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—————*Review Article*—————

**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.]

INTRODUCTION

NO MATERIAL has received so much attention, found so many useful applications, and presented so many challenges as a group of chemical agents making up a body of dissimilar substances collectively grouped under the generic term, plastics. No longer a laboratory curiosity of several decades ago, plastics have become an everyday way of life in our complex society. No item or product from the simple dish stand in the kitchen to the complexly engineered space capsules has escaped the touch of one or more plastic materials. The ingenuity of the polymer chemist and the skill of the product engineer make it possible for the plastic industry and all its related affiliates to create and produce products which to a previous generation either were made from the more conventional materials or could not be made at all. Plastics have had a profound effect upon our economy and no doubt will become an economic necessity in the future if our nation is to maintain its accustomed high standard of living.

Even though the use of plastic materials had reached large proportions in other areas, its introduction to pharmacy and medicine was of more recent times and in more limited applications. Natural reluctance by the various health professions and by those servicing these professions to introduce new, untried materials without careful analysis for potential harm prevented the same degree of expansion as seen in many other fields. This state of affairs, however, has changed and is continuing to change as may be witnessed by reviewing the number of items used in pharmacy and medicine made in part or whole of a plastic substance. The many advantages which can be fashioned from the proper plastic material will undoubtedly give further impetus to the use of plastics in the health professions.

The rapid introduction of plastic items, such as containers, syringes, tubings, sheetings, prosthetic devices both internal and external, and a host of other items, to the practice of pharmacy and medicine has not been without certain difficulties. It appears that a greater scientific body of knowledge must be accumulated to guide the manufacturer to produce a plastic item which will repeatedly behave in an identical manner under various conditions of storage and use and which will insure that no possible harm will directly or indirectly fall upon the patient. In recent years there has been some concern gener-

ated on the possible harmful effects on animals and humans in the use of plastics in medicine. No attempt will be made here to review the toxicity aspect of plastics. The reader if interested in this facet of the subject is encouraged to ferret out some of the references listed (1-8).

As the outline indicates, the review will cover a number of topics which the author felt would be pertinent to the overall presentation of plastics to a pharmaceutical group. Some topics have received more attention than others but this should not suggest that these other topics are of minor importance for it certainly is recognized that to certain individuals and groups these less emphasized topics may indeed be of paramount importance. The reader may also be distressed in not seeing certain facets on the subject of plastics covered at all in this review. Here the author has taken some liberty in the selection of the material in order to conserve space and to limit the discussion to those areas which would seem to be appropriate to pharmacy and medicine. No one review can cover adequately any subject and this is even more true of a subject which has so many applications and which is in a continual state of growth. It is hoped, however, that what will be presented here will serve as a source of useful information to all those interested in finding more and better uses of plastics while at the same time alerting others to the problems which may be created by the use of plastics if proper precautions are not taken.

History

The impetus to our present "world of plastics" can be directly and logically traced back to the years of the Second World War, when a sudden need developed in both the Allied and Axis camps to find and produce in sufficient volume suitable replacements for scarce war materials. Scientific and engineering talents met the challenge by the expanding use of well-established plastics as well as exploiting those polymeric materials which were hardly more than laboratory curiosities. It was natural that this pool of knowledge, personnel, and equipment would be directed to civilian needs after the war years and to the present. One must, however, go much further back in history than the Second World War to assign a time for the invention of the first plastic.

A lack of adequate supply in the 1860's of ivory for the production of billiard balls inspired a printer by the name of John Wesley Hyatt to experiment with pyroxylin. In 1868 he fashioned an ivorylike material which soon became known as Celluloid, a combination of pyroxylin and camphor (9). The new material became the

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Editor's note: Additional considerations of plastics in pharmaceutical practice will be discussed in the concluding portion of this review, Part II, which will appear in the February issue of THIS JOURNAL.

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^a

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

^a "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

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

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.

an unlimited number of substances. By far the most appropriate definition thus far given may be stated as follows (13):

A large and varied group of materials which consist of, or contain as an essential ingredient, a substance of high molecular weight which, while solid in the finished state, at some state in its manufacture is soft enough to be formed into various shapes, usually through the application, either singly or together, of heat and pressure.

Plastics may further be divided into two general classes: (a) the *thermosets*, those substances which when heated to a melt and cooled will not regain their original identity, and (b) *thermoplastics*, those substances which will regain their original identity. There are instances where a plastic material can be made to behave as either one or the other but for the most part one may consider a plastic as either belonging to the one class or the other.

Because of the unusual versatility of thermoplastics, they have found a wider application than the thermosets especially in the medico-pharmaceutical field. For this reason the main emphasis will be placed on this group of plastics in the present review.

Often the term *resin* is used in plastics technology and indicates the polymer or polymers making up the plastic material. A number of plastics can be prepared for specific applications without the addition of any other ingredient to the resin but others may contain beside the resin, plasticizers, antioxidants, stabilizing agents, fillers, antistatic agents, colorants, or other specific agents, to impart a definite quality to the final plastic product. These other ingredients may vary in concentration from a few parts per million parts of resin up to as high as 60% of the total weight of the plastic.

In recent years new dimensions have been added to plastics by chemically combining different monomers to form polymers. These polymers can then be considered as being composed of two types of plastics. The term *copolymer* is used to distinguish these plastics from those which have been synthesized from one type of monomer.

Once the basic resin is manufactured in bulk quantities, one or more steps of processing are usually necessary to have the material in suitable form for actual use in making a specific item. Depending upon the specific plastic item, other steps may be necessary in fabricating and finishing the item before it is actually ready for market. Clearly, it is not a simple chain of events. Much scientific technology and art come into play with many groups adding their

particular touch to the final product. It may thus be appreciated why there can be so many variations in a plastic product even though for all intents and purposes the product is designated with a specific generic name such as polyethylene, polypropylene, etc.

GENERAL INFORMATION ON A SELECTED NUMBER OF PLASTICS

To gain the most from plastics, one must have working knowledge of the various plastic materials which are currently being used in the medico-pharmaceutical field and, further, one must be cognizant that no one material can be selected which will give all the advantages without any disadvantages for a particular application. Each application is a special project and must be treated as such. The more information which is available to the user of the plastics, the less time and effort will be required in selecting the proper material or at least in setting a scheme which will permit proper evaluation of the plastic for the specific application. There is no doubt that the packaging department of a pharmaceutical firm must be highly concerned with such matters.

