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Plastics in Pharmaceutical Practice and Related Fields. Part I

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[Contents for Part II will accompany the concluding part of Dr. Autian's Review Article next month.]

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first commercial plastic and soon was being used as denture plates, parts of wearing apparel (wipe-clean collars, cuffs, etc.), windows, photographic film and in 1882, the first motion picture film.¹ Fraenkel (10) in 1890 recorded the first published information in the use of Celluloid in surgery as a replacement of bone in a portion of the skull of a human.

Celluloid reigned supreme as the only plastic material for a period of four decades until Dr. Leo Henrik Baekeland in the year 1909 developed a phenol-formaldehyde resin which was given the name of *Bakelite* for its creator (9). The '20's and '30's saw the introduction of other plastic materials which, in a real sense, gave rise to a new industry—the plastic industry. As a brief review of the chronological history of plastics development, the reader should see Table I.

TABLE I.—A CHRONOLOGICAL HISTORY OF PLASTICS DEVELOPMENT*

Date	Material
1868	Cellulose nitrate
1909	Phenol-formaldehyde
1909	Cold molded
1919	Casein
1926	Alkyds
1926	Aniline-formaldehyde
1927	Cellulose acetate
1928	Polyvinyl chloride
1929	Urea-formaldehyde
1935	Ethyl cellulose
1936	Acrylic
1936	Polyvinyl acetate
1938	Cellulose acetate butyrate
1938	Polystyrene or styrene
1938	Nylon
1939	Polyvinyl acetals
1939	Melamine-formaldehyde
1939	Polyvinylidene chloride
1942	Polyester
1942	Polyethylene
1943	Silicones
1943	Fluorocarbons
1945	Cellulose propionate
1947	Epoxy
1948	Acrylonitrile-butadiene-styrene
1956	Acetal resin
1957	Polypropylene
1957	Polycarbonate resin
1959	Chlorinated polyether

* "Modern Plastics Encyclopedia"—Issue for 1962, New York, p. 18.

Each of the plastics has an interesting story and one must go to published texts on plastics to appreciate the scientific minds of individuals and groups who helped synthesize these materials. Swallow (11) gives a very revealing and at times amusing account of the developments leading up to the first isolation of polyethylene, which as the author points out really commenced in 1932

¹ A point of reference should be made here. Polystyrene has been known for over a hundred years and, in fact, a German pharmacist, Simon, is credited with the discovery of the styrene monomer in 1839 but its commercial use had to wait until around 1938.

when he (Swallow) and Perrin, working for Alkali Division of I.C.I., England, recommended that studies on chemical reactions at high pressures should be conducted. Now that polyethylene was prepared, what possible market would be open to it? On this point Swallow writes:

Much is written, today, on the way in which a new product should be developed with a view to shortening the time between its discovery and its large scale production and commercial availability. To use phraseology of today it would have been difficult at that time to have carried out a "Market Survey" which would have led to any profitable conclusion, but here again the role of chance played a part.

The chance Swallow refers to was the interest by those in the submarine cable field to find a material which would replace the insulation used for submarine telephone cables and in 1939 enough material was produced to insulate one nautical mile of submarine cable. The entry of England into the World War in the same year provided the coming of age for polyethylene and perhaps the saving of England during the early years of conflict. English scientists were working feverishly to develop a super-secret detection device (radar) for announcing the coming of enemy planes over their island. It became clear to the scientists that if radar was to be a practical success a new material must be found for insulating cables and other components of radar which could effectively handle high voltages needed in radar detection. The new material, it was soon to be found, was polyethylene. Perhaps no greater tribute could be paid to this plastic than by the inventor of radar, Sir Robert Watson Watt, who said: "And so polyethylene played an indispensable part in the long series of victories in the air, on the sea, and on land, which were made possible by radar" (12).

In the field of plastics one must recognize the contribution of many individuals from many countries but several deserve added attention, as for example W. H. Carothers (U. S. A.—nylon), Dr. K. Ziegler (Germany—low pressure method for producing plastics), and Professor Natta (Italy—isotactic plastics). It appears that the real history of plastics is yet to come. What has been recorded for the accomplishment of plastics in the past will be of small magnitude to what is to be expected in the future of the material called plastics.

Definitions

At the onset, one point must be made clear to the reader. Plastics cannot and should not be considered as one type of material but rather

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extremely high pressures (15,000 to 30,000 p.s.i.) while high density can be synthesized at moderate pressures with suitable catalysts. Medium density polyethylene may be prepared by a modification of the high-pressure method or by combining portions of low and high-density polyethylene.

Little information can be revealed on the structure of polyethylene by simple chemical methods other than elucidating the empirical structure, $(CH_2)_n$ etc. Various physical methods of analysis have been used and are being used to describe the structure. It is known, for example, that the polymer molecule may have from 800 to 100,000 carbon atoms, primarily in a straight chain structure. In the early days of polyethylene it was believed that each molecule had one terminal ethylene group and one or two methyl groups in each molecule. With improvement in instrumental analysis, it

was soon realized that the original model of the polymer (low density) was in error and that the polymer contained branched chains, a number of methyl groups (approximately two or three per 100 CH_2 groups), several types of unsaturations and several polar sites in the form of carbonyl or keto groups. A composite of these structures may be seen in Fig. 1 taken from Kresser (17).

