2-ethylhexyl phthalate (DEHP) content in human blood (open circles) and canine blood (closed circles) stored for various periods in polyvinyl chloride plastic bags [Source: Jaeger and Rubin, 1972].

which indicates that a log–log plot of concentration of the leaching substance vs. time should produce a straight line with slope equal to the constant, n, and the intercept equal to log k, as illustrated by Fig. 26.

Since the leaching process may depend on water or some other solvent entering the rubber matrix to dissolve the leachable substance, it would be reasonable to state that the leaching process could be related to Eq. (29), which describes sorption of the solvent.

d. Linear equation

Leaching of the plasticizer, di-2-ethylhexyl phthalate, from polyvinyl chloride bags into blood contained within them can be plotted in a simple linear fashion (Fig. 27). The simplicity of this leaching process can be attributed to the following factors: a large concentration of di-2-ethylhexyl phthalate present in the polyvinyl chloride, good water solubility of di-2-ethylhexyl phthalate, and a non-tortous path by which the leaching substance can diffuse.

The linear equation, though it is the simplest, was derived from a complex model that assumes the bulk solution to be well stirred, mass transfer at the polymer-solution interface to be the rate-limiting step, and the exposure period to be very short (Till et al. 1982).

e. Desorption equation

The general diffusion equation (Eq. 8) for the sorption process discussed in Section IIIA.-2. can be modified to describe desorption. In the case of

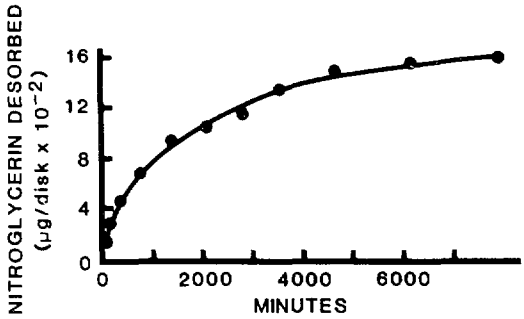


Figure 28—Relationship between the amount of nitroglycerin lost from a plastic disk initially containing 1652 μg and time under sink conditions at 30°. The symbols are experimental data, and the line was that generated by nonlinear least-squares fitting of Eq. 32 [Source: Yuen et al. 1979].

desorption under sink conditions, where there is an infinite amount of solution, the value α, the ratio between volumes of solution and polymeric materials, becomes infinitely large. The solution of Eq. 13 is $q_n = (n + \frac{1}{2})\pi$. The diffusion equation becomes:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi} \exp\{-D(n+\tfrac{1}{2})^2\pi^2 t/l^2\} \qquad \text{(Eq. 32)}$$

which is the same expression as given in Eq. 8 in Section III.A.2.d. Yuen et al. (1979) studied the desorption of nitroglycerin from polyvinyl chloride sheets and showed good agreement between the experimental values and the desorption-time profile generated by a non-linear least squares fit of Eq. (32) (Fig. 28). The diffusion coefficients thus determined were approximately 1.1 cm^2/sec for desorption and ca. 2.0 cm^2/sec for sorption.

Simplifying Eq. (32) by assuming t to be sufficiently large, we obtain:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2} \exp\left(-\frac{\pi^2 D}{4l^2} \cdot t\right) \qquad \text{(Eq. 33)}$$

Therefore, a plot of $[1 - (M_t/M_\infty)]$ vs. time as a semi-logarithmic plot will produce a straight line, the slope of which is $\pi^2 D/4l^2$; the slope permits calculation of the diffusion coefficient.

Hung and Autian (1972) used thermal gravimetric analysis to monitor desorption of aliphatic alcohols from a polyurethane sheet with thickness of $2l$. At constant temperature, weight (W)change was recorded as a function of time, Eq. 33 becomes:

$$1 - \frac{M_t}{M_\infty} = \frac{W_t - W_\infty}{W_0 - W_\infty} = \frac{8}{\pi^2} \exp\left(-\frac{\pi^2 D}{4l^2} \cdot t\right) \qquad \text{(Eq. 34)}$$

A semi-logarithmic plot (Fig. 29) illustrates the linear relationship of Eq. 34.

The ratio of $(W_t - W_\infty)/(W_0 - W_\infty)$ represents the amount of desorbing substance present (remaining) in the plastic material. Equation (34) also resulted in a first-order relationship similar to Eq. (27). Paradoxically, the semi-logarithmic relationship for Eq. (34) was derived from the diffusion equation, whereas the other semi-logarithmic relationship for Eq. (28) was considered to be a dissolution-controlled process.

3. Factors Influencing Leaching

a. Temperature

It is probable that diffusion plays an important role in the leaching process. As can be seen in Table XIII, the activation energy of diffusion (E_d) varies from 3 to 26 Kcal/mole depending on the drug and the polymer. Therefore, the effect of temperature on leaching, as reported in the literature, varies considerably.

Using the square-root-of-time equation, Eq. 25, Boyett and Avis (1975) determined the diffusion rate constants of a zinc component leaching from rubber closures. An Arrhenius plot of these rate constants showed an activation energy of less than 3 Kcal/mole, representing only a modest temperature dependence. Milano et al. (1982) showed that when aluminum is leaching out from rubber closures, temperature has almost no effect. In contrast, Reznek (1953a,b) reported a significant increase in the amount of substance leached at elevated temperatures. By thermogravimetric analysis, the activation energy of desorption for various aliphatic alcohols was found to range from 10 to 13 Kcal/mole, a range in which the leaching rate doubles for every 10°C increase in temperature (Hung and Autian, 1972).

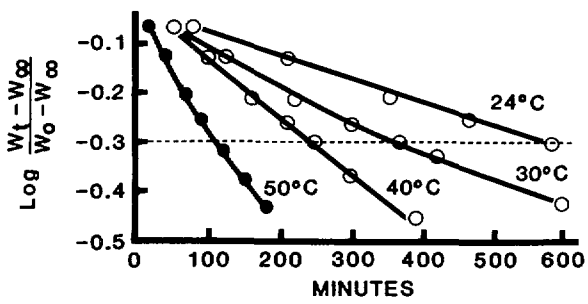


Figure 29—Plots of fractional loss of 1-octanol from polyurethane vs. time at 24, 30, 40, and 50°, according to Eq. 34 [Source: Hung and Autian, 1972].

TABLE XXIII
Amount of Zinc Leached from Butyl Rubber Closures at 2-week Intervals, 70 °C

Manufacturer	Lot	Zinc leached (mg) Buffer pH 1.9	Zinc leached (mg) Buffer pH 4.6	Zinc content (mg) per closure
A	1	0.048	0.017	40
	2	0.051	0.034	76
B	1	2.13	0.58	67
	2	3.73	0.78	125

Source: Boyett and Avis (1975).

b. pH

The solubility in the leaching medium of the material being extracted has a profound effect on the amounts extracted. Although the solubility of metals, e.g., zinc, aluminum, is generally higher in a more acidic solution, the effect of pH on leaching is frequently unpredictable. Reznek (1953a,b) showed that, although more zinc leached out of natural rubber in more acidic solutions, the effect of acid strength on the leaching rate within a particular lot of rubber was less than that due to variations between lots. From four lots of butyl rubber (two manufacturers), Boyett and Avis (1975) consistently showed that more zinc leached into pH 1.9 buffer than into pH 4.6 buffer (Table XXIII). Again, there was greater variation between rubber closures from different sources than was caused by changes in pH.

The effect of pH on leaching of organic substances is very different from that on the leaching of metals. Monitoring ultraviolet absorption, Shanker et al. (1967) observed an increase in absorbance at high pH; a steep increase was noticed when the pH rose above 7. It is conceivable that the increase in the amount leached can be attributed to better aqueous solubility of phthalate, thiocarbamate, or mercaptobenzothiazole at higher pH. However, leaching from polyvinyl chloride up to 48 hr was minimal over a pH range from 3.5 to 9.5 (Moorhatch and Chiou, 1974b). The lack of effect of pH on leaching of di-2-ethylhexyl phthalate was confirmed by Corley et al. (1977) who conducted the investigations at pH ranging from 3 to 11.

c. Excipients

The addition of alcohol to parenteral solutions in contact with elastomeric closures has been shown to increase the amount of leaching. Shanker et al. (1967) reported increased ultraviolet absorbance when butadiene-acrylonitrile rubbers were extracted with aqueous solutions of 10% ethanol or 50%

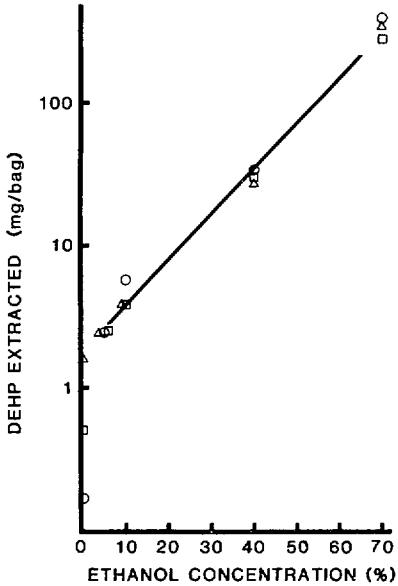


Figure 30—Effect of ethanol concentration on the amount of di-2-ethylhexyl phthalate (DEHP) extracted from polyvinyl chloride bags, Key: triangle, agitated sterile water; circle, Ringer's injection; square, agitated Ringer's injection [Source: Plotted from data given by Corley et al., 1977].

polyethylene glycol 300. Corley et al. (1977) studied the effect of ethanol concentration on the leaching of di-2-ethylhexyl phthalate from polyvinyl chloride. A linear relationship was observed between the logarithm of the extractable quantity and the concentration of ethanol as presented in Fig. 30. Moorhatch and Chiou (1974b) found an increase in ultraviolet absorbance when polyvinyl chloride infusion bags were exposed to polysorbate 20 or 80 solutions ranging in concentration from 0.01 to 0.04%. These surfactants appear to enhance the leaching of the plasticizer, di-2-ethylhexyl phthalate because of their solubilizing effect.