The following section will include a discussion of a number of plastics which are currently being used. It will be obvious that not all materials will be dealt with and that rather brief accounts will be made of the ones discussed. The variety of materials which could be discussed under the term plastics would be too staggering for one paper and probably would not serve to the best interest of the reader. Those plastics which have been included are, however, representative of materials which have or probably will have application to the pharmaceutical field and to the related medical sciences. Certain omissions and simplifications have also been necessary in order not to weight the contents of the discussion.

Polyethylene (14, 15, 16)

Polyethylene, as the name clearly indicates, is a long chain polymer prepared from ethylene. Depending upon the mode of synthesis and the presence of selective catalyst a variety of polyethylenes can be prepared. It is, however, possible to classify polyethylenes into three general classes by simply considering the density of the polymeric material. These classes are: (a) *low density* (may also be called conventional, regular, branched, or high pressure), (b) *medium density*, and (c) *high density* (may also be called linear, low pressure). The low density is the original polyethylene which is prepared at

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, $(\text{CH}_2)_n$ 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,

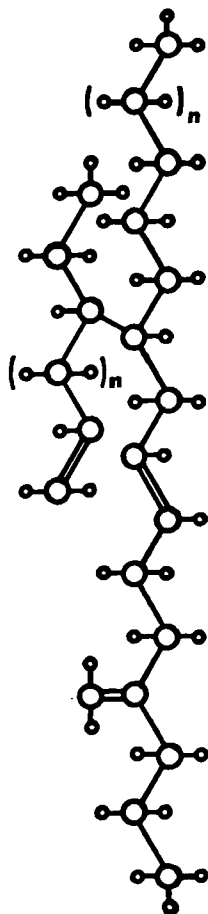


Fig. 1.—Polyethylene molecule showing some characteristic structures. Large circles represent carbon atoms; small circles, hydrogen atoms; double lines represent double bonds. [From Kressler, T. O. J., "Polyethylene," Reinhold Publishing Corp., New York, N. Y., 1961, p. 41.]

and \bar{M}_n^a the number-average molecular weight raised to a power, a . Often, rather than using molecular weight values, viscosities are used to convey molecular size and it can thus be understood why often comparison of data from one polyethylene to another becomes quite impractical.

Another expression of molecular weight, referred to as the weight-average molecular weight (\bar{M}_w) can be determined from light scattering experiments. This method actually measures a mean radius of a molecule in solution and not the molecular weight since two molecules having the same molecular weight may show different results if one has more branching in the chain than the other. The ratio \bar{M}_w/\bar{M}_n , however, helps to reveal the distribution of molecular weights in the same polymer, the larger the ratio, the broader the distribution.

Since it was early shown that polymers could be characterized by rheological properties, a standardized technique was devised to measure the viscosity of a polymer under specified conditions. The term *melt index* (MI) came into being and was defined as the number of grams of molten polymer which will flow through a standard orifice at a standard temperature and pressure (20). Unfortunately this method of measurement was soon found not to be very meaningful except for control purposes since two polymers produced by different manufactures but having the same melt index did not necessarily behave in the same manner during processing. The melt index, however, may be used as crude indication of molecular weight in an inverse fashion, *i.e.*, the higher the melt index the lower the molecular weight.

The various methods used to depict the size of polymers, as already stressed, is a form of an average. It would be extremely helpful if more information could be obtained on the exact distribution of the molecular sizes in a given polymer but technical difficulties which as yet have not been sufficiently overcome prevent reasonably accurate size frequency distributions to be charted. Attempts have been made, however, to fractionate polyethylene and thereby to reveal a molecular distribution with some limited success. In general the distribution has been found to be extremely broad. Important advantages may be gained by keeping the molecular weight distribution in a narrow range. For example, it has been found that such properties as tensile strength, stress cracking resistance, film impact strength, and low brittleness can be improved if the molecular weight distribution is narrowed.

It has now been clearly established that polyethylene as well as other plastics have in essence two zones of structure running through the material: a crystalline zone and an amorphous zone (see Fig. 2). Crystallization occurs when the polymer chains orient themselves side by side to form a more compact configuration. In a given polyethylene sample these compact zones of polymers, or crystallites, are dispersed throughout the amorphous zone of the material. The ratio of crystalline to amorphous structures in polyethylene impart various physical properties to the polyethylene. For example, the density of the crystalline zone by X-ray measurements indicates a density of 1.00, while for the amorphous zone, a density of 0.76 to 0.85 has been found. Conventional polyethylene has approximately 60 per cent of crystalline structure while high density polyethylene has a much greater content of crystallites.

Bunn (21) has made intensive studies on the crystalline zones of polyethylene and has found that the unit cell has an orthorhombic structure with $a = 7.40\text{\AA}$, $b = 4.93\text{\AA}$, and $c = 2.53\text{\AA}$. The crystallites are not separate entities as may be found in metals but rather the chains composing the crystallites run through one or more amorphous zones as may be shown in the highly diagrammatic model in Fig. 2.

Thin samples of polyethylene show clarity while thicker samples display an opaque appearance. The opacity is due to the scattering of light which was thought to be due to the individual crystallites in the sample, but it is now known that the phenomenon of opacity is due to larger structural units than a crystallite. These larger units form a spherulite which comes about by proper arrangement of a number of small crystallites forming a nearly distinctive zone radiating outward from a central point (22).

A number of methods for evaluating the crystal structure of polymers have been devised (23, 24). Perhaps the most useful techniques are X-ray diffraction, infrared, density, nuclear magnetic resonance, and electron microscopy studies. It should be apparent that a number of factors will alter the ratio of crystalline to amorphous composition of a plastic material. Some of these factors are (a) structure of the molecule *i.e.*, chain length, degree of branching, length of chains in the various branches, degree of unsaturation, presence of other constituents, etc., (b) the temperatures, and (c) mechanical treatment (drawing or pulling the plastic material). An example of the effect of temperature on polyethylene may be noted by observing

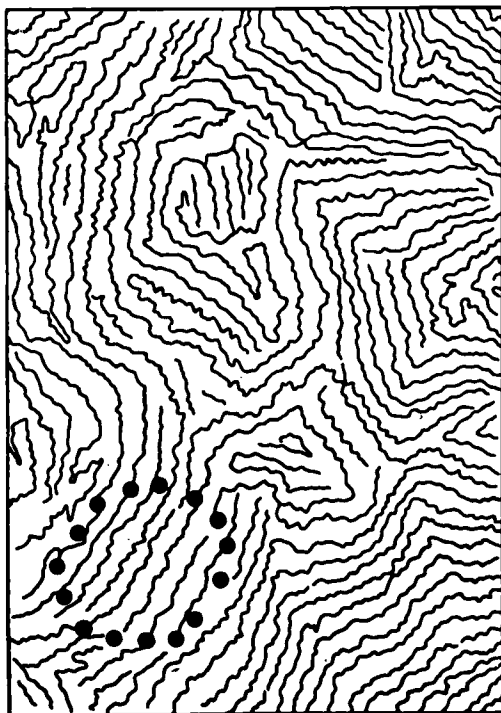


Fig. 2.—Plane projection of chains showing amorphous and crystalline (enclosed in dots) regions. [From Kinney, G. F., "Engineering Properties and Applications," John Wiley & Sons, Inc., New York, N. Y., 1957, p. 11.]