As with most polymers, the size of the polymer will play a very important role in imparting certain physical and mechanical properties to a finished plastic material. Unlike pure chemical compounds, polyethylene as well as other plastics, is not composed of an exact molecular size but rather that a distribution of molecular sizes are present. It is thus impossible to assign an exact molecular weight to a particular polyethylene and whatever value is assigned is some form of an average value. The determination of even these average molecular weights for high polymers is not a simple task and consequently highly refined physicochemical methods are used in an attempt to find a molecular weight. Since there are great technical problems associated with molecular weight determinations of high polymers, a number of methods for expressing molecular weight or size are evident in current practice and one must understand there may be considerable differences of values from one method to another. Techniques for these determinations are found in standard texts on plastics or polymers (18, 19).

One general method of expressing molecular weight of an unfractionated sample of polyethylene is to use the number-average molecular weight ($\bar{M}_n$) which may be depicted as

$$\bar{M}_n = \frac{\sum M_i n_i}{n_i} \quad (\text{Eq. 1})$$

where M_i is the molecular weight of molecules of a definite size i , and n_i , the number of that size. Measurement of colligative properties such as boiling point elevation, osmotic pressure, and freezing point depression of polymeric solutions will lead to the number average-molecular weight ($\bar{M}_n$).

A more convenient, but indirect, method for approximating $\bar{M}_n$ is through viscosity measurements. A number of equations have been developed connecting viscosity with molecular weight but in general they may be reduced to the empirical relation

$$\eta_0 = K \bar{M}_n^a \quad (\text{Eq. 2})$$

where η_0 is the intrinsic viscosity, K a constant,

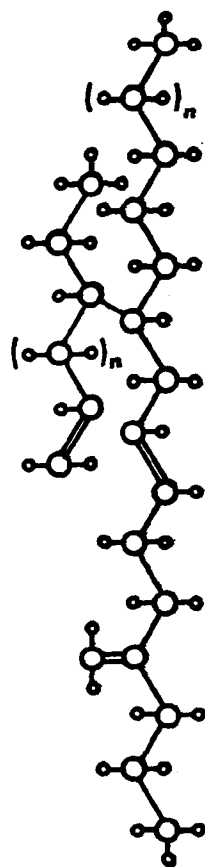


Fig. 1.—Polyethylene molecule showing some characteristic structures. Large circles represent carbon atoms; small circles, hydrogen atoms; double lines represent double bonds. [From Kressler, T. O. J., "Polyethylene," Reinhold Publishing Corp., New York, N. Y., 1961, p. 41.]

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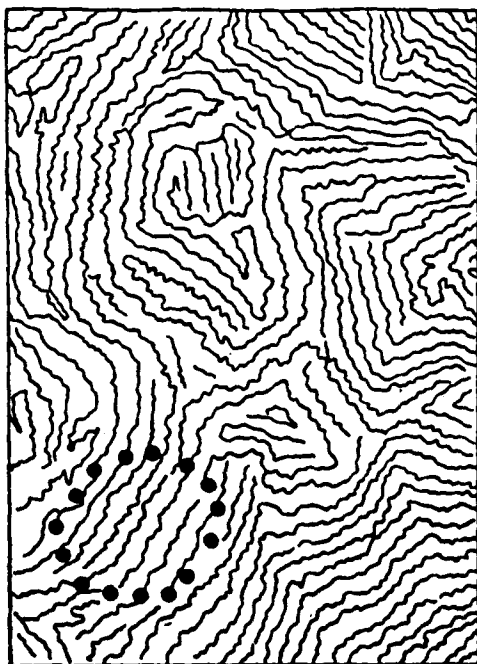


Fig. 2.—Plane projection of chains showing amorphous and crystalline (enclosed in dots) regions. [From Kinney, G. F., "Engineering Properties and Applications," John Wiley & Sons, Inc., New York, N. Y., 1957, p. 11.]

Table II where the degree of crystallinity is shown to decrease with an increase in temperature.

Mechanical treatment of a plastic sample such as pulling the material along one axis will help orient the polymers by straightening out the chains so that they become more parallel and closer to each other. This treatment favors crystalline structures in the plastic.

The degree of crystallinity in polyethylene will be a determinant for certain applications. For example, by experience it has been found that as the crystallinity of the material increases, stiffness increases, surface hardness increases, chemical resistance increases, permeability decreases, and film toughness decreases.

From what has been said it should be clear that the selection of a particular polyethylene for a specific application requires much care and it is wise not to succumb to the use of one or two parameters in defining the quality of the polyethylene. A prudent user should define his particular polyethylene by a number of parameters including important data such as density, melt index, molecular weight distribution, chain structure, and branching. The user should also have a complete background of

the history of the plastic with pertinent and detailed information on additives which have been added directly or which have been introduced in the processing of the material.

