Elastomeric Closures for Pharmaceutical Packaging

By GEORGE H. HOPKINS

The use of specialized rubber products for the pharmaceutical industry is reported with respect to closures. The applicable physical and chemical properties of elastomers are discussed in some detail; their pertinence to the closure function and the methods by which they can be altered within specified limits are outlined. Those properties that are predominantly an inherent function of the particular polymer system are identified, and representative values of the most popular elastomer types are given. Coring, permeability, sorption, and leaching are considered the most pressing problems in present closure applications, and comments are offered regarding specific areas of improvement in each of these functions. A new elastomer is promising in the prevention of leaching. The effectiveness of several representative polymeric coatings as leaching barriers is measured on present closures.

THE PHARMACEUTICAL industry is an important consumer of specialized rubber[1] products for packaging applications. The primary use of rubber in this field may be classified under the general heading *closures*. A closure is used to establish a seal in the open end of a container, to confine a product within a given area, and to protect the packaged material from contamination by outside influences. The closure's function is not confined to serve merely as part of the container; it must also permit removal of the product when needed, usually by single or multiple penetration with a hypodermic needle.

A unique combination of properties qualifies rubber for use as a closure. It permits easy passage of a hypodermic needle without bending or blunting the point and without requiring undue force to penetrate the diaphragm, and it maintains a sufficient resiliency to provide immediate reseal after withdrawal of the needle. The elastomer is easily molded and is capable of sterilization by any of the current production techniques. Rubber's flexibility, resilience, and elasticity give it the ability to adapt itself to depressions and crevices and conform to contours by pushing tightly against the opposing sealing surface; thus, fluid flow through the interface is prevented.

Considerable progress has been made from the time when the major elastomer available for use as a closure was natural rubber, then defined (1)

as "a botanical substance of no fixed composition." With the advent of synthetic elastomeric materials such as polyisoprene, butyl, neoprene, butadiene copolymers, silicone, urethane, and others, combinations of properties are demonstrated different from those available with natural rubber.

Because of differing applications, where either a single property or an unusual combination of properties is of particular importance, no single elastomeric composition can serve all uses. The growing legion of pharmaceutical preparations that are administered parenterally has focused more and more attention upon the favorable and unfavorable aspects of rubber.

Kaestner (2) has said, "We are still seeking the perfect closure; one that is chemically inert, one that can be easily worked, one which when pierced with a needle will not core, and one which will not bleed." Milosovich (3) wrote that, although closures produced by compounding rubber have been found superior to those produced from other materials there are areas where they fall short of perfection.

Over the past several years, many investigators have analyzed the properties of rubber pertinent to closure use, and specifications have been suggested (4–6) or actually adopted (7). The British Standard was discussed by a panel (8) before the Parenteral Drug Association in 1961.

DISCUSSION

Compounding

Rubber is capable of modification by compounding to achieve a wide range of values in any single property. The compounding materials may be classi-
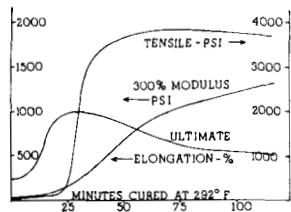
Fig. 1.—Properties *vs.* cure time.

fied under the following general headings: (*a*) elastomer, (*b*) vulcanizing agent, (*c*) activator, (*d*) accelerator, (*e*) reinforcing agent, (*f*) plasticizer, (*g*) antioxidant, (*h*) antiozonant, (*i*) pigment, and (*j*) special purpose.

Some or even all of these materials may be present in a given formulation, depending upon the desired end characteristics. The vulcanization of a compounded rubber stock is a complex process, but its main feature is the introduction of cross-links between otherwise independent linear molecules of the raw rubber. All the physical properties of rubber do not reach their optimum values after the same length of vulcanization time.

The vulcanizing process requires that heat and pressure be applied for a given length of time. The vulcanization of rubber is accompanied by a considerable change in mechanical properties as the vulcanizate is formed (9); therefore, the course of cure can be followed by graphing the values of a selected property against time.