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^a

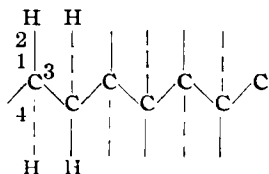
Temperature, °C.	Wt., % Crystalline Material
0	55
20	55
40	55
50	55
60	55
70	55
80	50
90	45
95	45
100	40
105	35
110	25
115	10

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

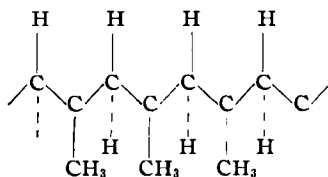
Two types of polypropylene are possible. The first of these will be called an *atactic* polymer while the second an *isotactic* polymer. First, however, it will be necessary to define or at least to visualize another term which will be designated as *tacticity*. If a polymer is composed of molecules whose basic units follow each other in the same spatial configuration, a tactic polymer is achieved. Depending upon the particular polymer, many possibilities arise for a variety of tacticities, even though only two will be discussed in this section.

The definition of atactic thus becomes a simple matter and indicates that no tacticity is present (no steric order present). Isotactic may be defined as a polymer in which parts of the molecule are oriented in space in the same manner for each unit of the polymer.

It will be helpful in understanding the term isotactic to compare the polymerization of ethylene and propylene to produce polyethylene and polypropylene, respectively. In the polymerization of ethylene, one molecule will join another by rupture of the double bonds forming, in an idealized fashion, a chain which may be depicted as



where lines 1 and 3 are in the plane of the paper, line 2 is from the paper toward the reader, and line 4 (dotted line) passes from the paper downward at the same angle as line 2. The structure depicted above is perfectly symmetrical and cannot be isotactic. Propylene on polymerization will follow the same addition steps to become a structure which might be visualized as



Here it will be noted that an unsymmetrical structure results with every other carbon being bonded to a methyl group. Since each methyl group is in the same spatial position (coming up from the paper) this molecule is isotactic. If the methyl groups were distributed in a random fashion (*i.e.*, some up and some down), the polymer would be referred to as an atactic polymer.

Another term now must be introduced, *syndiotactic* polymer. This refers to a structure whereby the methyl group alternates up and down in a regular pattern.

The above structure for polypropylene is for convenience and it should not be interpreted that in reality the chain would exist in this fashion. In fact it would be extremely difficult for several of these chains to approach each other since the methyl groups from two chains would repel each other. In an isotactic polypropylene, the chain forms a spiral, one spiral in three propylene units. The spiral formation permits the interlocking of two or more polymers into tight segments which in turn give rise to the crystal structure in polypropylene.

It is possible to prepare 100% isotactic polypropylene even though most commercial samples are never this high. In general, as the isotacticity increases, crystallinity increases in approximately the same order and often this relationship holds fairly well but it must be emphasized that there is no numerical correlation between the two. As with polyethylene, other factors will influence crystallinity, particularly time-heat treatment. This fact should caution one to be alert in designating polypropylene by only one or the other parameter (crystallinity and tacticity) if a specialized use is to be made of the polypropylene.

The degree of crystallinity, the size and shape of the individual crystallites, in any plastic material will affect both the physical and mechanical properties of the material. For example, it has been found that small and uniform crystallites will cause less stress points in the material. Crystallite size in polypropylene is approximately 150Å in diameter and 50–60Å thick. These crystallites form larger aggregates (spherulites) and it is necessary to control the growth of these spherulites since large sizes will invariably weaken points in the plastic which in turn lead to cracks or breaks (26).

Usual methods of molecular weight determination are used to characterize polypropylene but these values may be in gross error or may not really serve a useful purpose. Viscosity measurements appear to be the most used method of correlating molecular weight and it appears that such a factor as molecular weight distribution is an important consideration in designing a specific use for the plastic. Greater difficulties, however, are encountered in fractionating polypropylene than polyethylene in an attempt to collect size distribution data and newer techniques must be developed before reliable information can be accumulated.

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 5Å 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

effect, reduces the bond strength between adjacent chains and imparts polymer mobility. "External plasticizers" are those modifying ingredients which are added to the polymer mass but which do not become an integral portion of the chain. These "external" ingredients are meant when one speaks about a plasticizer being added to a plastic material and it will be helpful to all concerned if the term "internal" is not used at all except in the specific instances where copolymers are discussed.

If one were to itemize all of the currently suggested plasticizers, he would assemble an imposing list of ingredients. This large number of ingredients has been extremely difficult to classify and for this reason many different classifications have been suggested. Boyer (30) has given a simple classification by dividing plasticizers into three distinct types: (a) the solvent type, (b) the nonsolvent type, and (c) the polymeric type. Each of these types behaves in a different manner but in effect all reduce the cohesive forces between two or more of the polymer chains thereby imparting chain mobility. Often commercial classifications of plasticizers are more conveniently divided under their chemical types as, for example, glycolates, sebacates, adipates, laurates, stearates, abietates, esters of polyhydric alcohols, etc.

Neither the art nor the growing science in the plasticizer field has produced the one universal plasticizer and it is doubtful if in fact this objective will ever be reached. Undoubtedly newer and better ones will come into being but more for particular applications.