The list of applications for polyethylene is in a sense unlimited. Production in 1962 amounted to 1.45 billion pounds (25). In medical and pharmaceutical practice much use is being made of this material for containers both as bottles and as film packaging materials, tubings, syringes, and other units for the administration of drugs and blood or for the collection of body fluids. Polyethylene coating on various surfaces has ushered in many new uses which could not be anticipated a few years ago.

Polypropylene (26)

In 1954 Professor Natta of the Institute di Chimica Industriale del Politecnico, Milan, Italy, introduced a new plastic material which was synthesized by stereospecific polymerization. This new material was polypropylene which in a period of a few years has created a mild sensation for product designers because of certain advantages over the polyethylene line. Perhaps even more important than the introduction of a new plastic material was the sudden intense interest of polymer scientists in a new field of stereopolymers which may make possible newer plastic materials having superior properties over the conventional materials.

Commercial use of polypropylene started in 1958 and by 1961 had reached a production of approximately 80 million pounds which is estimated to increase to 425 million pounds by 1965 (25).

Polypropylene is colorless and odorless with a density of 0.90-0.91, which makes this material one of the lightest plastics known. The physical properties of polypropylene are in direct relationship to the molecular structure and to the geometry of the constituents in the chain.

TABLE II.—EFFECT OF TEMPERATURE ON THE CRYSTALLINITY OF POLYETHYLENE*

Temperature, °C.	Wt., % Crystalline Material
0	55
20	55
40	55
50	55
60	55
70	55
80	50
90	45
95	45
100	40
105	35
110	25
115	10

* Hunter, E., and Oakes, W. G., *Trans. Faraday Soc.*, 41, 49 (1945).

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As may be anticipated with a molecule containing a hydrogen attached to a tertiary carbon, polypropylene is more susceptible to oxidation than the polyethylenes and the inclusion of an antioxidant is a necessity for sustaining product life. Polypropylene is quite resistant to chemical attacks and products prepared from this plastic can be repeatedly autoclaved without any real harmful effect. Presently the material is being used for films, bottles, jars, household items, and industrial machinery to mention a few uses. In medicine and pharmacy the material is finding use as bottles, jars, syringes, cups, basins, sanitary ware, tubings, laboratory ware, and film packaging material. In completing this section, it is imperative to stress that varied properties, sometimes quite different, can exist between two or more polypropylenes. One should not surmise, therefore, the failing or success of a particular polypropylene product to mean that exact results will be duplicated when another polypropylene is used.

Polyvinyl Chloride (27, 28, 29)

One of the most versatile plastics is polyvinyl chloride (PVC) produced from the monomer vinyl chloride in a number of ways. Its present importance may be recognized by noting that approximately 950 million pounds of the homologous polymer and its copolymers were manufactured in this country in 1961 (25).

The simplest structure representing PVC may be shown with alternating (up and down) atoms of chlorine throughout the chain. If the chain is considered in its most extended form, repeating units occur at a distance of $5\text{\AA}$ along the chain. Since the structure reveals asymmetric carbon atoms, isotactic polymers are conceivable but as yet practical realization of this type of material with PVC has not occurred. Viscosity measurements as well as other physicochemical studies reveal little indication that branching occurs in the polymer. Commercial samples of PVC vary in molecular weight from around 50,000 to 150,000 and most of these samples show a wide distribution of molecular weights.

Unmodified PVC is a hard, transparent plastic. In general, 60% of the material is in an amorphous state. On long standing in the presence of light, PVC shows a tendency to decompose by releasing hydrogen chloride. This reaction is accelerated with temperature and catalyzed by traces of zinc and iron. It is, therefore, necessary to include from one to two per cent of a suitable stabilizer to ensure an acceptable material. All types of PVC are susceptible to chemical attacks with organic materials such as

ketones, esters, aromatic, and chlorinated hydrocarbons.

Polyvinyl chloride has unique properties which permit it to be modified in numerous ways giving a spectrum of end uses not seen with the other plastic materials. By far the most important modifying agent is the plasticizer. Often this ingredient may constitute up to 60% of the total weight of the finished material.

The use of plasticizers is not new, even though their economic impact is of more recent times. Early recorded history reveals that oil was added to pitch in order to make it pliable enough to squeeze between fittings in ships thus preventing leakage. Hyatt, as has already been mentioned, prepared flexible Celluloid by using camphor (a plasticizer) (9). The Second World War stimulated production of PVC for war needs and the years following the war saw a great many advancements in the use of plasticizers. Even though a great many studies have since been reported on various aspects of plasticizers, the selection of the proper plasticizer for a particular application is still considered an art.

A recent book by Mellan (29) is devoted exclusively to the behavior of plasticizers and should be consulted for quick references by those in need of authoritative information on the subject. Mellan points out in his text that "the term plasticizer means different things to different users, who apply it to those qualifications which lie within the limits sought by their particular industry." He, however, gives a definition for the term which appears to be adequate for this discussion:

A plasticizer is generally defined as a substantially nonvolatile, highboiling, nonseparating substance which, when added to another material, changes certain physical and chemical properties of that material. (Ref. 29, p. 4).

One general behavior of the polyvinyl chloride, modified with the addition of the plasticizer, is flexibility and softness. Other physical properties are altered depending upon the particular plasticizer or plasticizers and the concentration present. It is the diversity of physical properties which can result by the proper use of a plasticizer which makes possible the broad range of end uses now seen for PVC.