The curve in Fig. 1 ascends as the curing process starts, then flattens at some near-maximum value and forms a plateau which may be quite short or relatively long, depending upon the property measured and the type of accelerator system used. At the end of the plateau, a sudden break downward indicates that reversion has set in. Reversion is the state where the breakdown of cross-linkages predominates over the simultaneous reformation of cross-linkages (10). Since the time required to reach maximum value and the length of the plateau varies with the property being tested, it may be impossible to produce a material giving maximum values simultaneously in two, three, or more properties.

The term "reinforcement" is used to describe the physical effects produced in a rubber vulcanizate by the inclusion of a second solid phase. The finely divided materials used as reinforcing agents affect elastic modulus, hardness, stiffness, resilience, tensile strength, tear resistance, abrasion, and other properties of the finished vulcanizate.

Basic Physical Properties

The various properties of closures that are of interest to the pharmaceutical user are discussed below. Representative values are given for the most popular elastomers.

A. Sorption.—The sorption of materials by rubber is of prime importance, for this area encompasses an admitted shortcoming of present closures. An ingredient of a pharmaceutical preparation, if sorbed into the elastomeric closure to any appreciable extent, could eventually result in a product which does not meet specifications. Sorption is affected by temperature, concentration, polarity, surface-active agents, and pH (11).

Since a great many parenteral preparations are aqueous in nature, the sorption of water has been studied by many investigators (3, 12). Scott (13) found that absorption upon immersion is proportional to the square root of the time period. Clark and Swartz (14) developed an interesting method of measuring water sorption by using radioactive isotopes and working with silicone-treated rubber closures. Hopkins (15) reported on the amount of water sorbed by test closure 20-mm. disks after 42 days of complete immersion, following predrying in a vacuum oven. Butyl absorbed 0.74%, natural rubber 1.54%, and neoprene 6.16% water. Variations in the cure conditions had no measurable effect. Solvents other than water have been investigated for use in pharmaceutical preparations involving difficultly soluble materials (16, 17). The effect of binary solvents on rubber has been reported (18).

The sorption of preservatives from solution has been studied by many investigators. The most recent was Lachman *et al.* (19), who for the first time considered separately the loss of preservative content traceable to the instability of the preservative itself, and also that due to the influence of the closure. Lachman (20) reports the per cent retention of methylparaben after 12 weeks of inverted storage at 60°, where he finds butyl retains 100% of initial concentration, natural rubber 94.5%, and neoprene 89%.

B. Solubility (Swelling).—This property is of minor interest to pharmaceutical manufacturers (21), except as it represents an extension of the sorption process. Sorption of a solvent into elastomers leads to the swelling of the material to a degree dependent upon the type and concentration of cross-links and the nature (polarity) of nonrubber compounding ingredients and the nature of the solvent. Polymers mix with low molecular weight liquids chiefly by diffusion (22). Swelling equilibrium is reached where the tendency of the solvent to swell the rubber is counteracted and finally stopped by the stretching of the chain network.

Although the natures of the elastomer molecule and of the solvent are important, the effect of the creation of additional cross-links during vulcanization and the loss of intermolecular forces due to thermal or oxidative degradation can be measured. Thus, swelling has been used to measure the degree of cure (23) and the onset of reversion (24). Boonstra and Dannenberg measured the effect of fillers and concluded that, compared to the effect of polymer–solvent interaction, the influence of fillers on swelling is relatively small.

Salomon and Van Amerongen (25) investigated the effects of solvent, polarity, temperature cross-linking, pressure, and mechanical strain. Using chloroform as a solvent, the equilibrium swelling volume of unfilled elastomer vulcanizates is reported to be butyl 350%, natural rubber 460%, neoprene 520%, and Buna N 630%. Tanaka (26) reports that urethane is slightly higher than natural rubber. Le Bras (27) compared the resistance of various elastomers to oil by measuring per cent volume swelling after 7 days immersion at 160° F. and reports butyl 220%, natural 170%, neoprene 25%, and Buna N 3%.