Boyett and Avis (1975) found that the addition of 1% disodium edetate, a chelating agent, caused only minimal increases in the amount of zinc leached from rubber closures.

4. Leaching from Rubber Closures

Materials leaching out of rubber closures are generally accelerator residues (e.g., mercaptobenzothiazole, tetramethylthiuram disulfide), activators (e.g., zinc oxide), inert fillers (e.g., wax), softening agents (e.g., oils),

lubricants (e.g., stearic acid), coloring agents, and any vulcanization products of these components (e.g., zinc stearate, zinc salt of dithiocarbamates). The Technical Methods Bulletin No. 1 on "*Extractables from Elastomeric Closures: Analytical Procedures for Functional Group, Characterization and Identification*," published in 1981 by the Parenteral Drug Association, provides some general procedures for the extraction, separation, isolation, and identification of extractables. It also provides a comprehensive list of compounding ingredients commonly used in pharmaceutical rubber formulations.

Kinetic studies of the leaching process should lead to a better understanding of the mechanisms involved. Boyett and Avis (1975) reported the extraction rates of zinc from butyl rubber closures that contain zinc oxide (1.9–5.9%) and zinc dimethylcarbamate (0.11–0.53%). Their data fit nicely to both Eq. (25) and Eq. (27), as demonstrated by the resultant linearity in Figs. 24 and 25 plotted from the same set of data.

For the purposes of delineating the rate-controlling factors in the leaching process, Eqs. (25) and (27) describe leaching processes controlled by diffusion and dissolution, respectively. Schwartz et al. (1968) developed a more stringent test to differentiate the two mechanisms when plots by either equation were linear. Employing this test, Boyett and Avis (1975) found some of their data compatible with a diffusion-controlled mechanism, whereas other data yielded inconclusive results.

Studying the extraction rate of aluminum from chlorobutyl rubber closures, Milano et al. (1982) also showed the fit of their data to both Eq. (25) and Eq. (31). Because a solid inorganic salt would not be expected to diffuse through an organic rubber matrix, their results were most reasonably explained by a desorption model. It was hypothesized that when water is absorbed into the rubber matrix, aluminum salts are solubilized and subsequently desorbed (extracted) into the injectable solution.

Distinguishing mechanisms, or even generating consistent data, is made difficult by the following factors that are unique to rubber closures:

a. Effect of "bloom" causes an uneven distribution of the leaching substances in the finished closure.

b. Leaching is dependent upon the kinetic characteristics of diffusion of the solvent into and out of the rubber matrix. Swelling of the rubber matrix is one of many causes that could change the characteristics of solvent diffusion.

c. Minor changes in rubber composition sometimes result in a significant change in the leaching rate. Boyett and Avis (1975) reported a 50-fold increase in the rate of zinc leaching when 0.36% stearic acid was present.

d. Closures of the same composition often exhibit great batch-to-batch variation in the amount of leachable substances. Variation in temperature and pressure during vulcanization can result in different amounts of reaction products in the closures, which, in turn, exhibit different leaching rates.

e. Monitoring a leaching substance by a nonspecific method, such as determining the amount of zinc or ultraviolet absorbance, can be misleading because the apparent leaching rate may be a composite of the rates of many substances, each of which may leach out at its own characteristic rate and, perhaps, by a different mechanism.

f. The effect of storage position has been misconceived or overlooked by many investigators. According to Milano et al. (1982), bottles standing upright experienced more leaching of substances than did inverted bottles the closures of which were immersed in liquid. This result is attributable to Soxhlet extraction by water vapor.

Reznek (1953a,b) reported leaching rates of zinc salts from various rubber closures. The quantity of leached zinc tended to reach a maximum after a relatively short period, approximately 2 days. Acidifying the solution promoted leaching, although the acid strength had less effect on the rate of leaching within a particular lot than resulted from variation among the lots alone.

Jetton et al. (1976) conducted extensive analyses of the metal content in a variety of large-volume injection bottles. Rubber stoppers appeared to be the major source of metal contamination in the large-volume injectable solutions. Up to 2.7 μg of magnesium, 11.7 μg of calcium, and 130 μg of zinc were detected and were attributed to leaching from the closure. The findings showed a pattern of inconsistency; comparable closures undergoing the same treatment showed a 12-fold difference in the amount of zinc leached.

Determination of nonmetallic leaching substances has been hampered by lack of specific assay methods. Inchiosa (1965) identified 2-(methylthio)-benzothiazole and another undetermined substance as the water-soluble extractives from the rubber plunger of a disposable syringe. Aktulga (1971) identified and quantified the leaching components: zinc dimethyl dithiocarbamate and tetramethylthiuram disulfide. Lachman et al. (1966), and Shanker et al. (1967) identified numerous leaching substances from natural rubber, polyurethane rubber, and butadiene-acrylonitrile rubber. All these investigators employed ultraviolet spectra to identify the leaching substances.

By mass, NMR, and UV spectroscopic methods, 2-(2-hydroxyethylmercapto)benzothiazole was identified as the contaminant leaching from

disposable syringes (Petersen et al., 1981). In the same report, however, it was postulated that this compound could be a reaction product of the vulcanization accelerator, 2-mercaptobenzothiazole, and the sterilizing agent ethylene oxide.

When atomic absorption spectrophotometry was used as the detection method, various quantities of silicone lubricant, ranging from nondetectable to 4 μg, were flushed out of disposable syringes by distilled water (Miller et al., 1969). Gas chromatography was used as the detection method in an investigation of the source of haze in a number of reconstituted lyophilized parenterals. The haze was found to arise from the adsorption of some volatile closure components, such as of paraffin wax and sulfur, by the lyophilized cake (Pikal and Lang, 1978). During the vacuum cycle of lyophilization, vapor-phase diffusion is fast enough to allow significant quantities of these volatile rubber components to transfer from the rubber closure to the product surface, where adsorption occurs.

The interction of leaching substances with drug has apparently not been reported. However, substances leaching from rubber-stoppered Vacutainer® tubes were reported to have interfered with the theophylline assay in blood samples (Chrzanowski et al., 1976), protein binding of alprenolol and propanolol (Piafsky and Borga, 1976), and meperidine assay (Wilkinson and Schenker, 1975). The culprit in these tubes was identified as plasticizer, viz., tri-2-butoxyethyl phosphate (Shah et al., 1982). The inactivation of thimerosal by leaching substances in rubber-closure sealed vaccine bottles was reported by Birner and Garnet (1964). Tsuji et al. (1964) reported similar results when aqueous extracts of rubber closures were added to thimerosal solution, and eventual photodecomposition of thimerosal was accelerated.

The aforementioned leaching studies used aqueous vehicles. The effect of oleaginous vehicles needs to be investigated, because the spectrum of materials extracted by organic solvents could be entirely different.

The toxicity of extracts from a number of different types of closures was studied with animal cells in tissue cultures (Parker et al., 1951). The U.S. Pharmacopoeia describes a biological test procedure in the section on "Rubber closures for injection." Acute systemic toxicity and intracutaneous reactivity tests are evaluated with solutions prepared by extracting rubber closures in an appropriate extraction medium, such as normal saline solution, polyethylene glycol, or cottonseed oil. This procedure requires autoclaving the closures with the extraction medium. Both the extract and blanks are then injected into animals for toxicological evaluation.

To minimize the amount of extractable substances present in injectable products, one may resort to cleaning, surface coating, or both. Boyett and

Avis (1976) tried prewashing rubber closures with acetone or sodium lauryl sulfate solution and pretreatment in an autoclave at 121 °C, but could not reduce the amount of zinc extractable from these closures. Milano et al. (1982) subjected chlorobutyl rubber stoppers to an autoclave cycle at 121 °C, either in water or in 0.1% disodium edetate solution, but neither treatment completely eliminated leaching of aluminum into the injectable solution.

Use of a protective lining between the elastomer and the extracting medium has produced some satisfactory results. Lachman et al. (1966) reported that Teflon® lining essentially eliminated the sorption and leaching problems of polyurethane and natural rubber stoppers, 2 years after he had reported that an epoxy lining gave only a marginal protection. Hopkins (1965) reported the superiority of Teflon® coating over urethane coating. A more quantitative, detailed study showed an effective reduction in leaching from Teflon®-faced natural or butyl rubber closures when the investigator monitored pH shifts, amounts of zinc ion, and oxidizables (Adams, 1978). When protective linings are not used, polyurethane and silicone rubber have been recognized as the elastomers that produce the least amount of extractables.

Review articles by Hopkins (1965) and by Wood (1980), the guidelines developed by Anschel (1977) and the PDA Technical Methods Bulletin No. 1 on extractable (1981), all provide perspectives on leaching as a criterion in the selection of proper elastomeric closures for sterile pharmaceutical products.

5. Leaching From Plastic Containers

A major concern about leaching from a plastic container is the possible diffusion of toxic stabilizers and plasticizers from the plastic material into an IV solution. A plasticizer used in PVC bags, di-2-ethylhexyl phthalate ester (DEHP), also known as dioctyl phthalate (DOP), has received most attention. It is known that the plasticizing agent is not firmly bound to the polymer but is believed to be loosely attached to it to form a gel-like structure and, as such, it may be extracted by a variety of organic solvents. Guess et al. (1967) used carbon tetrachloride to extract an anticoagulant acid citrate dextrose (ACD) solution stored previously in PVC-blood bags and then analyzed the extract by thin-layer chromatography (TLC). The leaching substances were found to be di-2-ethylhexyl phthalate, 2-ethyl hexanol, and a few other phthalates.