Often two adjectives (internal and external) are used with plasticizers which should now be clarified. The term "internal plasticizer" should be relegated to the copolymers and implies that the ordinary polymer chain has been modified by the inclusion at repeating intervals, in the chain proper, another structural unit which, in

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and often these materials may be further classified as (a) intermediate-impact, (b) high-impact, and (c) super-impact polystyrenes.

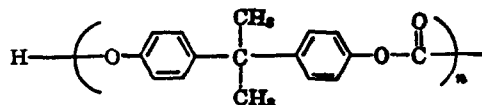
Crystalline polystyrene can be prepared by stereopolymerization following Natta's work and, as with the polypropylenes, isotactic polymers are possible. Commercial use of these stereopolymers is still in its infancy and little practical information is at present available to judge the merits of the material.

Added dimension has been achieved by copolymerization of the styrene monomer with other monomers. In particular, these copolymers are more stable to chemical agents and heat and are finding a long list of special applications. Combination of polystyrenes with fibrous glass makes possible other uses for this material. Finally polystyrene can be made into a foam which can take on any shape desired. The resultant light, porous material has numerous industrial and household applications.

Use in pharmacy and medicine may be listed (in part) as follows: syringes, parts of administration sets, containers, cups, plates, rigid glass-like tubings for various purposes, and other items where rigidity and clarity are desired.

Polycarbonate (32)

Polycarbonates represent a large group of esters of carbonic acid but the most successful material is prepared from the monomer, bisphenol-A [2,2-bis(4-hydroxyphenyl)propane]. The structure formula for the bisphenol-A polycarbonate may be depicted as



Commercial production of polycarbonate began in Germany in 1959 and was followed by the United States in 1960. A number of important properties has stimulated a great interest in this material. Commercial polycarbonate has an extremely high molecular weight—weights up to one million have been produced. One of the outstanding characteristics of the polycarbonates is the resistance to physical changes in a broad range of temperatures (-215 to 250 – 275°). The plastic is known for its dimensional stability, high impact strength, resistance to stain, low water absorption, and transparency. Much of the characteristic properties of the polycarbonates can be directly attributed to the structural configuration of the chains which impart a great deal of rigidity to the molecules. This rigidity

is probably due to the rather long monomer units anchored to the pivotal carbons (between two phenyl groups). If the pivotal carbon is replaced with an alkyl group, a definite increase in flexibility will occur. The rigidity of the chains can be further emphasized by comparing the glass transition temperature of this new plastic with several of the other well-known polymeric materials. For example, the glass transition temperature of polycarbonate is 145° to 147° for nylon 66, and -135° for polyethylene. Replacement of the methyl groups on the pivotal carbon with larger radicals increases the rigidity of the chain while substitution with hydrogens increases the flexibility.

Originally it was believed that all of the polycarbonates were completely amorphous but recent studies have indicated that various degrees of crystallinity can be produced. In those samples where crystallinity has been induced the crystallites are usually smaller than the visible wavelength of light and transparency is still maintained even for materials which may be several inches thick.

Polycarbonates are quite stable to degradation by oxygen because of the high degree of aromaticity. Further resistance to oxidation is enhanced due to the absence of secondary or tertiary carbons. The lack of reactive hydrogen atoms in the vicinity of the ester linkages helps stabilize the polymer and prevents degradation or cleavage of the chains. Most solvents do not attack the plastic material even after prolonged periods of time but solvents such as the chlorinated hydrocarbons, cyclic ethers, and tertiary amines will have solubilizing effect.

Polycarbonates have extremely large molecular weights, at times reaching a value of one million. Increase in molecular weight will offer certain advantages for a particular application but a molecular weight range may be reached where further increase in weight will serve no real advantage but, instead, may have a pronounced objectionable effect on several of the properties. As with all plastic substances, molecular weight distribution will influence a number of the properties but not enough experimental data are at hand to delineate the exact influence.

Much use is already being made of this material in both industrial applications and in household applications. The medical and pharmaceutical field is turning its attention to the polycarbonates for such devices as animal cages, parts of surgical equipment which require a window, and replacement of conventional materials where toughness, heat resistance, and transparency are needed

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packaging of surgical items such as sutures or delicate and expensive surgical items. No doubt the polyamides will find wider use in medical practices as the cost of the material is reduced.

Cellulosics (35, 36)

Under this heading belong a number of thermoplastic products having considerable commercial value as packaging material, especially of the film type. For example, the following would fall under the so-called cellulosic-type plastics: cellulose acetate, cellulose acetate butyrate, cellulose propionate, cellulose nitrate, and cellophane. Each material may find advantages over the others for a specific application. These groups of materials have apparently reached a plateau in yearly consumption which should remain about constant for the next several years. Approximately 141 million pounds of cellulosics were consumed in 1962 (25).¹

Cellulose nitrate, as has already been mentioned, is the oldest plastic material which has found successful commercial application. In an attempt to find a less flammable material than celluloid, cellulose acetate was developed in the early part of this century and as early as 1912 cellulose acetate was used in photographic film. True commercial success of this material, however, did not take place until around 1927. Since then, the other cellulose esters have been developed.