In general, flexible PVC items are prepared from a specific formulation which includes a number of ingredients. For example, a common formula for a garden hose may be

- Resin—100 parts 95 to 5 vinyl chloride-acetate copolymer
- Plasticizer—50 parts dioctyl phthalate
- Color—3 parts dye or pigment
- Stabilizer—2 parts thermal stabilizer such as dibutyl tin laurate
- Lubricant—1 part aluminum stearate
- Filler—as required

In any formulated plastic, there is always a propensity for one of the ingredients to migrate into the environment which has intimate contact with the material. This can become a serious problem, particularly when the material is used for foods or for drug products. Recent changes in the Food and Drug regulations in regard to foods require that only approved ingredients be included in packaging materials for food. At present there is no such regulation

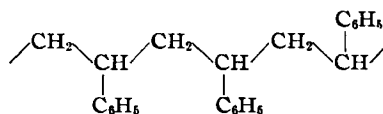
for devices for drug products or in general for plastic items used in medical practice. This point on migration will be discussed again in more detail in a later portion of the paper.

The primary use of the polyvinyl chlorides is in tubings for the administration of blood, drugs, nutritional fluids, and for the collection of blood and other body exudates. Other uses such as flexible containers for blood are in current practice.

Polystyrene (27, 31)

As was mentioned in an earlier portion of this review, polystyrene is one of the oldest plastics known but the real growth is a direct outcome of the Second World War. The sales of styrene-type polymers reached an impressive sales volume of 922 million pounds last year, placing it second to polyethylene in use (25). One of the main reasons for the high volume of use is the low cost per pound as compared to comparable resins to be used for the same application.

Polystyrene is formed from the monomer styrene in the presence of a catalyst and proper conditions to give a long chain configuration which may be represented in its simplest form as



When the term polystyrene is used it indicates that the plastic is composed of the homopolymers of styrene and often this material is referred to as *normal* or *conventional* polystyrene. Other types of polystyrene are also (modified and copolymers) produced, several of which will be alluded to presently.

Polystyrene (conventional) is a hard, amorphous solid, having transparent properties. The material is stable to distortion up to approximately 95° at which point it begins to become pliable, and as the temperature is further increased the material becomes soft and putty-like. Certain modifications in the structure of polystyrene will either increase or decrease the softening temperature. The brittle characteristic of conventional polystyrene may be overcome by combining various concentrations of rubber with the polymer producing the *impact* polystyrenes. Certain desired properties are lessened, however, with these impact plastics, as for example, lack of clarity and decrease of hardness. The shock resistance or toughness of impact polystyrene may be increased by increasing the content of rubber in the material

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

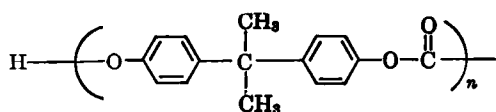
Crystalline polystyrene can be prepared by stereopolymerization following Natta's work and, as with the polypropylenes, isotactic polymers are possible. Commercial use of these stereopolymers is still in its infancy and little practical information is at present available to judge the merits of the material.

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 $250-275^{\circ}$). 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.

Nylon (33, 34)

In the late 1920's, W. H. Carothers of Du Pont became interested in synthesizing various types of polyamides. It was, however, in 1938 that Du Pont announced the realization of a new material resembling in many ways wool and silk. This new plastic material was baptized with the generic name nylon and now includes a number of different types of polyamides and copolymers. Nylon has distinctive properties such as high melting point, toughness, resistance to chemical attack, and resistance to abrasion, as well as other qualities which are desired for a number of applications.

In general, polyamides are synthesized by two methods: (a) condensation of a diacid with a diamine or (b) self-condensation of amino acids. Common to all nylons is the repeating amide linkage running through the chain. At present there are a number of nylon plastics but only four types appear to be enjoying commercial success. These are: (a) nylon 6/6, (b) nylon 6/10, (c) nylon 6, and (d) nylon 11. The numbers following nylon indicate that both the acid and amine used for synthesis contain six carbons. Commercial samples of nylon must contain an antioxidant since there will be a tendency for degradation of the polymer in the presence of ultraviolet light and air. Nylons are quite stable to heat but degradation by hydrolysis in an acid medium at high temperature is possible.

The polar sites (referring to the amide groups) are responsible for many of the properties of the nylon. Strong forces of attraction become possible between two parallel chains by hydrogen bonding. In this case, hydrogen atoms from the nitrogens in one chain bond with the oxygen

atoms in an adjacent chain. Clearly the more of these bonds per unit of polymer segment the greater will be the force of attraction. Table III lists a number of polyamides with their respective melting points and it can be seen that a great difference exists among the various melting points.

A number of studies have been conducted on the effect that substituent groups have on the property of nylon. It has been shown, for example, that if the hydrogens from the amides are replaced with other groups, *i.e.*, methyl, ethyl, propyl, and amyl, a decrease in molecular weight will occur. These substituted groups not only prevent hydrogen bonding but also by steric effect prevent close approach of parallel chains. This results in nylon having a lower molecular weight, higher solubility, and more flexibility. The same type of alteration in properties may be observed by immersing samples of nylon in phenolic solutions. In this case molecules of the particular phenol will penetrate the plastic and compete for polar sites, thereby breaking existing hydrogen bonds (between two chains). If sufficient concentration of a particular phenol is present, the nylon will dissolve.

The intermolecular forces between the polar sites (of adjacent molecules), as has been stated, holds the polymer chains firmly together but secondary valence forces are also present to stabilize the interaction. It should be obvious that each chain, if highly bonded, will be parallel to its neighbor chain. This gives rise to an orientation of polymer molecules in such a manner that a high state of crystallization becomes possible. Even though other polymers can be drawn with or without addition of heat, the polyamides are a very good example of a plastic material which can be made more crystalline by simply pulling the material. In effect this straightens out the chains and orients the molecules in a parallel direction which permits close spatial contact of the polar sites (through hydrogen bonding) in one chain to polar sites in another. Nylon filament to be used for textile purposes is manufactured as an amorphous polyamide which on cold-drawing up to six or eight times its original length gives a highly crystalline material.

Many industrial uses have been found for nylon such as gears, machined parts which may have to withstand heavy mechanical shock and high temperatures, tires, tubings, instrument casings, and films for packaging oil products and food. In medical and pharmaceutical practice, nylon has been used for syringes, parts of administration kits, containers, and film

TABLE III.—APPROXIMATE MELTING POINTS (IN AIR) FOR VARIOUS NYLONS^a

Diamine	Dibasic Acid	M. p. of Nylon, °C.
Ethylene	Sebacic	254
Tetramethylene	Adipic	278
Tetramethylene	Suberic	250
Tetramethylene	Azelaic	223
Tetramethylene	Sebacic	239
Pentamethylene	Glutaric	198
Pentamethylene	Adipic	223
Pentamethylene	Pimelic	183
Pentamethylene	Suberic	202
Pentamethylene	Azelaic	178
Hexamethylene	Sebacic	209
Octamethylene	Adipic	235
Octamethylene	Sebacic	197
Decamethylene	Carbonic	200
Decamethylene	Oxalic	229
Decamethylene	Sebacic	194
Piperazine	Sebacic	153

^a Floyd, D. E., "Polyamide Resins," Reinhold Publishing Corp., New York, N. Y., 1958, p. 41.