C. Moisture Vapor Transmission.—In the packaging of moisture-sensitive materials such as penicillin, dihydrostreptomycin, and lyophilized products, it is essential to obtain a package that will pro-

TABLE I.—RUBBER DIFFUSION CONSTANTS

Gas	Mol. Wt.	Diffusion Constant[a]
H_2	2	8.5×10^{-6}
O_2	32	2.1×10^{-6}
CO_2	44	1.1×10^{-6}

[a] Square centimeters per second at 25° C.

TABLE II.—RELATIVE GAS PERMEABILITY

Elastomer	H_2	N_2	O_2	CO_2	Air
Natural rubber	100	100	100	100	100
Buna N 80/20	51	31	35	48	33
Buna N 73/27	32	13	17	24	15
Buna N 68/32	24	7.5	10	14	8.5
Buna N 61/39	15	2.9	4.1	5.7	3.4
Butyl	15	4.0	5.6	4.0	4.8
Neoprene G	27	14	17	20	15

vide protection; a suitable closure is vital. Considerable work has been performed in this area and a test method to measure the MVT of the actual closure and container combination has been developed. Technical Report No. 8 and four appendices thereto (28) have been circulated and describe the moisture vapor transmission of many formulations. Butyl rubber has been found to have no appreciable rate of MVT after exposure to 95–100% RH at 47.5° for 20 weeks. Natural rubber averages about 7 mg. of water per gram of alumina desiccant, neoprene 8 mg., Buna N about 30 mg., and silicone and polyvinyl chloride about 100 mg.

D. Gas Permeability.—To those who package preparations under vacuum or under a blanket of some inert gas, such as nitrogen, it is essential that this situation be maintained through the life of the product. The gas permeability of elastomeric polymers has been studied and the parameters measured.

It is known that rubber membranes are permeable to gases and that the rate of permeation is a specific function of a given gas and rubber system. Van Amerongen (29) explains that the process involves solution of the gas molecules on one side, diffusion through the rubber membrane, and evaporation from the other side. Thus, permeation is made up of several independent processes. Solution and evaporation are governed by Henry's law, and diffusion is governed by Fick's law. In this consideration, diffusion is by far the most important and depends only to a slight extent upon the degree of vulcanization. Rubber is intermediate between solid and liquid substances (30) and rather more like a liquid, although it differs from an ordinary liquid because the diffusion constants decrease notably with increase in molecular weight of the diffusing substance.

The rate of diffusion of gases through elastomers depends mainly on the interaction forces between the elastomer molecules, and is therefore lower in methylated polymers and in elastomers with polar groups. The size of the molecule of the diffusing material is also important. Table I is taken from Grun and illustrates the effect of molecular weight.

The permeabilities at 25° for various elastomers relative to natural rubber (after Van Amerongen) are given in Table II. The influence of the polar nitrile group is particularly evident if one studies the

effect of increasing acrylonitrile content in the butadiene-acrylonitrile (Buna N) copolymer.

Summary of A, B, C, D.—Sorption, solubility (swelling), gas, and water vapor transmission are interrelated characteristics and are subject to similar influences. The dominant factor in all cases is the molecular structure of the elastomer, the number of cross-links per cubic centimeter of polymer, or the average length of molecular chain between cross-links. The main determining mechanism is diffusion and is determined by the size of the invading molecule and the length of the free path. The polarity of the elastomer and that of the diffusing medium have a direct bearing. The degree of vulcanization, temperature of test, and the incorporation of filler have measurable but relatively small effect. In gas transmission, the parameters affecting permeation do not change materially during the process; but in sorption of liquids, the swelling of the elastomer reduces the number and size of "holes" in the polymer membrane and therefore changes the rate.