Using TLC, Gesler and Kartinos (1970) identified di-2-ethylhexyl phthalate in the extract of plasma stored in plastic packs. In assessing the

metabolism and accumulation of the plasticizer in biological systems, Jaeger and Rubin (1970) found that di-2-ethylhexyl phthalate was not metabolized by the liver. Quantitative analysis showed that blood stored in plastic containers could extract the plasticizer, which reached a concentration of 5–7 mg/100 ml during a 21-day storage period. This high concentration could easily support a previous finding that a significant quantity of the plasticizer was found in tissues of patients who had received blood transfusions. A comprehensive study on the toxicity of phthalate ester was made by Autian (1973).

Moorhatch and Chiou (1973) studied leaching of chemicals from IV fluid bags containing various solvent media. By UV spectrophotometry, they found that only polysorbate (Tween) 20 and 80 solutions produced a sufficient increase in absorbance to indicate leaching of UV-absorbing material. Nevertheless, the authors estimated that 2.5 mg of di-2-ethylhexyl phthalate had leached out to 200 ml of 0.04% polysorbate 80 solution in 48 hr.

The low aqueous solubility of di-2-ethylhexyl phthalate sometimes causes problems through the formation of globules or particulates. Whitlow et al. (1974) first noticed that PVC bags containing infusion fluid showed a larger number of particulates when shaken vigorously. In the same laboratory, Needham and Luzzi (1973) discovered that colloidal globules found in PVC IV bags containing normal saline were di-2-ethylhexyl phthalate. These globules, 2.3–5.0 μ in diameter, could be effectively eliminated by use of a 0.22-μ cellulose filter; the number of globules was reduced by filtration from 20,000 counts/ml to fewer than 1200 counts/ml. Horioka et al. (1977) analyzed particulate counts made before and after shaking, but found that the concentration of di-2-ethylhexyl phthalate did not correlate well with particulate counts. In a study to provide more information to hospital pharmacists, Corley et al., (1977) found that neither the duration of administration nor the pH of the system affected the amount of di-2-ethylhexyl phthalate delivered. On the other hand, the presence of ethanol increased the concentration of di-2-ethylhexyl phthalate found in IV fluids. At 5 and 10% ethanol levels, the concentration of di-2-ethylhexyl phthalate in IV fluids increased from a control level of about 1 ppm to between 2 and 6 ppm. The data from Corley et al. (1977) showed linearity when the logarithm of the amount of di-2-ethylhexyl phthalate was plotted against ethanol concentration (Fig. 30), similar to solubility plots of solutions with varying concentrations of organic solvent.

Without identifying the leaching substances, Ross (1964) reported the presence of surface-active substances in extracts from plastic materials used in hospitals. Kordon (1965) reported finding fluorescent contaminants leached from plastic containers.

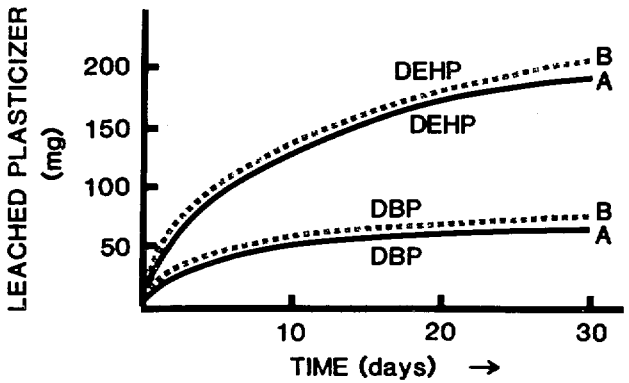


Figure 31—Effect of the composition of phthalate plasticizer on the migration of dibutyl phthalate (DBP) and di-2-ethylhexyl phthalate (DEHP) from polyvinyl chloride into olive oil (A) and cottonseed oil (B) [Source: Kampouris, 1976].

To study the interaction between leaching substances and the components of sterile products, aqueous extracts of plastic material can be placed in glass containers. In this manner, loss due to sorption of any of the components to the plastic can be avoided. Youssef et al. (1973) produced some aqueous extracts from polyethylene granules to study their compatibility with preservatives. The degradation of phenylmercuric nitrate, phenol, chlorocresol, and methylparaben was much greater in the extract (15% or more over a period of 30 days at 50 °C) than in the control (less than 5% in the same period).

Giving fat emulsion intravenously is becoming increasingly popular as a total nutrient system. Reports in the area of food technology provide some insight into the leaching of plasticizers from polyvinyl chloride to edible oils. Using ^{14}C-labeled dibutyl phthalate and di-2-ethylhexyl phthalate, Kampouris (1976) determined the amounts of these plasticizers leaching into olive, cottonseed, corn, and soybean oils. Dibutyl phthalate exhibited a lower leaching rate than did di-2-ethylhexyl phthalate. Figure 31 compares the leaching rates of these two plasticizers from a test piece (2 × 25 × 50 mm) of polyvinyl chloride that was plasticized with 50 parts of plasticizer to every 100 parts of rubber, then immersed in 250 ml of the oil. Kampouris et al. (1976) also studied the rate of leaching of plasticizers into a group of alcohols, ranging from methanol to 2-ethyl hexanol. In the case of dibutyl phthalate, the higher the molecular weight of the alcohols, the less was the amount of plasticizer leached to the bulk solution. For di-2-ethylhexyl phthalate, a reverse trend was observed. The mechanisms of leaching from plastic and the mathematical equations developed to interpret the phenomena were presented by Quackenbos (1954) and by Reid

et al. (1980). As described by Till et al. (1982), the leaching process can be separated into three consecutive time periods. Within a short period of time, immediately after the plastic piece has been exposed to the solvent, the loss of plasticizer varies with t^n, where $n > \frac{1}{2}$. Then, for a longer period of time, the amount of leaching is proportional to $t^{1/2}$ and, at the final stage, the rate decreases ($n < \frac{1}{2}$). These trends can be rationalized in a qualitative manner by assuming that, initially, the external mass transfer is the rate-controlling process; at the intermediate stage, the diffusion of plasticizer within the polymer controls the rate; and, finally, at longer times the depletion of the plasticizer within the polymer begins to affect the rate.

Appendant to the sorption studies, desorption was also investigated for sorbic acid from polyamide tubing (Autian and Shaikh, 1960), for benzalkonium chloride from polyvinyl chloride (Guess et al., 1962), for butyl paraben from polyethylene (Kakemi et al., 1971), and for nitroglycerin from polyvinyl chloride (Yuen et al., 1979).

6. Corrosion of Glass Surface

Depending upon composition, glass can be soluble in water, acid, or base, or virtually insoluble. Most glasses are largely insoluble in aqueous solutions, though some surface solubility or corrosion does occur.

Corrosion may occur in a number of ways:

a. The glass surface may react with corrosive solutes in solution to form new compounds.

b. Some glass ingredients may be preferentially dissolved, producing a porous surface zone.

c. The glass components as a whole may be slowly dissolved in the aqueous solution resulting in a receding boundary.

The chemical durability of glass containers is a function of the composition of both glass and solution. For example, ordinary water, stored in a typical soda-lime glass container for a year, may extract as much as 30 mg of glass components; on the other hand, the same water stored in a borosilicate glass container will contain less than 1 mg of extractive (Bacon, 1968).

The rate of corrosion is pH-dependent. The data (Fig. 32) indicate that USP Type I and Type II glasses behave similarly in an alkaline region, but that Type I glass is more resistant to attack by acid than is Type II glass.

In Type I glass, an "idealized" acid attack mechanism governs and the alkali elements in the glass are selectively extracted, mainly by exchanging with hydrogen or hydronium (H_3O^+) ions in the aqueous medium. This is a diffusion-controlled process. The deeper the sodium ion depletion zone

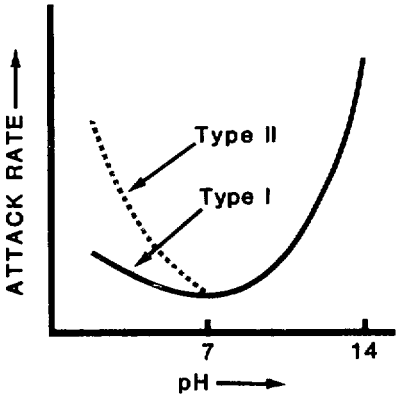


Figure 32—Effect of pH on the rate of chemical attack on Type I and Type II glasses [Source: "Properties of Glasses and Glass-Ceramics", Corning Glass Works, Corning, N.Y., 1973].

is from the glass surface, the longer it takes to extract additional sodium ions. The effect of hydronium ion concentration on the rate of corrosion for Type I glass is relatively small.

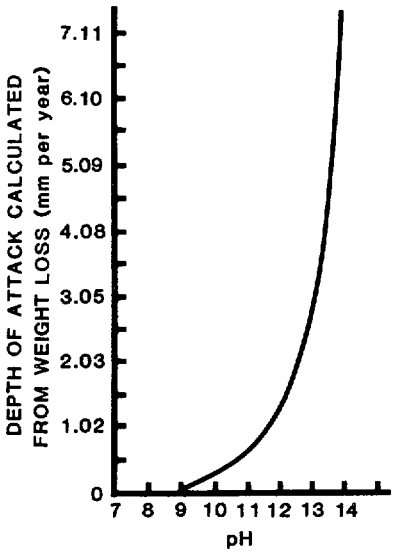


Figure 33—pH dependency of the attack rate for a representative borosilicate glass. The numbers shown are only relative in magnitude [Source: "All About Glass," Corning Glass Works, Corning, N.Y., 1968].