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).²

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

² Note that this does not include cellophane.

are composed of a molecular backbone of alternating atoms of silicon and oxygen. Organic groups are attached to this backbone in repeated intervals. The silicones can be produced to yield physical properties from various viscosities as a liquid to a solid material. They can be used as coating material for glass and other materials and as encapsulating agents. Other uses, too numerous to mention in this short résumé, have also been found which give great versatility to the silicones. The advent of silicone rubber has made it possible to expose tubing to very extreme temperatures without altering the physical or mechanical properties of the material. Many uses have been found for the silicones in pharmacy and medicine. The coating of glassware for water repellency is now widely used in most laboratories and by the pharmaceutical industry for bottles and ampuls. Surgeons are finding a great deal of success with the silicone rubbers as prosthesis for various segments of the body. No doubt more and varied uses will be found for this group of plastics in the near future.

Others³

Some consideration has been given to a number of plastics but it should be kept in mind that there are other important plastic materials which may have individual advantages for specific applications in both pharmacy and medicine. One would not be doing justice to plastics in general if mention were not made of the *acrylics* which have been employed for a great period of time in the field of dentistry. The *acetals* are of more recent vintage and should find favorable use as parts of equipment which previously were made from metals. A number of *fluorocarbons* have been introduced since 1943 when the first successful material was manufactured. These materials have good thermal and chemical resistance and are finding uses in medical practice as tubings, synthetic prosthetic devices, and replacement for rubber and metals where good wear is desired. The *isocyanates* or, perhaps more correctly, the *polyurethanes* are an interesting group of materials. Various shapes and sizes of flexible foams can be prepared from polyurethane which take on the characteristics of rubber or rigid foams can be produced for special applications. These materials are finding use in surgery as prosthesis and as packing material for certain pharmaceuticals or agents which need extreme care in shipment. *Polyvinyl alcohol* behaves quite differently from most of the

other plastic materials. This particular material will dissolve when placed into hot water. Use is now being made of this unique property to design packets which will contain a product to be eventually dissolved in water. All that needs to be done is to place the packet into warm water and, in a brief interval of time, the container will dissolve, releasing its contents. Measured amounts of ingredients can thus be assured without the need of the user to do the measuring or even to come in direct contact with the product. A group of polymeric materials which range from brittle solids to low viscosity liquids are the *epoxies*. These compounds are used as coating materials and in cementing various types of materials with such adhesion that often the components will break before separation at the cement point.

DRUG-PLASTIC CONSIDERATIONS

Introduction

In the previous section devoted to general information, the reader had an opportunity to explore, in a mild manner, a number of insoluble polymeric materials collectively called plastics. Even though the discussion on the selected plastics was brief, it should be evident that a large number of materials exist which have properties quite different from each other. Furthermore, it has been pointed out that even a plastic material having the same generic name can be dramatically different from the same named material from another source. Added to this already complex picture are the numerous modifications which are possible in formulating a final plastic material. From this maze of materials, often not clearly defined as to specifications, the pharmaceutical scientist must select one or more materials for a specific application. In the same manner, the surgical house must, with the utmost caution, find the proper plastic material for the numerous devices presently entering the hospital field in part or whole of a polymeric material.

The task of selecting the "right" material for a specific application was at one time given little attention in the pharmacy and medical fields. A prior assumption was made that plastics were quite inert and no serious problems could develop. It soon became evident that this was not the case and interest and energies were directed to evaluate materials as to their pharmaceutical and medical acceptability. Information and guidance were solicited from the various segments of the plastic industry to help formulate materials and devices which would prove

³ See "Modern Plastics Encyclopedia" (1962 issue) for further information on plastics.

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.^a

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

^a 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

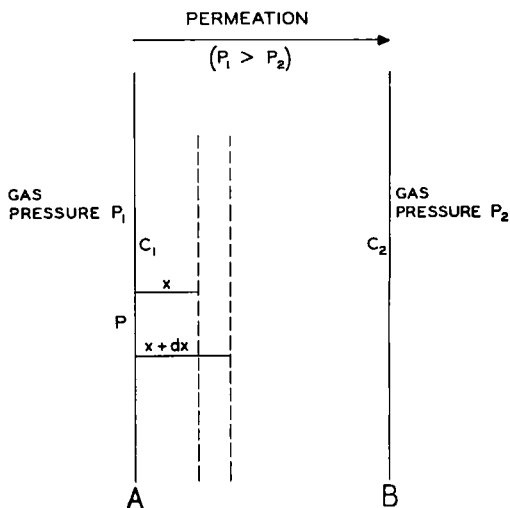


Fig. 3.—Representation of a gas entering and passing through a film from surface A to B .

two planes in the film, and $x + dx$ another distance between two planes. Designating the rate of gas permeation at x as q ml. per second and permeation at $x + dx$ as $q + (dq/dx)dx$, the amount retained per unit volume will equal $-(dq/dx)$ which can be equated to the rate of change of concentration c with time or

$$-\frac{dq}{dx} = \frac{dc}{dt} \quad (\text{Eq. 3})$$

When a steady-state condition is reached, $dc/dt = 0$ and q will become a constant.