The various cellulosics are prepared from purified cotton linters or wood cellulose which contain high content of alpha cellulose. Each cellulose molecule has approximately 3000 glucosidic units, each unit having three available hydroxyl groups. It is the esterification of these hydroxyl groups with a particular agent which gives rise to a specified plastic.

Cellulose Acetate.—This cellulosic-type plastic has numerous uses today from such items as ladies' shoe heels to transparent windows in envelopes and cartons. The material is tough and has high impact strength. A clear transparent material can be prepared and a variety of colored items are possible with the use of cellulose acetate. The material has advantages over some of the other thermoplastics because of its dimensional stability. The flexible plastic must contain various proportions of plasticizers. In pharmacy and medicine the most use is being made of this material for one form or another of film packaging.

Cellulose Acetate Butyrate.—This material has many of the properties of cellulose acetate

but appears to have improved dimensional stability. It tends to absorb less water than its close cousin and, because higher boiling plasticizers can be used, less plasticizer is needed in a cellulose acetate butyrate formula than for cellulose acetate. These two factors aid in producing a more stable material. It is imperative that cellulose acetate butyrate not be contaminated with other plastic materials since this may cause a diminution of the quality of the item being produced. A variety of uses have been found for this particular material, especially for items which will be exposed to various weather conditions. In the pharmaceutical field it is used as a packaging medium, particularly for blister and skin packaging.

Cellulose Propionate.—This is an extremely tough plastic and requires approximately half the quantity of plasticizer which must be added to cellulose acetate for a particular application. The use of this material for parts of equipment and instruments is due to its toughness and durability to shock.

Cellulose Nitrate.—This plastic is considered the toughest of the thermoplastic materials. A number of disadvantages, however, have decreased the use of this material with the advent of the other cellulosics and newer thermoplastics. The chief disadvantages are its flammability and tendency to become brittle and to discolor in the presence of light.

Regenerated Cellulose or Cellophane.—This substance is not considered as a plastic material even though, often for convenience, it is included as such. We will also include it here with the cellulosics since it has a very close relation to the other materials, being a product of cotton or wood. The use of cellophane as a film packaging material is well known and probably this material has had more applications for a variety of items than any other packaging material. In the late 1920's, a process was patented by Du Pont which made possible moisture-proof cellophane. It was this event which ushered in the transparent flexible packaging industry.

Silicones (37)

The silicone products came into commercial use during the Second World War even though they were known as laboratory curiosities in the last century. Properties such as stability to high and low temperatures, resistance to oxidation, water repellency, and unusual inertness have aided the growth of these materials for a number of special applications where use of other plastic materials is not always possible.

The silicones are a group of materials which

¹ Note that this does not include cellophane.

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of equal quality to those standard materials which have been used for countless decades. Even this approach, it was soon found, was not enough since applications to pharmacy and medicine required special studies which had not been conducted by the plastic industry and which, it appeared, would have to fall on the shoulders of both the pharmaceutical industry and the surgical houses manufacturing and distributing devices for medical practice. A number of firms, representing both groups, are now pursuing an active and conscientious research program to eliminate possible problems in the use of plastics or to at least circumvent these problems to the advantage of all.

The point has been reached to become more specific in this review and discuss those problems which have or may become of consequence to both the pharmaceutical worker and to those other individuals and groups who will, in one manner or another, be involved in the chain of events leading to the ultimate use of the plastic item. In particular, the attention of the reader will be directed toward drug-plastic problems. Since plastics are relatively new to the practice of pharmacy and medicine, it will be convenient to classify these considerations in a rather arbitrary manner to facilitate the presentation. For this reason drug-plastic consideration is subdivided into five parts: permeation, leaching, sorption (including adsorption and absorption), chemical reactivity, and alteration in the physical properties of the plastic. As will be noted in due time, certain aspects of the various problems will be common to more than one class or section.

Permeation

One of the chief advantages of glass containers, for pharmaceutical solutions, is the lack of penetration of molecules from the solution in and through the glass walls or, conversely, the entrance of gas molecules through the glass wall into the solution. With plastic materials, one is immediately confronted with the problem of permeation in two directions: (a) from solution through the plastic into the ambient environment or (b) from the ambient environment through the plastic into the solution. It should be obvious at this point that the permeation rate will depend primarily upon the particular plastic material used (see Table IV).

Theory.—When a gas or a vapor is placed on one side of a plastic film, molecules of the gas will tend to dissolve at the surface of the film and will diffuse under a concentration gradient through the film reaching the other side (or the

TABLE IV.—TYPICAL GAS TRANSMISSION RATES OF PLASTIC FILMS AT 23° C.*

Plastic Film	Gas Transmission Rates, ml./m ² —24 hr.—1 atm.)		
	O ₂	N ₂	CO ₂
Cellulose acetate	350	1500	7,800
Methylcellulose	1300	450	6,800
Polyethylene			
0.917	2700		
0.950	1700		
0.960	1600	440	...
Polyethylene terephthalate	50	8.4	240
Polystyrene	4500	640	11,000
Polyvinyl chloride, plasticized	190–3100	58–810	430–19,000
Polyvinyl chloride, rigid	120	20	320
Polyvinyltoluene	5700	1200	17,000
Rubber HCl	390	62	1,100
Saran	16	2.5	50
Styrene-acrylonitrile (copolymer)	900	120	2,800

* Brown, W. E., and Sauber, W. J., *Mod. Plastics*, 36, 107 (Aug. 1959).

low pressure side) of the film. After a short period of time a steady state will be reached whereby the gas will diffuse through the film at a constant rate, providing that a constant pressure difference is maintained across the film.