For a Type II glass, acid attack is not selective. It is a process of dissolution and disintegration, with a strong pH dependency. The rate of attack increases with an increase in temperature.

Most glasses are labile to attack by alkaline solutions (Adams, 1977). The mechanisms are comparable to those for attack by acid (e.g., see Type II glass in Fig. 32). Alkaline attack occurs even in borosilicate glass, which is normally believed to be chemically inert (Fig. 33).

The rate of corrosion from either alkaline solution or superheated water was found to increase rapidly with increases in the solution temperature (Fig. 34). Corrosion begins to occur at a much lower initial temperature for alkaline solution than it does for water. On the other hand, the rate of corrosion in an acid solution is only moderately increased by increasing temperatures.

The rate of corrosion can be significantly affected by the types of ions or organic compounds present in solution:

a. Phosphate, oxalate, and citrate accelerate the rate of corrosion by alkali.

b. An aqueous solution of an organic chelating agents, such as disodium edetate, is as corrosive as is a strong alkali.

c. $BeO_2^{=}$, $SiO_3^{=}$, and $ZrO_3^{=}$ inhibit the rate of corrosion by alkali.

d. Accumulation of reaction products on the glass surface will slow the corrosive action of alkali.

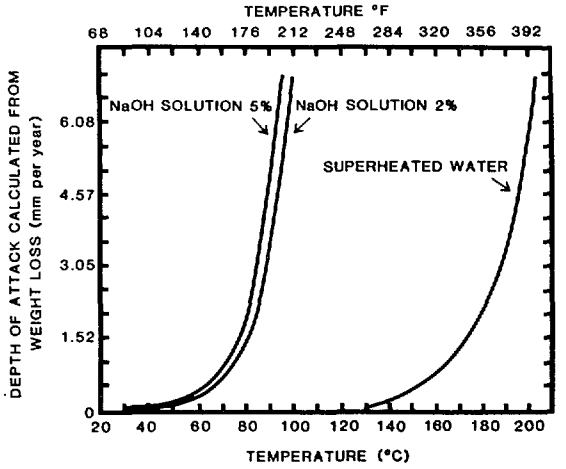


Figure 34—Effect of temperature on the rate of chemical attack of borosilicate glass by NaOH solution and superheated water [Source: "All About Glass", Corning Glass Works, Corning, N.Y., 1968].

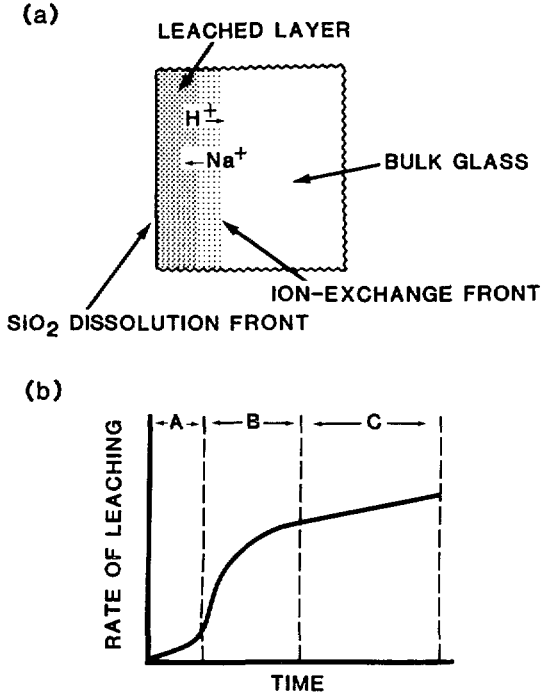


Figure 35—(*a*) Schematic illutration of the leaching process: (*b*) leaching rate profile of glass in acid solution—Region A: rate is slowed downed by SiO_2-rich skin; Region B: typical diffusion-controlled reaction; Region C: steady-state leaching process [Source: Courtesy of Dr. J. D. Andrade, The University of Utah, Department of Bioengineering, Salt Lake City, Utah].

Neutral solutions tend to extract sodium in the glass network preferentially at the beginning of corrosion and then begin to attack other components of the glass until the composition of total extracted material in solution approaches the composition of glass. An unbuffered solution gradually becomes alkaline, and the rate of corrosion increases until equilibrium has been reached.

Special alkali-resistant glasses, such as Corning #7280, are commercially available. They contain high concentrations of ZrO_2 (see Table II).

Corrosion of glass containers occurs by either of two mechanisms:

a. Etching process

Etching is a uniform process that occurs in an alkaline medium, whereby the silicon-oxide network is attacked:

$$2\ NaOH + SiO_2 \rightarrow Na_2SO_3 + H_2O \qquad \text{(Eq. 35)}$$

The silicon oxide network is slowly destroyed, thus releasing the other glass constituents of the glass.

b. Leaching process

Leaching is a selective corrosion process. It is primarily an ion-exchange process for glass modifiers, such as Li^+, Na^+, K^+, Mg^{++}, Ca^{++}, and Al^{3+}:

$$Na^+\ (glass) + H^+\ (solution) \rightarrow H^+\ (glass) + Na^+\ (solution) \qquad \text{(Eq. 36)}$$

A schematic view of this leaching process is given in Fig. 35.

It is generally recognized that hydrogen fluoride facilitates the etching process. However, solutions of sodium fluoride in the pH range of 3–9 stored in a soda-lime glass container showed only an insignificant change in fluoride concentration after 6 months' storage (Hattab, 1981). Precipitation of sodium fluosilicate, Na_2SiF_6, was detected in a multi-vitamin solution stored between pH 2.4 and 4.3 in a Type I glass container (Tingstad et al., 1963). However, the precipitation did not cause any detectable loss of fluoride in the solution.

C. *Permeation*

1. General

Permeation is, by definition, the process of crossing a barrier. In the field of sterile pharmaceutical products, examples of permeation are benzyl alcohol passing through intravenous plastic bags, chlorobutanol passing through polyethylene ophthalmic bottles, and oxygen passing through rubber closures. In all these cases, permeation can be detrimental to the pharmaceutical product.

Permeation involves three steps: (*1*) dissolution of the permeant (or penetrant) on the near side of a barrier; (*2*) passage of the permeant through the barrier matrix by diffusion; and (*3*) evaporation or extraction of the permeant from the far side of the barrier. Since sorption involves both the first and second of these steps, permeation occurs when sorption is followed by egress of the permeant from the barrier. It is often difficult to distinguish between sorption and permeation when a volatile component has been lost from a sterile package, because the amount of volatile substance evaporated from the exterior is very difficult to determine. In general, the loss of any component can be attributed to its sorption by the packaging material, but some finite quantity of a volatile substance may have been lost through permeation and evaporation. There are, however, only a few reports that discuss the permeation phenomenon with respect to packaging.

Permeation is a process of great physiological significance. Studies of drug absorption and extraction have yielded great quantities of information pertaining to mass transport through biological or synthetic membranes. Flynn et al. (1974) provide a comprehensive review of mass transport phenomena and models for their study. Components of the primary packaging material constitute a much less complex barrier for permeation than do biological membranes. Nevertheless, concepts pertinent to mass transport are of great value in delineating the mechanisms of physicochemical interactions between sterile pharmaceutical formulations and packaging materials. Discussed in this section are those reports that deal specifically with permeation of bottles or other packaging materials, as well as the results of some studies in which "packaging-worthy" polymers (polyethylene, polyvinyl chloride, rubber, Silastic® etc.) were employed as model membranes for mass transport.

Many technologies require an understanding of permeation for we routinely employ polymer films as barriers to interrupt the free transmission of gases, liquids, or vapors across phase boundaries. For instance, paint or varnish is used to protect metal or wood, paper is coated to rendered it moisture-resistant, or a free-standing film is used to package foodstuffs.

Developments in polymer science have led to a fundamental understanding of the mechanism of permeation. Two reviews (Van Amerongen, 1964; Bixler and Sweeting, 1971) provide a valuable detailed account of permeation through polymeric materials.

2. Mathematical Models

a. Diffusion Equations

A simple way to determine the amount of permeant passing through a membrane as a function of time is to use a permeation cell (Fig. 36). This apparatus, also called a diffusion cell, consists of two compartments: a donor half-cell and a receptor half-cell, separated by a polymeric membrane or film. At constant temperature, the amount of permeant migrating from the donor half-cell to the receptor half-cell at various time intervals is determined. Typical permeation data are plotted in Fig. 37. After some time, a condition of steady-state is reached in which the permeant molecules enter the donor side of the barrier at the same rate as they leave it and enter the receptor half-cell. As a result, the slope of the permeation profile becomes constant (Fig. 37). From the linear portion of the curve, a permeability constant, or permeation coefficient (P) can be determined by use of the following expression (Rodell et al., 1966):

$$P \text{ (in cm}^2\text{/sec)} = (q/t)\,(l/CA) \qquad \text{(Eq. 37)}$$

where q/t (in mg/hr), is the slope of the linear portion, l is the thickness of the film, C is the original concentration, and A is the surface area exposed to the solution. Equation (37) can be rearranged to:

$$q = \frac{P\,A\,C}{l}\,t \qquad \text{(Eq. 38)}$$

From this equation, it is clear that the amount permeating, q, is directly proportional to the initial concentration, C, and the surface area of the film, A, and inversely proportional to the thickness of the film, l. Some permeability constants determined in this manner are shown in Table XXIV.