E. Durometer.—A convenient means for obtaining an indication of the approximate hardness of rubber articles is furnished by determining the indentation of rubber with the durometer (31). As shown in Fig. 2, the instrument consists of a tapered indentor point backed by a calibrated spring and acts upon at least 0.25 in. of thickness. Surface indentation rarely bears any relation to the ability of a rubber product to function properly and therefore is not vital to pharmaceutical practice; but it has some significance where it reflects the resistance to penetration of a hypodermic needle. As part of the closure function, stoppers must be soft enough to conform to irregularities in the glass neck and lip, and this requirement is usually served if the durometer of the closure is between 45 and 65 shore A.

In some ways it has a relationship to resilience, which is a composite property depending upon hardness and internal friction of elastomer (32). Table III (after Shaw) gives the inherent resilience of elastomers.

Fig. 2.—Shore durometer, type A-2.

TABLE III.—INHERENT RESILIENCE

Elastomer	% Recovery
Natural rubber	92
Neoprene	87
Thiokol	83
GRS	72
Buna N (low nitrile)	67
Buna N (high nitrile)	43
Butyl	33

TABLE IV.—NUMBER OF CORES PER 100 PUNCTURES
(20-GAUGE NEEDLE)

	Regular	Disposable	"Dull Heel"
Polyurethane	7	...	0
Natural gum	10	...	0
Buna N	15	...	0
Natural filled	23	...	0
Butyl	29	28	0
Neoprene	32	24	0
Silicone	55	...	0

The durometer is mainly affected by differences in vulcanization time and the amount and type of reinforcement.

F. Compression Set.—This property is determined by measuring the residual decrease in thickness expressed as per cent of original deflection after the constant application of a known load or the maintenance of a definite deflection for many hours of time. The residual decrease is measured 30 minutes after removal of stress (31). The initial set is a product of plastic flow and elastic deformation. Usually, if recovery time is permitted equal to the time of loading, rubber set is quite small. Secondary relaxation sets in and becomes dominant after long periods at normal temperature or short periods at high temperature and is due to oxidative deterioration of the rubber molecule (33). This property indicates within rough limits the ability of a closure to maintain a good tight seal.

G. Tensile Strength.—Tensile strength is the force per unit cross sectional area applied at the time of rupture of the specimen when it is stressed in tension. Elongation is usually measured concurrently. Tensile strength has little application to pharmaceutical packaging because only rarely is a closure stressed in tension in actual use.

Summary of E, F, G.—These properties—durometer, compression set, and tensile strength—are affected by the amount and type of particulate reinforcement and also by differences in accelerators and in vulcanization time. Although compression set has some application to conditions of use, tensile and hardness are of little value in a closure specification. The traditional use of these properties is for manufacturing control of formulation and vulcanization.

H. Coring.—This term is used to describe the cutting away of fragments from rubber stoppers during the passage of a hypodermic needle. In the first comprehensive investigation of this phenomenon, Hopkins (34) measured the factors influencing the coring of rubber closures. Although 11 contributing factors were listed, he discovered that a simple modification of the common needle design would eliminate the production of rubber particles due to coring. This conclusion has been verified by subsequent investigators—Padgett (35), Lindenmeyer (36), and Michel (37).

In spite of the fact that this paper was published in 1958, no needle manufacturer has made such a "dull heel" needle commercially available, although several have developed the design in experimental production successfully. One manufacturer has discovered that the application of silicone to needles will reduce coring as long as the lubricant stays on the needle surface, usually for one or two punctures.

The closure manufacturers are consistently requested to make noncoring formulations, and constant research continues. However, should they be successful, the problem is but half solved. Gibson and Norris (38) studied the problem of skin fragments removed by injection needles. Working with surgically excised live tissue and material available at autopsy, they concluded after 300 tests that a needle thrust through skin commonly cores out a fragment of tissue. They warned that inclusion dermoid cysts may follow subcutaneous injections. Tinker and Hill (39) report that literature abounds in instances of cross infections, abscesses, and other conditions which may be traceable to parenteral injections. If we have to work with present-day needles, the development of noncoring closures will have to be accompanied by the development of noncoring humans.