No permeation will occur when the concentration gradient is zero and extremely high rates of permeation when the gradient is very large. The mathematical relationship between permeation and the gradient of concentration can be expressed by Fick's first law or

$$q = -D \frac{dc}{dx} \quad (\text{Eq. 4})$$

where D is defined as the diffusion coefficient or constant. Fick's second law as an equation may be developed by combining Eq. 3 with Eq. 4 to get

$$\frac{dc}{dt} = \frac{d}{dx} \left(D \frac{dc}{dx} \right) \quad (\text{Eq. 5})$$

If the diffusion constant, D , is independent of concentration, Eq. 5 reduces to

$$\frac{dc}{dt} = \frac{Dd^2c}{dx^2} \quad (\text{Eq. 6})$$

At a steady state of diffusion the rate of permeation, of q , will be constant and by integrating Eq. 4 between the two concentrations, c_1 and c_2 , Eq. 7 will result

$$q \int_{x=0}^{x=l} dx = -D \int_{c_1}^{c_2} dc$$

or

$$ql = -D(c_2 - c_1) = D(c_1 - c_2)$$

$$q = \frac{D(c_1 - c_2)}{l} \quad (\text{Eq. 7})$$

Henry's law relates the concentration of gas at each surface in the film to the partial pressure of the gas or

$$c = S \cdot p \quad (\text{Eq. 8})$$

where S is the solubility coefficient of the gas in the film at equilibrium and p the partial pressure. Substituting $S \cdot p$ for the concentration terms in Eq. 7 will give Eq. 9

$$q = \frac{DS(p_1 - p_2)}{l} \quad (\text{Eq. 9})$$

The permeability constant, P , can now be defined as $P = D \cdot S$ or

$$P = \frac{q \cdot l}{(p_1 - p_2)} \quad (\text{Eq. 10})$$

If a plot is made of q versus time for a particular material, as appears in Fig. 4, it will be noted that a short time period must pass before a linear relation is reached. This portion of the curve indicates that a steady state of diffusion has been reached. The initial time period (non-linear portion of curve) is considered the non-steady state and Fick's second law applies (Eq. 5 or 6). No true solution for this equation for a finite solid has been developed, but for those cases where the diffusion coefficient is independent of concentrations and boundary requirements are stated, a number of mathematical approaches have been postulated. Of these, the works of Daynes (39) and Barrer (40) are perhaps the most widely accepted.

The equation which has found considerable use in the evaluation of D , P , and S is Barrer's equation (40), often referred to as the "time-lag" equation or method, which may be stated as

$$D = \frac{l^2}{6\tau} \quad (\text{Eq. 11})$$

where l is the thickness of the film and τ is referred to as the "time lag" which may be found by extrapolating the linear portion of the curve (see Fig. 4) to the time axis. This value, τ , may then be used to calculate D in the above equation. The permeability constant, P , can be evaluated from the slope of the linear portion of the line. Since D and P are known it is a simple matter to find S .⁴

As may be expected, temperature will have a direct effect on D , S , and P . Experimental data at various temperatures will follow the Arrhenius relationship and thus

$$D = D_0 \exp. (-\Delta E_D/RT)$$

$$S = S_0 \exp. (-\Delta H/RT)$$

$$P = P_0 \exp. (-\Delta E_p/RT) \quad (\text{Eq. 12})$$

where D_0 , S_0 , and P_0 are pre-exponential factors, ΔH is the heat of solution, ΔE_D the activation energy for the diffusion, and ΔE_p activation energy for permeation.

Studies of transmission of gases through permeable materials are not new. Graham, in the 1860's, had investigated the penetration of gases through rubber. Greater emphasis on these types of studies increased with the development of the synthetic materials for both theoretical and practical reasons.

⁴ $D = \text{cm.}^2/\text{sec.}$; $P = \text{ml. (S.T.P.)mm./cm.}^2/\text{sec./cm. Hg.}$; $S = \text{Gm./Gm./cm. Hg.}$ It should be noted that other units have and may be used for these three terms.

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

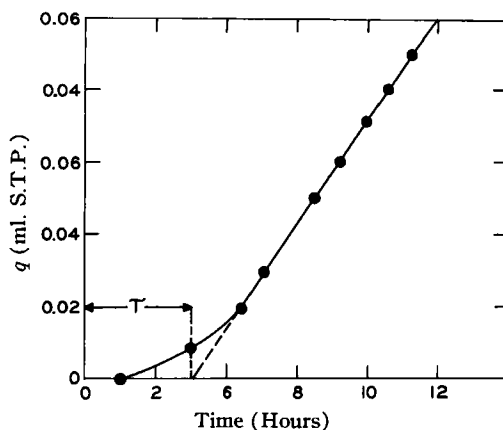


Fig. 4.—Plot of gas transmission vs. time through a plastic film.

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

appears that permeation follows in somewhat the same general order as seen for rubber—the more crosslinking, the less permeation (54).

Table V is taken from the work of Rogers, Meyer, Stannett, and Szwarc, and indicates the influence of crosslinking on the permeability of unirradiated and irradiated polyethylene to three gases. The higher dosed plastic showed a reduction in the permeation rate revealing an appreciable increase in crosslinking, whereas the lower dosed material apparently had little change in the crosslinking, as may be surmised from the lack of a significant change in the permeation rate.

Many of the currently used plastic materials for packaging purposes have various degrees of crystallinity. As has been indicated, the greater the degree of crystallinity the less will be the permeation rate. This is an oversimplification of a rather complex phenomenon, but a number of authors have attempted to describe the influence of crystallinity on the permeation rate (55, 56). An example of the effect of crystallinity on permeation may be noted by observing Table VI. With both polyethylene and polychlorotrifluoroethylene with the three gases, a decrease in permeability takes place as the approximate crystallinity increases.

It has been theorized that a decrease in permeability of permanent gases in materials of high crystallinity is probably due to the decrease in the diffusion constant, since little

change occurs in the solubility constant of the gas in the material. At one time, it was believed that the diffusion constant was related by simple proportion to the amorphous content of the plastic (57). This has since been proved as false (56). Other reasons influence the diffusion constant of the gas. Crystallite zones may have an effect on the geometric structure of the amorphous zones, giving rise to difference in diffusion and, of course, on permeability. Michaels and Parker clearly state that diffusion of a gas in polyethylene is not solely a function of the degrees of polymer crystallinity, even though it is highly dependent upon it (58). They point out that the crystallite shape has an influence in altering the diffusion which, in turn, alters the permeability.