It should be pointed out that the initial phase of a permeation plot is nonlinear. The curve, shaped like a hockey stick, permits evaluation of the apparent diffusion coefficient, D, by use of the lag-time equation of Barrer (van Amerongen 1964), given as:

$$D = l^2/6L \qquad \text{(Eq. 39)}$$

where l is the thickness of the film and L is the lag-time intercept, obtained by extrapolation of the linear portion of the line to the time axis of the plot, converted into seconds. This equation is one of the most frequently used

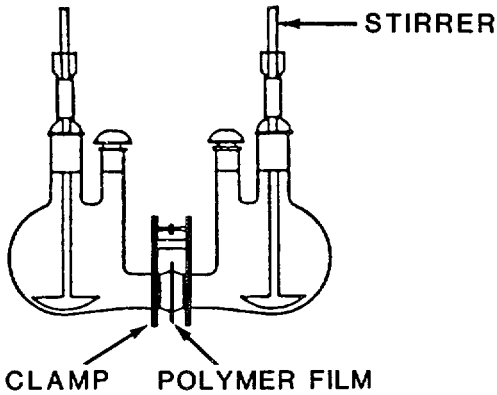


Figure 36—Diagram of a permeation cell [Source: Anderson and Motzi, 1982].

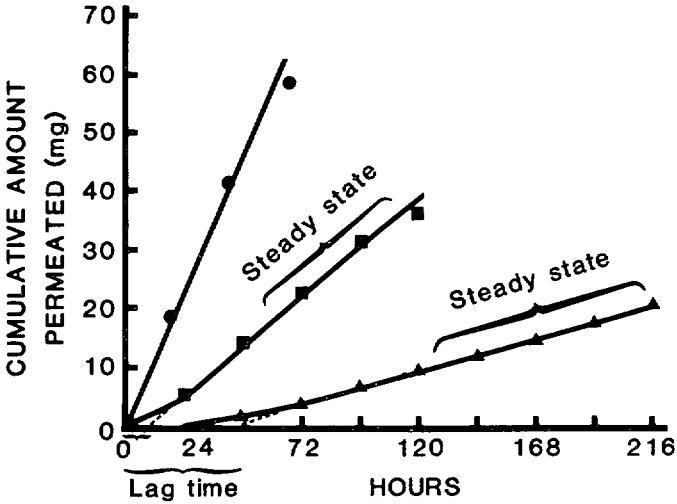


Figure 37—Determination of lag-times for nitrobenzene permeating through a polyethylene container. Key: Triangles, 37 °C; squares, 54.5 °C; circles, 71 °C [Source: Polack et al., 1979].

for determining the diffusion coefficient of a substance passing through a polymeric film. Diffusion coefficients listed in Table XXIV were determined by this lag-time approach.

It is timely to point out here the differences between these often confused terms, diffusion and permeation: diffusion is the process by which a substance is transported from one part of a section of polymer matrix to an-

TABLE XXIV
Permeability Constants (P) and Activation Energy for Permeation (E_p) Determined in a Permeation Cell

Compound	Polymer Film	Temp. (C°)	P (cm²/sec)	Reference
Acetanilide	Polyethylene	50	3.07×10^{-9}	Serota et al. (1972)
Acetophenone	Polyethylene	24.4	3.03×10^{-8}	Jordan and Polack (1973)
Benzoic acid	Polyethylene	50	1.0×10^{-8}	Gonzales et al. (1967)
		60	1.7×10^{-8}	
		E_p = 17.2 kcal/mole		
Benzoid acid	Polyamide	50	1.08×10^{-7}	Rodell et al. (1966)
		60	1.65×10^{-7}	
		70	2.50×10^{-7}	
		E_p = 9.22 kcal/mole		
Benzyl alcohol	Polyethylene	50	7.7×10^{-9}	Gonzales et al. (1967)
		60	1.49×10^{-8}	
		70	4.00×10^{-8}	
		E_p = 11.5 kcal/mole		
Methylparaben	Polyamide	50	1.35×10^{-7}	Rodell et al. (1966)
		60	2.29×10^{-7}	
		70	3.37×10^{-7}	
		E_p = 10.2 kcal/mole		
	Silicone rubber	30	1.74×10^{-7}	Anderson and Motzi (1982)
	Natural rubber	30	1.82×10^{-8}	Anderson and Motzi (1982)
Propylparaben	Polyamide	50	3.11×10^{-10}	Rodell et al. (1966)
		60	5.56×10^{-7}	
		70	9.16×10^{-7}	
		E_p = 11.9 kcal/mole		
Nitrobenzene	Polyethylene	24.4	8.45×10^{-8}	Jordan and Polack (1973)
Phenol	Polyethylene	50	6.4×10^{-9}	Nasim et al. (1972)
	Polyurethane	50	4.3×10^{-7}	De and Autian (1975)

other; permeation is the process of crossing a polymeric film, but includes dissolving into and exiting from the film. Diffusion is often rate-limiting in the permeation process. The diffusion coefficient, D, is related to the permeability constant, P, by:

$$P = D \times K \qquad \text{(Eq. 40)}$$

where K is the partition coefficient of a permeant between the polymeric material and the vehicle in the donor compartment.

For the case of permeation by a gaseous permeant or by water vapor, a detailed testing method is given in a review by Lebovits (1966). To determine the permeability constant for a gas or vapor, the partition coefficient

in Eq. (40) would be replaced by the solubility coefficient, S, which is defined as the volumetric gas solubility (at 0 °C and 1 atm) per unit volume of polymer per unit pressure:

$$P = D \times S \qquad \text{(Eq. 41)}$$

Therefore, the amount of permeant, q, at steady-state can be expressed as:

$$q = DSA\ (p_1 - p_2)t/l \qquad \text{(Eq. 42)}$$

This equation indicates that the rate of permeation for steady-state flow of a gas through a polymeric barrier is proportional to surface area, A, and the partial pressure difference, $(p_1 - p_2)$, but is inversely proportional to the thickness, l, of the barrier. The presence or absence of another gas is immaterial.

b. Compartmental equations

In dealing with an entire sterile package, it is difficult to monitor the amount of permeant lost from the package surface. There is a need for equations that will allow one to study permeation by following the change in concentration within the container. Tasmanian workers, using pharmacokinetic concepts, developed a compartmental model to describe the loss of a permeant from within polyethylene bottles (Fig. 38). The disappearance-time profile of permeants with high affinity for polyethylene, as illustrated in Fig. 39, reveals a rapid and significant uptake of permeant from solution by the container wall, followed by a slower, and essentially irreversible, loss of permeant to the atmosphere (Polack et al., 1979). Mathematically, the fraction of permeant in solution, F_s, is related to time by the following bi-exponential equation:

$$F_s = Ae^{-at} + Be^{-bt} \qquad \text{(Eq. 43)}$$

where A and B are the fractional zero intercepts ($A + B = 1$) and a and b are the fast and slow rate constants. The microscopic rate constants are:

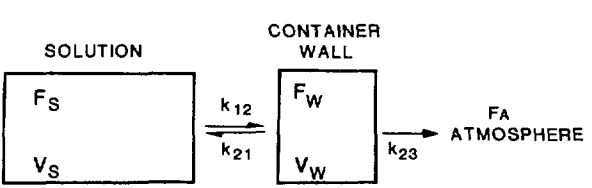


Figure 38—Model used to examine the disappearance kinetics of solutes from aqueous solutions stored in polyethylene containers. F and V refer to the fraction of solute remaining in, and the volume of, each of the "compartments," solution (S), container wall (W), and atmosphere (A) [Source: Roberts et al., 1979].

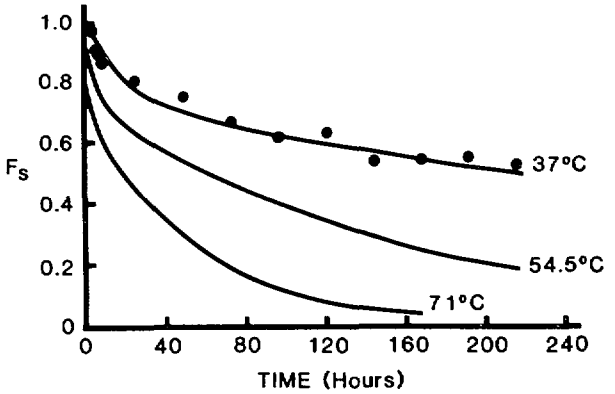


Figure 39—Effect of temperature on the disappearance of nitrobenzene from solution in a polyethylene bottle. The lines show the fraction of solute remaining in solution (F_s), as predicted by Eq. 43. The points were experimentally determined [Source: Polack et al., 1979].

$$k_{12} = Aa + Bb \qquad \text{(Eq. 44)}$$

$$k_{23} = ab/k_{12} \qquad \text{(Eq. 45)}$$

$$k_{21} = a + b - k_{12} - k_{23} \qquad \text{(Eq. 46)}$$

The bi-exponential curves shown in Fig. 39 are for the same compound and the same polymeric material as shown in Fig. 37. The parameters of Eqs. (44) through (46) can be analyzed by nonlinear regression analysis using the program NONLIN (Metzler, 1969).

When the permeant has low affinity for the container wall, only an insignificant amount of permeant is sorbed by the wall, and the bi-exponential equation can be reduced to a mono-exponential form:

$$F_s = Be^{-bt} \qquad \text{(Eq. 47)}$$

Benzyl alcohol and chloroxylenol stored in polyethylene bottles were found to disappear in this fashion (Goss et al., 1968; Roberts et al., 1979).