In order to develop the usual equations for diffusion, consider a film having a thickness of l cm. and of unit area (38). One side of the film will be a pressure P_1 (high pressure side) while on the other, a pressure of P_2 (low side) will exist. A schematic representation of this situation is shown in Fig. 3.

For simplicity at layer A of the film, a concentration of gas equal to c_1 will be present while in the last layer (at B) the concentration will be c_2 . The letter x will designate a distance between

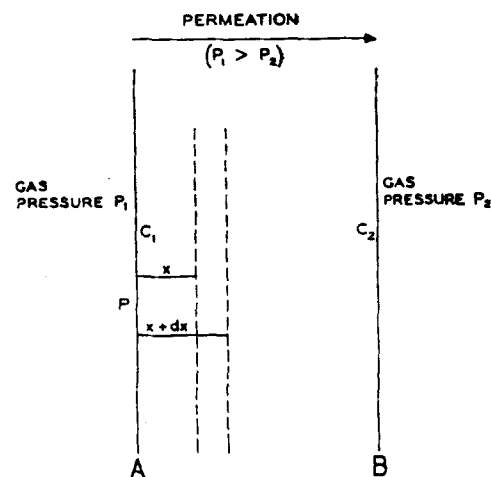


Fig. 3.—Representation of a gas entering and passing through a film from surface A to B.

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Measurement of Permeation.—A variety of methods for studying gas permeability through plastics have appeared in the past decade (41–44). It is apparent that measurements of this type are not always quite as simple as may be thought. Major and Kammermeyer (45), in a recent publication, cite that they have finally reached the conclusion, after thousands of permeation measurements, "that they are anything but simple and often can lead to frustrating experiences." This perhaps is one reason why permeation data often do not agree when different laboratories have conducted studies on permeation on the same type of material. Keeping in mind that problems may arise in permeation studies, it is still possible to list a number of general methods which have been used. For this listing it is convenient to refer to the work of Brown and Sauber (46) who mention five methods of measuring permeation: thermal conductivity, refractive index, mass spectrometry, gas analysis by chemical means, and pressure-volume-temperature (*PVT*) methods. Of these, the last method appears to be the most practical and, in fact, is used as an *ASTM* test for gas transmission rate of plastic sheets (47).

In general, the *PVT* method employs a cell which contains two compartments separated by the particular sample of film to be studied. Gas is introduced to one side of the film and the pressure change on the other side recorded over a period of time. From these data the volume of gas transferring from the high pressure side to the low pressure side may be calculated, which in turn can be used to calculate the permeation rate or constant. Brown and Sauber (46) developed the type of instrument which is now included in the *ASTM* test, referred to above. This instrument lacks high accuracy if very exacting permeation data are needed, but serves to give acceptable data when rapid measurements are needed as might be the case for control work or for other industrial applications. The already mentioned authors, Major and Kammermeyer (45), suggest a new instrument which operates basically in the same manner as the *ASTM* instrument, but which seems to give greater accuracy without the loss of speed.

For more precise and accurate permeation data using a *PVT* method, it will be necessary to set up a more elaborate instrument such as used by Stannett and co-workers in their numerous permeation studies (48–51). Certain advantages, however, can be gained by the use of this latter instrument since the accumulated data can then be calculated to give both the solubility

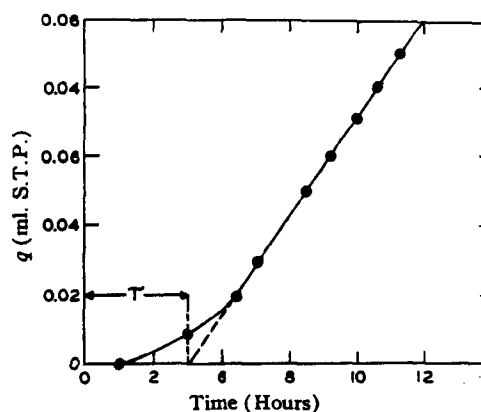


Fig. 4.—Plot of gas transmission vs. time through a plastic film.

and the diffusion constants (see Fig. 4). The chief disadvantage of Stannett's instrument is the painstaking techniques which are needed for proper operation.

Penetrant Molecules.—Permanent Gases.—The particular plastic material will influence the permeation rate of a gas as may be noted by referring to Table IV. Even for the same generically named plastic, the rate may differ due to such factors as molecular weight, molecular weight distribution, branching, degree of crystallinity, and the presence of other ingredients. Some of these factors have been investigated in some detail, but a great deal still has to be done to have a true indication of the influence a combination of these factors has on the penetration of gas molecules. One must be content to examine several of the factors individually, keeping in mind that other forces are also exerting an influence even though these may not be so apparent.