Several investigators have indicated that polyethylene permeability can be related in a linear fashion to the density of the material (59, 60). This prediction seems not to have been verified by Brandt (61). Lasoski and Cobbs (62) postulate that permeation will be more apt to be related to the square of the density of the material. Alter (63) in a critical investigation of permeation and using the previous concepts of Myers, *et al.* (64), Klute (59), and Lasoski and Cobbs (62) developed the simple expression $P = K(1 - d)^n$, where K is a constant characteristic of each gas, n is an exponential value without further definition, and d is the density, for relating permeation to

TABLE V.—PERMEABILITY CONSTANTS FOR POLYETHYLENE (INFLUENCE OF CROSSLINKING)^a

Gas	Temp., ° C.	Unirradiated	Irradiated	
			10 ⁷ rad	10 ⁸ /rad
Nitrogen	0	2.59 × 10 ⁻¹⁰	2.67 × 10 ⁻¹⁰	1.46 × 10 ⁻¹⁰
	15	7.84	7.72	4.36
	30	21.5	20.1	11.0
	45	54.6	50.6	27.4
Oxygen	0	11.0	...	5.91
	15	27.5	...	15.3
	30	69.4	...	34.8
	45	143	...	73.7
Carbon dioxide	0	54.7	54.6	29.7
	15	130	129	72.7
	30	280	277	152
	45	540	542	287

^a In part: Rogers, C. E., Meyer, J. A., Stannett, V., and Szwarc, M., "Permeability of Plastic Films and Coated Papers to Gases and Vapors," Tappi Monograph Series No. 23, New York, 1962, p. 20.

TABLE VI.—EFFECT OF CRYSTALLINITY ON GAS PERMEABILITY^a

Polymer	Approximate Crystallinity, %	P, at 30° C.		
		N ₂	O ₂	CO ₂
Polyethylene	60	1.9 × 10 ⁻⁹	5.5 × 10 ⁻⁹	25.2 × 10 ⁻⁹
	69	0.66	2.1	7.4
	81	0.27	1.1	4.3
Polychlorotrifluoroethylene	30	0.008	0.05	0.11
	80	0.004	0.013	0.03

^a Myers, A. W., Rogers, C. E., Stannett, V., and Szwarc, M., "Permeability of Plastic Films and Coated Papers to Gases and Vapors," Tappi Monograph Series No. 23, New York, 1962, p. 53.

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.

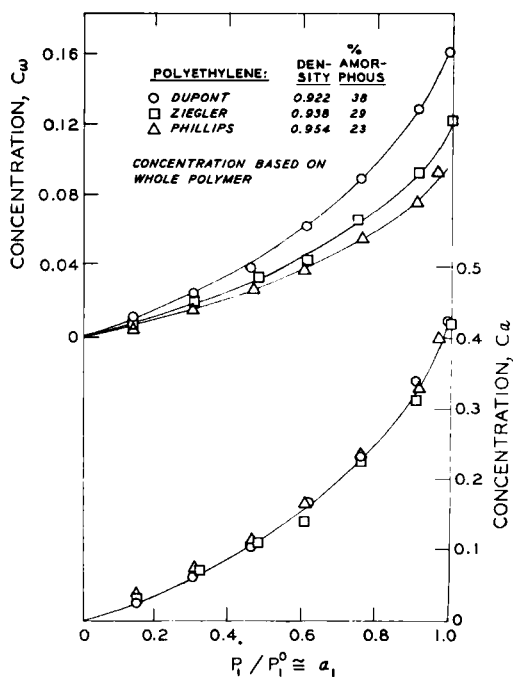


Fig. 5.—Sorption isotherm for polyethylenes and methyl bromide to 0°C. [From Rogers, C. E., Stannett, V., and Szwarc, M., *Tappi*, **44**, 715 (1961).]

As has already been noted on organic vapors, solubility plays an extremely important role in the permeation phenomenon. Reference has also been made that the chemical structure of the penetrant will either increase or decrease the solubility in a particular plastic. One other factor must now be brought to light in permeation of organic vapors: the geometry of the particular organic molecule. It has been found, for example, that as the size and the shape of the penetrant molecule increases, a similar increase in solubility will occur. Figure 6 illustrates a linear relationship between solubility and the molar volume of various penetrants. Solubility (at zero concentration of penetrant) appears also to increase as the cross-sectional area of the penetrant increases. The overall effect upon permeation is not as great as might be expected, since diffusion decreases as the volume and shape of the penetrant increases. Other factors, of course, are involved and for this reason it becomes quite difficult to predict the behavior of certain organic vapors in a particular plastic material.

In general, permeation will usually increase with an increase in temperatures. For the permanent gases, the permeability-temperature relationship follows the accepted Arrhenius relationship. With organic vapors, however, this may or may not be the case, depending upon the vapor pressure. For example, it has been found that certain vapors (at a definite vapor pressure) will show a gradual decrease in permeation as the temperature is lowered until a critical temperature is reached, at which point further decrease in temperature will reveal

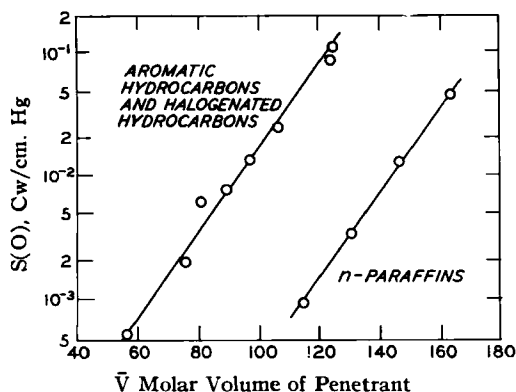


Fig. 6.—Effect of molar volume of penetrant on $S(O)$; polyethylene density 0.922 Gm./ml. at 25°C. NOTE: $S(O)$ is the intrinsic solubility coefficient for a penetrant of zero molar volume. [From Rogers, C. E., Stannett, V., and Szwarc, M., *Tappi*, 44, 715(1961).]

an increase in permeation (51). From what has been discussed on vapor pressure permeability, it may be seen that the phenomenon is not a simple mechanism and will be altered by many factors, each having some part in the overall mechanism.

Water Vapor.—Water vapor transmission through plastic materials, like a number of the organic vapors, is quite complex and often the results are difficult to interpret. Earlier measurements on water vapor permeability have been found to be in error because of the presence of dissolved air in the vapor (66). The method of evaluating the diffusion constant by the time-lag method will also lead to serious errors (67). Myers, *et al.* (67), found it necessary to calculate the diffusion constant from sorption and permeation data. The rate of permeation is, as might be expected, dependent upon the physical and chemical properties of the particular plastic film. In general, it is possible to describe two general types of permeation: (a) those that are dependent on pressure and (b) those that are independent of pressure. Past experience has demonstrated that the pressure-dependent permeation follows for most of those polymeric materials which are hydrophilic in nature, such as cellophane, nylon, and polyvinyl alcohol, while the pressure-independent permeation is seen for the hydrophobic polymers, such as the polyethylenes (see Fig. 7).