To determine whether loss of a component from a product was due solely to sorption, Roberts et al. (1979) used saturated polymeric films in their studies. The polymeric film of plastic bottles was first soaked in a solution containing a permeant, then mounted in a diffusion cell and exposed to a fresh solution of the same permeant. The disappearance profile of the permeant was parallel to the terminal phase (B in Eq. 43) of the profile generated when a virgin piece of the same polymeric ie film was used (Fig. 40). From this observation, it was deduced that the beginning phase (A)

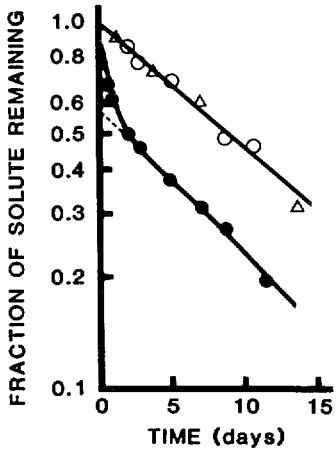


Figure 40—Effect of presoaking the container in an aqueous solution of nitrobenzene (0.05% w/v) on the loss of nitrobenzene from aqueous solutions (0.05% w/v) in polyethylene containers at 37 ± 1 °C. Key: open circles, presoaking for 1 week; open triangles, presoaking for 1 month; closed circles, no presoaking [Source: Roberts et al., 1979].

of the bi-exponential profile is a result of sorption, and that a slow and steady evaporation follows in the B phase.

3. Factors Influencing Permeation

The rate of permeation is influenced by the same factors that influence the rate of sorption except that, in the case of sorption, the time factor is less important than the amount sorbed at equilibrium. This is because a steady-state flow never exists in the sorption process. Under steady-state flow, permeability is governed by the diffusion coefficient and the partition coefficient, as indicated in Eq. (40). Thus, it can be demonstrated that permeability is also affected by permeant concentration, pH, oil solubility, vehicle in the formulation etc., i.e., factors that affect partition coefficient. Crystallinity of the polymer and branching and substitution of the polymer also influence permeability through their effect on the diffusion coefficient. Some factors, such as temperature, influence both partition coefficient (solubility coefficient, in the case of a permanent gas) and diffusion coefficient.

a. Concentration

The concentration gradient is the driving force behind permeation. Permeation *rate*, i.e., the amount permeating per unit time, increases with increasing concentration (Fig. 41). However, the permeability constant,

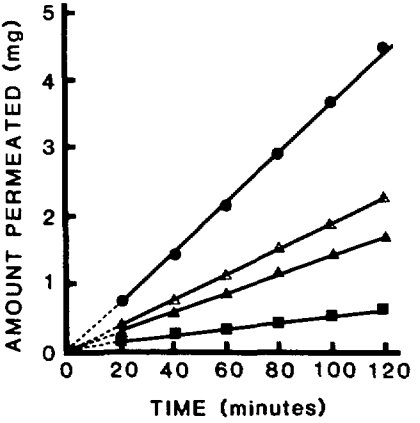


Figure 41—Effect of concentration on the permeation of acetophenone through "saturated" polyethylene membrane (6 mil) at 40.2°. Key: closed circles, 3.91×10^{-2} M; open triangles, 2.25×10^{-2} M; closed triangles, 1.83×10^{-2} M; closed squares, 0.82×10^{-2} M [Source: Jordan and Polack, 1972b].

as the term implies, is constant with respect to a range of permeant concentrations. This is so because the diffusion coefficient is, for practical purposes, concentration independent and the partition coefficient is also concentration independent for a dilute solution.

For the permeation of gas or moisture, permeability should be independent of relative vapor pressure, but often is not. The permeation of water through natural rubber, however, showed increased permeability when relative vapor pressure exceeded 0.75 (75% relative humidity) (van Amerongen, 1964).

b. Partition coefficient

Whether permeability is expressed by a permeability constant or as percentage loss under a given set of conditions, various authors have successfully demonstrated a correlation between permeability and partition coefficient. Compounds with a high partition coefficient exhibit faster permeation. Russell and Stock (1966) studied the loss of phenyl alkyl alcohols, with the alkyl group varying from C_1 to C_5, through polyethylene bottles as a result of autoclaving. The permeation rate of each of these compounds exhibited a direct correlation with its hexane/water partition coefficient. Polack et al. (1970) extended this correlation to phenol derivatives. The same linear relationship was found by Jordan and Polack (1972b) to exist for several other compounds (Fig. 42). Serota et al. (1972) studied the effect of structure on permeability through polyethylene of substituted aniline in aqueous solution. The permeability constants were also found to correlate well with the hexane/water partition coefficients.

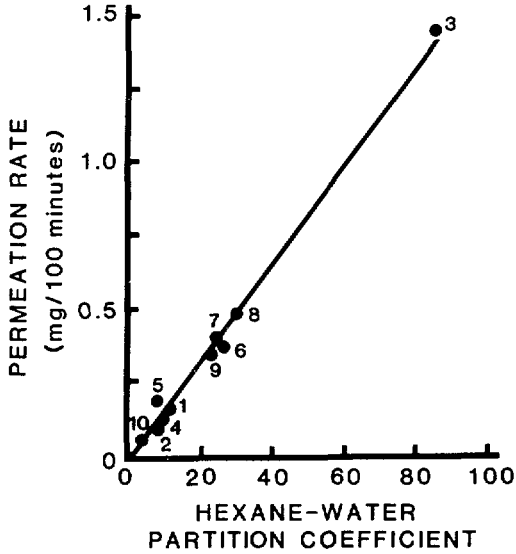


Figure 42—Linear relationship between hexane/water partition coefficient (at 24.4 °C) and permeation rate through polyethylene membrane (6 mil) at 24.4 °C. Initial concentration of 1×10^{-2} M for ten substances. 1, Acetophenone; 2, Anisaldehyde; 3, Anisole; 4, Benzaldehyde; 5, 2,4-Dichlorophenol; 6, *p*-Methylacetophenone; 7, Nitrobenzene; 8, *o*-Nitrophenol; 9, *p*-Tolualdehyde; 10, *p*-Toluidine [Source: Jordan and Polack, 1972b].

Furthermore, Nasim et al. (1972) found the same relationship for substituted benzaldehydes, acetophenones, benzoic acids, and phenols. De and Autian (1975) demonstrated a correlation between octanol/water partition coefficient and permeation rate for a variety of phenol derivatives through polyurethane film at 50 °C. Garrett and Chemburkar (1968c) correlated the chloroform/acetate buffer partition coefficients of barbitals with their permeation rates through Silastic® membranes.

c. pH of the solution

Similar to sorption, the un-ionized, rather than the ionized, species of permeant is primarily responsible for permeation. Figure 43 shows that the permeation-pH profile for *o*-nitrophenol overlaps the hexane/water partition coefficient pH profile. From the relationship shown, it is clear that the effect of pH on permeability is tied to the partition coefficient. This type of permeation-pH relationship was also reported by Roberts et al. (1979) for nitrophenol and aniline in polyethylene bottles, by Nasim et al. (1972) for benzoic acid and aniline with polyethylene film, and by Garrett and Chemburkar (1968c) for barbitals with Silastic® membranes.

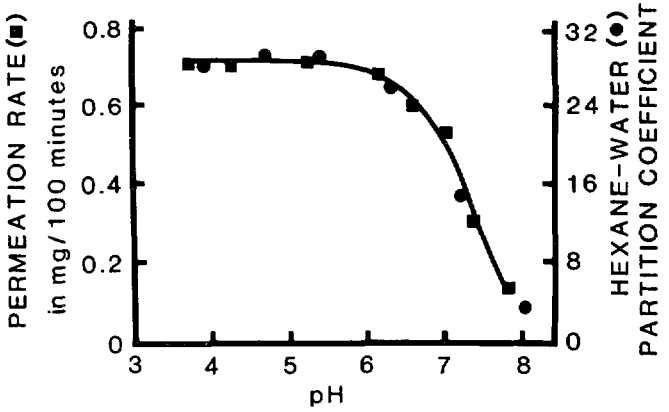


Figure 43—Effect of pH on the permeation rate of *o*-nitrophenol through polyethylene membrane (6 mil) at 35.2° and on the hexane/water partition coefficient of *o*-nitrophenol at 24.4°. Permeation rate measured for initial concentration of 7.18×10^{-3} M (using 0.1M acetate, phosphate or THAM buffer). Key: squares, Permeation rate; circles, Hexane/water partition coefficient [Source: Jordan and Polack, 1972b].

d. Formulation components

Permeation is also affected by other components in the product. The addition of glycerin significantly reduced the permeation of acetophenone through polyethylene membranes (Jordan and Polack, 1972b). The permeation of 4-aminopropiophenone through a Silastic® membrane decreased with an increase in concentration of ethanol in the diffusing solution (Garrett and Chemburkar, 1968c). Nasim et al. (1972) studied the permeation of polyethylene membrane by propylparaben and isobutyl *p*-aminobenzoate and found that any increase in the ethanol concentration reduced the permeability constants. These results can be explained on the basis of changes in the solution/membrane partition coefficient. The solubility of compounds in the solvent of the donor compartment is increase by an increase in ethanol concentration. This change leads to a reduction in the magnitude of the partition coefficient toward the membrane and, thus, slows down permeation of the compounds. When peanut oil was used as the solvent in the donor compartment, permeation of progesterone and dextromethorphan through the Silastic® membrane was reduced approximately 2- to 3-orders of magnitude (Garrett and Chemburkar, 1968c).