From simple theoretical considerations gas molecules must find "holes" in the plastic material to travel through the material. Any hindrance to this passage will of necessity tend to decrease the permeation rate. Polymeric materials, which have a great deal of crosslinking, will retard the movement of the gas molecules. Crystallite formation and the degree of crystallinity in the plastic material will have a very appreciable effect on permeation and it is now generally accepted that gas molecules probably travel through the amorphous zone. High crystalline materials would thus have low rates of permeation.

Considerable work has been done on the influence of crosslinking in rubber on permeation of various gases (52, 53). Less information is available on the crosslinking of plastics, but it

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density. Experimental data for nitrogen, oxygen, and carbon dioxide in various film samples of polyethylene having different densities followed in general the mathematical expression shown above. Alter (63) believes that there is more justification in relating permeability to density of the material than to the usual degree of crystallinity or to the volume fraction of the amorphous zone.

Organic Vapors.—The solubility coefficient and the diffusion coefficient are constants at any given temperature for penetrant gas molecules. Since the permeation coefficient is a product of the solubility and diffusion, P will also be a constant. Large permeation constants for a specific gas are primarily dependent upon an increase in the diffusion constant while, in most instances, for organic vapors, an increase in the permeation rate is much more dependent upon an increase in the solubility of the vapor molecule. The ability of a polymer to attract and sorb (increase in solubility) penetrant vapor molecules will obviously be related to the physical and chemical properties of both the penetrant and the polymer. As a first approximation then, it can be assumed that as the chemical structure of the penetrant becomes more similar to the polymer, greater solubility will result and as a consequence greater permeability. This has in fact been found to be generally true. For example, Bent and Pinsky (65) found that permeation through polyethylene increased in the following order: alcohols, acids, nitroderivatives, aldehydes, ketones, esters, and hydrocarbons.

Since very little interaction occurs between the permanent gases and a particular polymer, the permeability rate is not concentration dependent. Quite different, however, is the case for most of the vapors since many of these will interact (sorb) with the polymer. Increases in concentration of the penetrant in the plastic will usually have a material effect upon the diffusion. Part of this effect may be due to the ability of the penetrant when sorbed to swell the plastic or to act as a plasticizing agent, thereby permitting greater degree of traversivity or diffusion in the material. Often unusual or anomalous results are seen which become difficult to resolve on theoretical grounds.

There has been little success in relating, quantitatively, organic vapor permeation with crystallinity, amorphous content, or plastic density, but by indirect means, data have been accumulated at least to support the contention that certain vapors will follow a direct relationship with the amorphous content of the plastics.

Perhaps the best example to illustrate this point is the correlation of the data on methyl bromide sorption (consider solubility and sorption as being nearly identical) with the amorphous content in several polyethylenes (51). The top portion of Fig. 5 represents the sorption isotherm in three polyethylenes, each having a different density. As may be noted from this figure, the sorption decreases as the density of the material increases. The single curve at the bottom of the same figure has been recalculated on the basis of the amorphous content of the samples and it will be noted that all the points now fall on the one line. Other molecules, especially those molecules which are considered as good solvents for the plastic, will not show the single curve after recalculation on the basis of the amorphous content (51).

Crosslinking in a plastic material usually will decrease the permeation rate, more probably due to hindering the travel of the penetrant (diffusion) than to decreasing solubility. For those penetrants which are better solvents for the plastic, both the solubility and diffusion will increase slightly at low temperatures, but at higher temperatures the crosslinks prevent the usual swelling and decrease the mobility of the chains and, in consequence, both solubility and diffusion decrease.

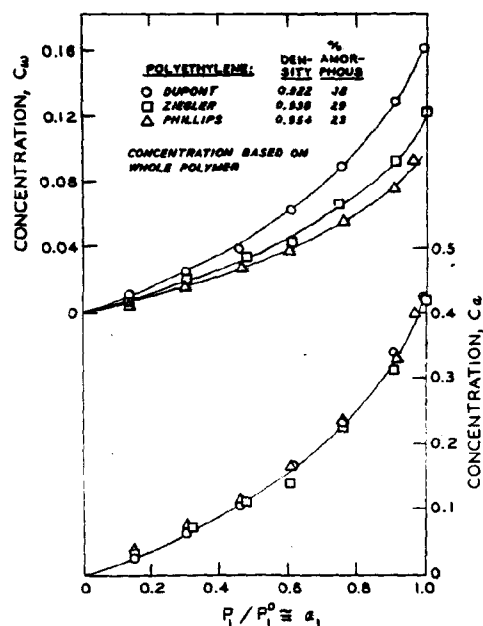


Fig. 5.—Sorption isotherm for polyethylenes and methyl bromide to 0°C. [From Rogers, C. E., Stannett, V., and Szwarc, M., *Tappi*, 44, 715 (1961).]