With the needles normally used today, unpigmented natural rubber and polyurethane are the lowest coring elastomers, followed by Buna N, pigmented natural, butyl, and neoprene. Silicone cores on every thrust, and many cores lodge in the needle. With a "dull heel" needle, no cores are produced in any of these elastomers. (See Table IV.)

I. Friction.—The sliding properties of rubber closures are important in the automatic chute feeding of stoppers to the capping station of the packaging line. Insertion into the glass bottle should be positive; but stoppers are designed with an interference fit, and excessive frictional drag may prevent seating. Rubber plungers for single-dose cartridges should slide down the barrel without requiring undue force.

Rubber is a state intermediate between liquid and solid, and the ordinary laws of friction are not applicable (40). A force applied tangentially to the top surface of an elastomer may move that surface, while the base remains at rest. The unmodified rubber has a high coefficient of friction (otherwise, tires and erasers would not work), but this may be altered to serve the needs of the user of closures.

There are several methods of modifying the rubber surface to reduce the friction coefficient: controlled surface oxidation [e.g., West Co. "oxiglazing" process (41) or controlled ultraviolet exposure], incorporation of waxes or oils which bloom to the surface, and the application of external lubricants such as water or silicones.

A method was developed recently (42, 43) to impart lubricity to rubber articles by graft polymerization involving perfluorination of the surface structure. By converting some of the CH groups near the surface into CF groups, the surface-free energy is reduced, and the coefficient of friction is lowered dramatically.

Chemical Reactivity

Once the desirable properties have been built into the elastomer formulation, it is essential that they change as little as possible during the life of the product. The subsequent reaction of the vulcanizate with outside influences is to be avoided insofar as possible. This is difficult to achieve when the pharmaceutical customer for closures subjects them to multiple washings, rinsings, autoclavings, dry heat cycles, then exposes them on one side to the most ingeniously contrived reactive organic com-

TABLE V.—LEACHABLE THIAZOLE

	Water	Isopropyl alcohol
Uncoated rubber	140	140 p.p.m.
Urethane coating	46	91
Y-40 coating	39	79
Teflon coating	a	a
Polyurethane stopper	a	a

a No peak; background absorbance only.

pounds known to man—in company with antioxidants, preservatives, ultraviolet stabilizers, pH buffers, and powerful solvents. The other side is exposed to light, heat, dust, bacteria, and fungi.

The chemical unsaturation of elastomers provides points of attack for oxidation and ozonation, the two most common examples of surface reactivity of elastomers.

Oxygen attacks rubber by initiating chain scission and further cross-linking through a free-radical autocatalytic mechanism, thereby reducing the desired flexibility, elasticity, and resilience. Antioxidants are included in the rubber formulation to inhibit this reaction. The most acceptable antioxidant materials are aromatic secondary amines or aromatic hindered phenols. The residues from some accelerators are also quite effective as antioxidants (44, 45).

Ozone reacts directly with rubber to form an ozonide of the basic rubber hydrocarbon, yielding a whitish blush on the surface known as frost (46, 47). This is common with natural and butadiene-acrylonitrile stocks, while neoprene and butyl are relatively resistant, and polyurethane is virtually immune (48). The ozonide when formed is hard and brittle; but if undisturbed, it serves as a protective film to decrease further penetration. To protect the surface from this reaction, antiozonants are added to the formula, usually in the form of paraffinic waxes or oils which bloom to the surface and form a protective film (49) on the surface of the elastomer.

Sulfur-cured elastomers frequently have sulfides available at the surface (50), and precipitation can take place with many metal ions. For example, these preparations are not recommended for use with mercurials (51, 52). There are other types of curing systems which will produce closures compatible with mercurials.

Leaching

Leaching is the result of a solvent coming in contact with a rubber surface and extracting soluble materials therefrom. It is probable that many of the compatibility problems proved to be due to rubber closures stem from the leaching of some soluble substance from the stopper into the preparation.