The rate of permeation can be increased or decreased in the presence of a complexing agent, and the magnitude of this effect is dependent upon the physicochemical nature of the agent. This fact is exemplified by the

experiments of Nakano and Patel (1970) with *p*-nitrophenol permeating a Silastic® membrane: (*a*) diethylpropionamide, which complexes with the permeant, *p*-nitrophenol, only in a nonpolar environment, was found to enhance permeation; (b) theophylline, which complexes with *p*-nitrophenol only in aqueous solution, was reported to reduce the permeability constant; (*c*) agents that complex with the permeant in both nonpolar and aqueous environments either increased or decreased permeation, depending upon the partitioning behavior of the complexing agents and the relative stability of the complex in both environments.

e. External environment

Since permeation is mainly controlled by partitioning from the donor phase to the polymeric membrane and then by diffusion across the membrane, it has been shown, as expected, that the composition of the receptor solution does not affect permeation rate (Garrett and Chemburkar, 1968c). However, vapor pressure in the autoclave chamber markedly affected the rate of permeation. The results in Table XXV suggest that placing into the chamber the same solution as is in the bottles could reduce the amount lost through plastic bottles during autoclaving. A saturated solution in the autoclave chamber could even increase the concentration in the bottles as a result of reverse permeation.

f. Diffusion in polymers

In permeation once the permeant has entered the polymeric matrix the permeation rate is governed entirely by the rate of diffusion into the matrix. In sorption, however, the rate and extent of sorption are sometimes independent of the rate of diffusion.

Diffusion within polymers has been the subject of many books and reviews; the phenomenon interests scientists in many different disciplines.

TABLE XXV

Effect of Atmospheric Composition in Autoclave[a] on Loss of Permeant from Solution in Polyethylene Bottles

Atmosphere in Autoclave	% Change in Permeant Concentration	
	Benzyl Alcohol[b]	chloroxylenol[b]
Water	−9.8	−32.1
Same solution as in the bottle	−4.9	−6.9
Saturated chloroxylenol	—	+30.8
10% Benzyl alcohol	+56.4	—

a. After Autoclaving at 115°C for 30 min

b. Initial concentration of the permeant was 0.5%

Source: Goss et al. (1968).

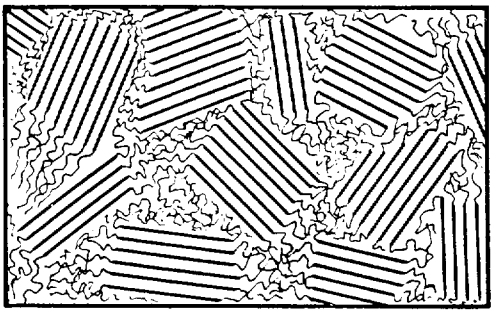


Figure 44—Artist's rendering of polymeric crystalline segments dispersed in a polymeric matrix.

Many theories, models, and equations have been derived to describe this phenomenon. Very few reports concerning the diffusion process, however, have appeared in the pharmaceutical literature.

Unfortunately, most studies of diffusion in polymers have not been done with actual components used in the pharmaceutical package. Rather, pharmaceutical chemists have had to rely upon the suppliers of polymers for data pertinent to permeation. Because it is practically impossible to form identical polymers from batch to batch or to obtain identical polymers from two suppliers, pharmaceutical scientists should be extremely cautious in evaluating the data from the literature or from manufacturers. Whenever a high level of accuracy is required, one should determine the permeability constant and diffusion coefficient of the materials employed.

In simplistic terms, the fact that no two molecules can occupy the same point in space at the same time means that permeant molecules must always travel through spaces, or holes, in the polymer. Polymer chains, in their amorphous regions, create by thermal vibration and rotation voids or spaces for passage of a permeant. Polymer chains, in their crystalline regions, like other inactive fillers, are rigid and do not permit passage of a permeant. Dispersion of crystalline regions in a polymeric matrix is illustrated in Fig. 44. Many of the plastic or rubber materials currently used for pharmaceutical packaging have various degrees of crystallinity. In general, polymers with higher degrees of crystallinity exhibit a lower diffusion rate and become less permeable. Melting of these crystalline materials as a result of elevation of temperature could, consequently, cause a sudden increase in permeability. The crosslinking of polymers, either by irradiation or by chemical reaction, restricts the mobility of the polymer chains to create spaces. Consequently, materials rich in crosslinking show low permeability. Introduction of methyl groups into a polymer chain reduces diffusivity as a result of decreased flexibility of the chain and increased steric hindrance.

The presence of pendant vinyl groups also produces a decrease in diffusivity. The addition of polymer sidechains yields an increase in cohesive energy of the polymer, leading to a reduction in diffusivity. Although predicting permeability from the chemical structure of the polymer can be hazardous, one may explain the trend of permeability by assuming that more spaces means greater permeability.

g. Temperature

The temperature dependence of permeability can be expressed by:

$$P = P_0 \exp(-E_p/RT) \qquad \text{(Eq. 48)}$$

where P_0 is a pre-exponential constant and E_p is the activation energy for permeation. R and T are gas constant and absolute temperature, respectively. This equation implies that plots of log P versus $1/T$ are straight lines.

For permeation of a gas, the permeability constant is a product of the diffusion coefficient and the solubility constant, both of which exhibit a temperature dependency that may be expressed in similar ways:

$$D = D_0 \exp(-E_d/RT) \qquad \text{(Eq. 49)}$$

$$S = S_0 \exp(-H_s/RT) \qquad \text{(Eq. 50)}$$

where E_d is the activation energy for diffusion and H_s is the heat of solution. From Eq. 41, it follows that:

$$E_p = E_d + H_s \qquad \text{(Eq. 51)}$$

The activation energy for permeation by itself has little meaning, except that it is a summation of the activation energy for diffusion and the heat of solution. This point is exemplified by the fact that, depending upon whether diffusivity (which increases with temperature) or solubility (which decreases with temperature) is the dominating factor, the permeability of a gas can either increase or decrease with temperature.

For permeation of a solute from a donor solution through a polymeric barrier, the activation energy is affected by the activation energy for diffusion in the polymer and the heat of solution for the solute in both the polymeric substance and in the donor solution. In most reports, diffusion coefficients, rather than permeability constants, were determined. Some activation energies for diffusion are listed in Table XIII and some activation energies for permeation are given in Table XXIV.

4. Permeation through Plastic Materials

There are far fewer reports concerning permeation across pharmaceutical packaging materials than there are on sorption into these materials.

In a few studies of sorption, the investigators have incidentally acknowledged the possibility of permeation through plastic containers. Tsuei et al. (1980) detected the characteristic odor of chloromethiazole and concluded that not only was the compound absorbed by the plastic IV administration set, but it was also lost to the atmosphere. Aspinall et al. (1980) reported the loss of radio-labeled mercury through a container wall to the atmosphere.

To quantitate permeation, Autian and his co-workers (Rodell et al., 1966; Gonzales et al., 1967; Powell et al., 1969; Serota et al., 1972; Nasim et al., 1972; De and Autian, 1975) studied the permeation of a wide variety of compounds through polyethylene, polyamide, and polyurethane films. The permeability constants for some compounds of pharmaceutical interest are given in Table XXIV. In most cases, the film thickness was about 0.01 cm. According to the data of Gonzales et al. (1967), approximately 100 mg of benzyl alcohol will permeate through a 25 cm^2 area in 48 hr from a 1% benzyl alcohol solution at 50 °C. If the thickness of the film were 0.1 cm, the approximate thickness of a polyethylene bottle, 10 mg of benzyl alcohol could be lost under the same conditions. From Table XXIV, the amount of permeation loss can be determined by the following relationship:

$$\text{Amount lost (g)} = P\ (\text{cm}^2/\text{sec}) \times \text{Surface Area (cm}^2) \times \text{concentration (g/cm}^3) \times \text{time (sec)/thickness (cm)} \quad \text{(Eq. 52)}$$

In a series of reports, scientists in Tasmania determined the permeation of preservatives, such as benzyl alcohol, chloroxylenol, and their derivatives, through polyethylene bottles under autoclave conditions (Russell and Stock, 1966; Goss et al., 1968; Polack et al., 1970). They studied a wide range of organic solutes permeating through a polyethylene film in a diffusion cell (Jordan and Polack, 1972a,b; 1973), and through polyethylene bottles (Polack et al., 1979; Roberts et al., 1979) and further examined some methods for the reduction of solute loss (Miezitis et al., 1979). These methods include adjustment of pH to increase ionization of the solute, selection of a solute with a medium polarity, addition of an organic cosolvent, pretreatment, i.e., presoaking of the bottles, and saturation of the external atmosphere. Most of these techniques were comparable to those described earlier in the sections on Sorption (III.A.3).

Using a simple test that determined the weight lost from polyethylene bags, Parliman (1948) calculated the permeability constant for a variety of solvents. The permeability constants (g/24 h per 100 in^2) for a few solvents of pharmaceutical interest across a polyethylene film (0.001 inch thick) at room temperature are: ethylene glycol, 0.02; water, 0.16; butyl alcohol, 1.2; ethyl acetate, 21; chloroform, 720. Additional permeability

constants were reported by Pinsky et al. (1954) for *n*-propanol, 0.495; acetone, 6.75; benzaldehyde, 6.8; and water, 0.28 when polyethylene bottles were used instead of polyethylene film.

Permeation of a vapor or a gas through a plastic wall can also cause physical or chemical changes in a sterile pharmaceutical product. Oxygen can degrade oxidizable substances, water vapor can hydrolyze moisture-sensitive compounds, and carbon dioxide can alter the pH of the solution. Permeation constants for a number of gases across a very wide range of plastics can be found in *Modern Plastics Encyclopedia* (1981–82 ed., pp. 540–544).

An extensive listing of permeation parameters, such as P, E_p, E_d, and H_s, for a variety of plastics can be found in *Science and Technology of Polymer Films* (O. J. Sweeting, Ed., Vol. II, 1971, Chap. 1). The permeability constants of some commonly used plastics for oxygen and carbon dioxide are listed in Table XXVI.

Permeation of water through polyvinyl chloride bags lacking an overwrap is of particular concern for hospital pharmacists because of the widespread use of Viaflex® containers for storage of IV admixtures. Stauffer et al. (1981) determined the permeation rates of water by weight loss. When 50-ml, 100-ml, and 500-ml bags were hung and exposed to ambient conditions for 84 days, weight losses were 14, 9, and 4%, respectively. The author suggested that permeation loss could be reduced by storing the bags in a refrigerator or freezer.