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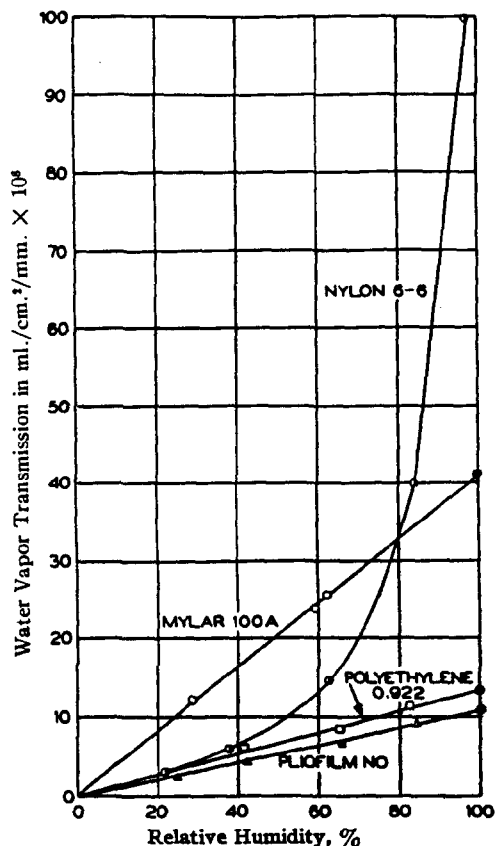


Fig. 7.—Water vapor transmission as a function of humidity for various plastic films. [From Myers, A. W., Meyer, J. A., Rogers, C. E., Stannett, V., and Szwarc, M., *Permeability of Plastic Films and Coated Paper to Gases and Vapors*, Tappi Monograph No. 23, 1962, p. 62.]

independent of the relative humidity. The mechanism for this type of permeation, as pointed out by Myers, *et al.* (67), is not quite as simple as it would at first appear. Strong experimental evidence is at hand to reveal that solubility increases with an increase in pressure, but that the diffusion decreases with an increase in concentration. One apparently compensates for the other, leading to a pressure-independent permeability constant.

Permeation Through Containers.—Permanent Gases.—In the discussion which has so far been presented on permeation of permanent gases, organic vapors, and water vapor, the plastic material has been in the form of a film which was then placed in an appropriate apparatus for the study of the penetration and transmission of the gaseous molecules. The parameters of the experiments were kept as simple and as constant as the experimental procedure

warranted. Even in these instances, however, as has been demonstrated, a number of anomalous results occurred. For the most part, these data with proper assessment have been utilized by various investigators to give theoretical treatments for penetrant-polymer interactions. Even though this information can serve as a useful foundation for those interested in permeation, certain problems of a more practical nature must still be handled by more empirical means, since the science still has not caught up with the art of manufacture of certain types of plastic devices. This appears to be true for the present plastic containers used in pharmaceutical practice.

Studies of permeation in the intact container for various gases appear not to have been considered in too serious a vein by those presently manufacturing plastic containers. Often the complete formulation of the plastic material, the actual handling of the material, and the exact history of the manufacture of the containers are not really known by the one utilizing the containers. It is possible that any change in a procedure from the acquisition of the raw materials to the final ejection of a completed container will have an influence on the permeation rate of gases. More time and space

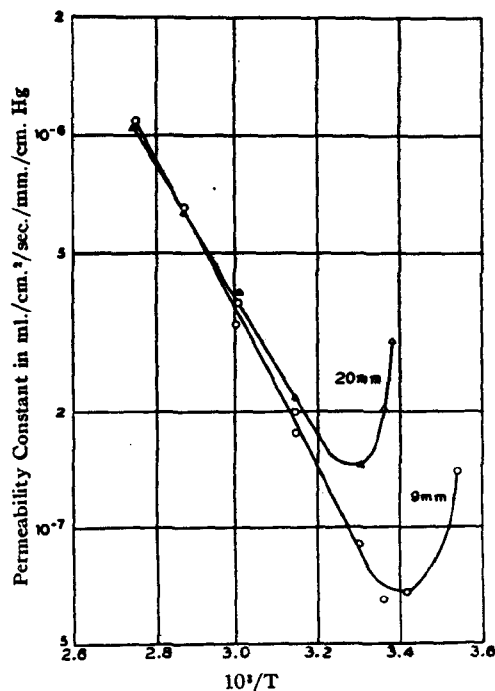


Fig. 8.—Temperature dependence of the permeability constant for water in nylon 66 at vapor pressures of 9 and 20 mm. Hg. [From Myers, A. W., Meyer, J. A., Stannett, V., and Szwarc, M., *Tappi*, 44, 58(1961).]

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impact test, leakage test, side-wall distortion test, and side-wall rigidity tests. Unfortunately, as stated earlier, there is little published information on drug products in plastic containers and it appears that one must study the specific product in each container before final evaluation of the container is possible.

One must not deal lightly with permeation in plastic containers. Some plastic materials will, of course, act as stronger barriers to permeation than others. It is now well known that the high density polyethylenes will give greater protection than the low density types. It has also been found that special types of coating can further prevent permeation. From all past and present indications, it appears that plastic containers for the pharmaceutical industry will have to be manufactured under very special and rigid conditions, a situation which at present, at least for the most part, is not true.

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