Analysis of leached materials showed that they are generally accelerator residues, antioxidants, antiozonants, processing oils, and sulfides. The effects appear to be discoloration, precipitation, or change in pH. Since these materials are essential for the formulation of elastomers having the desired properties outlined previously, they cannot be eliminated from the compound. Derivatives of mercaptobenzothiazole are used for about two-thirds of the acceleration systems in general use today, and the zinc salt of mercaptobenzothiazole is a common extract. The next most used system involves

thiuram sulfides which yield the zinc salt of dithiocarbamates. That materials can diffuse through rubber was noted earlier in this paper.

Alteration of Surface Reactivity

In recognition that these surface reactions could be modified if some inert barrier could be interposed between the rubber surface and the several reactants, closure manufacturers have developed coatings for rubber to perform this function successfully.

With a rubber formulation accelerated with mercaptobenzothiazole and using distilled water as a solvent, the efficiency of several coatings when applied to such a formulation were evaluated. After 5 weeks of inverted storage at 90°, the contents of the bottles were subjected to spectrophotometric assay. As a corollary to this, 5 weeks of inverted exposure to isopropyl alcohol at room temperature also was included. The results are given in Table V.

Obviously, the coatings in Table V effectively inhibit the leaching of material, and one of them prevents the transfer of soluble material from the closure into the contents of the bottle. The special urethane stopper also prevented a significant transfer to the solution.

The other alternative to a protective coating barrier between the elastomer and the extracting medium is to change to another elastomer that does not contain leachable materials as a necessary part of its formulation. One such elastomer has been developed and is being evaluated. (See Table V.) It is a special type of urethane polymer which seems to have considerable merit, even though it is more expensive than some of the other elastomers discussed.

Stability

So that pharmaceutical preparations may have a useful shelf life, it is essential that these preparations be so formulated and packaged that they are known to be stable for the required time. The literature is full of reports on various phases of stability testing. In fact, Jones (53) reports that a recent postgraduate school for English pharmacists on "the stability of pharmaceutical preparations" lasted 1 week without covering the subject. Garrett (54) and Lachman (19, 20) are two of the most prolific contributors in recent years.

Pharmaceuticals are subject to degradation by light, heat, auto-oxidation, hydrolytic decomposition, coagulation, and interaction with the closure. By running ampul controls, as recommended in the Packaging Institute procedure, closure interaction can be separated from the other mechanisms. Accelerated aging techniques are undependable (53–55), and long time tests are recommended.

As with other properties discussed, long-term compatibility is dependent upon the specific drug formulation and the closure involved (56). Prediction of stability from experience with other similar systems is to be avoided. A closure with low sorption and a minimum of leachable ingredients should function satisfactorily for most applications.

General Aesthetics.—Color, shape, odor, and surface texture are rarely performance specifications, and these properties fall into the area of aesthetics. Those familiar with present-day closures realize that our capabilities in this area seem to be adequate for current requirements.

Recommendations.—The author believes, as advocated by E. Meyers (56), that "a rubber closure should be selected on the basis of experiments made with it and the solution to be packaged in contact with the closure." Candidate materials for this type of selective test can be suggested by the closure manufacturer if the nature of the solution composition is made known and if the most important performance requirements are identified.

Once a particular closure formulation is found satisfactory, it is recommended that the pharmaceutical purchaser and the closure supplier construct a mutually acceptable specification. Subsequent shipments of the closures will be checked against the specification requirements and certified by the manufacturer as meeting the specification. The purchaser may select certain tests from the specification for use as quality control checks. This type of cooperation between supplier and consumer should result in considerable improvement over present conditions.

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ERRATA

In the article titled "One-Phase Solvent Systems for Paper Chromatography. Mixtures of *n*-Butanol, Acetic Acid, and Water" (1), the following corrections should be made in the symbols appearing in Fig. 1 on page 795:

1. P_l and B_l should be read for P_t and B_t, respectively.
2. The above terms and B_u, P_u, and M_u refer to the nearest points marked ⊡.

(1) Betts, T. J., THIS JOURNAL, 53, 794(1964).