Using a method outlined in the British Standards (B.S. 2782:1970), MacDonald (1974) determined the permeability to water vapor of test pieces removed from polypropylene bottles, from three types of polyvinyl

TABLE XXVI

Permeability Constants of Plastics for Oxygen, Carbon Dioxide, and Water Vapor at 20 to 30 °C

Plastic	Permeability constants [a]		
	O_2	CO_2	Water [b]
Polyethylene	1.45–7.79	5.68–37.0	15.8–277
Polypropylene	3.04	12.1	92.4
Polyamide	0.050	0.21	92.4–2240
Polystyrene	1.98–33	9.9–48.8	1320
Polycarbonate	2.64	11.2	924
Polyvinylchloride	0.16–0.79	1.35–4.88	343–832

[a] Units: 10^{-10} cm^2 sec^{-1} atm^{-1} for comparison with other units: 1 cm^2 sec^{-1} atm^{-1} = 2.2×10^{10} cc(STP)mil/100 in.^{2}/atm/24 hr. [b] for conversion to weight of water: 1 cm^2 sec^{-1} atm^{-1} = 1.06×10^5 g cm cm^{-2} sec^{-1} cm Hg^{-1}. Source: Lebovits (1966).

chloride bags, and from their polyethylene overwrap (outer bag). The permeability (in mg m^{-2} hr^{-1}) was 7 for polypropylene, 40–119 for polyvinyl chloride; and 8–25 for polyethylene overwraps, As indicated in Eq. (42), the amount of permeation is proportional to vapor pressure differential. The results of MacDonald's weight loss study showed the loss at 33% relative humidity to be twice that at 75% relative humidity. Guess et al. (1967) also reported data for weight loss from five polyvinyl chloride blood bags. As much as 30% loss occurred with storage at room temperature over a 6-month period, as compared with less than 3% loss with storage at 5 °C.

Permeability constants for water vapor of several plastic films are given in Table XXVI. Multiplication of the permeability constant by 215 gives for each plastic a water vapor transmission rate (mg/day), based on use of a film 1 mm thick, 1 mm^2 surface area, and a pressure differential of 100% relative humidity.

5. Permeation through Elastomers

The primary concern associated with permeation through elastomeric closures is water vapor transmission. Portner (1955) reported the decomposition of a lyophilized biological product by atmospheric moisture transmitted through rubber closures. Permeation of oxygen can also cause the degradation of compounds that are prone to oxidation. On the other hand, the permeation of drug substance or preservatives through elastomers has received only minimal attention, because only a small amount can permeate. As compared with plastic containers, the surface area of a rubber closure in contact with a drug solution is relatively small; in addition, the thickness of the barrier is considerably greater. Both factors result in conditions unfavorable for permeation.

The permeation phenomenon has been studied in great detail for a variety of gases (helium, hydrogen, oxygen, nitrogen, carbon dioxide), and hydrocarbons (methane, ethane, and benzene), etc. Reports of these studies have appeared mainly in the journals of polymer or rubber sciences. A valuable comprehensive review was provided by van Amerongen (1964) who compiled numerous tables and figures that serve as a ready reference for permeability constants, solubility constants, and other parameters. Table XXVII provides the permeability constants (P), diffusion coefficients (D), and of solubility constants (S), of four commonly encountered types of pharmaceutical rubber for O_2, N_2, and CO_2. It should be remembered that permeability is a product of the solubility constant and the diffusion coefficient ($P = DS$). Diffusion coefficients invariably depend upon the collision diameter of the gas molecule as determined from measurements

TABLE XXVII
Permeability Constants, Diffusion Coefficients, and Solubility Constants, of Various Rubbers for Oxygen, Nitrogen, and Carbon Dioxide

Rubber	Permeability[a] Constant (10^{-8} cm^2 sec^{-1})			Diffusion Coefficient[b] (10^{-6} cm^2 sec^{-1})			Solubility Constant[a] (cm^3 per cm^3)		
	O_2	N_2	CO_2	O_2	N_2	CO_2	O_2	N_2	CO_2
Natural	17.7	6.12	99.6	1.58	1.10	1.10	0.112	0.055	0.90
Neoprene	3.0	0.89	19.5	0.43	0.29	0.27	0.075	0.036	0.83
Butyl	0.99	0.247	3.94	0.081	0.045	0.058	0.122	0.055	0.68
Silicon	400	200	1600	17.0	13.2	—	0.126	0.081	0.43

[a] At 0°C and 1 atm. [b] 25°C

Sources: Permeability constants and solubility constants are from van Amerongen (1964), diffusion coefficients are from Stannett (1968).

of gas viscosity. Oxygen, nitrogen, and carbon dioxide molecules have relative diameters that rank in ascending order, therefore, diffusion coefficients for these three gases rank in descending order. Permeability constants for silicone rubber are much greater than those for other types of rubber. Silicone rubber shows a very high diffusivity for gases, apparently connected with the high internal mobility associated with the Si-O-Si configuration in the silicone polymer chains. The low diffusivity of butyl rubber is attributed to the steric hindrances in its molecular configuration. Although O_2 and CO_2 show comparable diffusivity, the permeability constants for CO_2 are much greater than those for O_2 because of the greater solubility of CO_2 in rubber.

Many organic solvents cause rubber to swell. The extent of swelling depends upon the compatibility of the rubber and the solvent, the degree of crosslinking of the rubber, and the relative vapor pressure of the solvent. Natural rubber, in general, swells faster than butyl rubber because the former has a higher diffusivity than the latter. In swollen rubber, permeability to air is increased markedly. The swelling agent has a great effect on the diffusion properties of a rubber with inherent low permeability and diffusivity, i.e., the effect is greater for butyl rubber than for natural rubber. To summarize, butyl rubber is slow to swell but, once swollen, its barrier properties are greatly reduced. Although natural rubber swells rapidly, its permeability to air is affected only slightly. These factors are important in the selection of a rubber closure for products containing propylene glycol or fixed oils.

Water deserves special discussion because it is the most commonly used ingredient in sterile pharmaceuticals. Its diffusion properties in rubber

differ from those of most gases and organic liquids, and it also affects various properties of the rubber. The permeability of water *per se* has not been studied in great detail.

The water-absorbing capacity of various rubbers was reported by Portner (1955). When rubber closures were held at 100% relative humidity, the amount of water absorbed was 2–3 mg/cm^3 for natural, 14 mg/cm^3 for neoprene, 1–8 mg/cm^3 for butyl, and 19 mg/cm^3 for silicone. Lowry and Kohman (1927) reported that, below a relative vapor pressure of 0.75 (75% relative humidity), the maximum quantity of water taken up at the saturation point is roughly proportional to the vapor pressure. Above a relative vapor pressure of 0.75, the amount of water absorbed at equilibrium increased greatly, resulting in swelling of the rubber in many cases. Impurities, fillers, or other water-binding ingredients in rubber are primarily responsible for the solubility of water in rubber. If two or more rubbers are to be considered comparable, even the excipients use in them must match.

Diffusion of water molecules in rubber is slower than that of oxygen. Diffusion follows Fick's and Henry's laws only at relative vapor pressures below 0.75. Again, the diffusion process controls the amount of water uptake. Lowry and Kohman (1927) showed experimentally that the amount of water absorbed is proportional to the square root of time, and that the time required to reach a given stage of saturation is proportional to the square of the thickness of the rubber. Drying, or desorption of water, is simply the reverse of the process of absorption. For this reason, one should expect that a relatively long time will be needed to dry out the residual amount of moisture in rubber closures, because the closures are not thin.

The permeability constants for water vapor of various rubber compounds, determined by ASTM D-814-76 (Buchanan, 1980) are listed in Table XXVIII. Values reported in two other sources are shown for comparison. The data demonstrate that butyl rubber provides the best moisture barrier. Teflon® coating of a rubber closure can effectively reduce the amount of leaching, but has little effect against permeation of gases or water vapor.

Anderson and Motzi (1982), employing a diffusion cell similar to the one shown in Fig. 36, determined the permeability (by Eq. 37) and diffusion coefficient (by Eq. 39) of natural and silicone rubber for methylparaben. The diffusion coefficient of silicone rubber is almost 70 times greater than that of natural rubber. Since the permeability differs only by a factor of 10 it can be deduced that methylparaben is 7 times less soluble in silicone rubber than in natural rubber. Partition coefficients calculated by Eq. 40 for methylparaben between water and rubber closures are included in Table XIX. The attempt of Anderson and Motzi (1982) was to predict sorption

TABLE XXVIII
Permeability Constants of Rubbers for Water Vapor

Rubbers	Permeability constants at 20–30 °C	
	10^{-4} mg-mm-mm^{-2}-day^{-1}	10^{-10} g cm cm^{-2} sec^{-1} cm Hg^{-1}
Natural	25.6[a]	1.84[b], 2.49[c]
Neoprene	11.7[a]	0.73[b], 1.45[c]
Polybutadiene	116[a]	4.07[b], 3.93[c]
Butyl	0.278[a]	0.03–0.16[c]
Chlorinated butyl	—	0.096[b]
Silicone	408[a]	562[b], 8.51[c]

[a] Buchanan (1980) 1 mg-mm-mm^{-2}-day^{-1} under 100% relative humidity is equivalent to 2.05×10^{-7} g cm cm^{-2} sec^{-1} cm Hg^{-1}. [b] Barrie (1968). [c] Lebovits (1966).

of methylparaben by a commercial rubber closure through the use of mathematical models and values obtained from the permeation of a rubber membrane.

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