Pressure dependent permeation (*i.e.*, with nylon) will show large rates of permeation as the vapor pressure increases. This result is due to the ability of the nylon to attract water vapor molecules which are then sorbed to the various polar sites. As the concentration of water in the nylon increases, a swelling and plasticizing effect takes place, which in turn aids the diffusion process. Since both the solubility and the diffusion constants are increasing, the final permeation constant will also be increased. An unusual effect may also be noted with nylon, which in a manner has already been mentioned with certain of the organic vapors (67). For example, an increase in temperature after a certain point will show a decrease in permeation (see Fig. 8). This may be explained in the following way. As the temperature is decreased at a fixed vapor pressure, the relative humidity increases. This increase in humidity is reflected by an increase in solubility in the nylon which accelerates the diffusion process to a much greater extent than the decrease in diffusion normally attributed to a reduction in temperature.

Permeation through the hydrophobic plastics (*i.e.*, polyethylenes) for the most part are

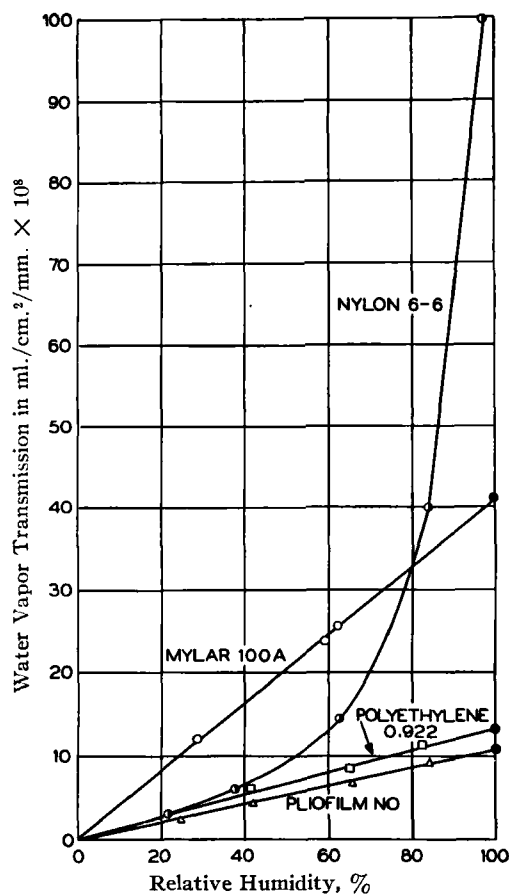


Fig. 7.—Water vapor transmission as a function of humidity for various plastic films. [From Myers, A. W., Meyer, J. A., Rogers, C. E., Stannett, V., and Szwarc, M., *Permeability of Plastic Films and Coated Paper to Gases and Vapors*, Tappi Monograph No. 23, 1962, p. 62.]

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

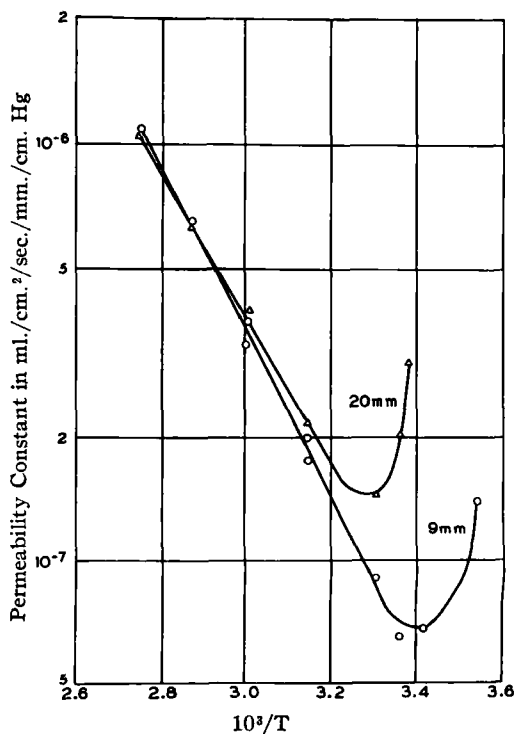


Fig. 8.—Temperature dependence of the permeability constant for water in nylon 66 at vapor pressures of 9 and 20 mm. Hg. [From Myers, A. W., Meyer, J. A., Stannett, V., and Szwarc, M., *Tappi*, 44, 58(1961).]

than presently available would be needed to explore the various factors which might alter the container to permeation.

Let us for a moment consider some consequences of gas transmission through the walls of a plastic container into a particular drug system. For those agents which are prone to oxidation, a rapid degradation may take place before the useful shelf-life of the product has been reached. Various product development laboratories have noted this effect with one or more of their drug products. Often, even the product development groups have not properly assessed their product in a plastic container to the embarrassment of the company, since reports start arriving indicating that a change in color or a precipitate has formed when the pharmacist, medical practitioner, or patient is about to utilize the medication. Oxygen or air perhaps is the most serious offender in destroying the product, but at times the transmission of carbon dioxide alters the pH of the preparation enough to catalyze degradation by either an oxidation or hydrolysis mechanism. Other problems may be seen due to the transmission of ambient gases, either inside the container or outside. For example, distortion of the container, either collapsing or bulging of the bottle, may be attributed to the transmission of air either out of the container or into the container. Even though there may not be any adverse effect upon the therapeutic efficacy of the medication, the distorted appearance of the container will certainly not add prestige to the company's name.

Vapors and Liquids.—Since 1950 a number of investigators have directed their attention to studying advantages and disadvantages of plastic containers (68-75). Perhaps the most work has been done on regulation-size bottles composed of one of the polyethylenes. Invariably these studies include filling a bottle with a specific ingredient (liquid), stoppering, and exposing it to various temperatures for short and long periods of time, while noting the loss or gain in weight. Pinsky, Nielsen, and Parlman (68) have reported in one study the results of 67 typical chemicals which can be represented by one of the following groups: (a) inorganic acids, (b) alkalis, (c) organic acids, (d) alcohols, (e) polyhydric alcohols, (f) esters, (g) ethers, (h) aldehydes, (i) ketones, (j) anhydrides, (k) terpenes, (l) nitrogen-containing compounds, (m) aliphatic hydrocarbons, (n) aromatic hydrocarbons, (o) chlorinated hydrocarbons, and (p) miscellaneous. In studies of this type, it is usually found that for the

same material, liquid permeability will invariably be higher than vapor permeability. Table VII will show this trend, taken from the work of Martinovich and Boeke (76). Even though theoretically it is assumed that permeability should vary inversely with the thickness of the plastic, in actual practice, using bottles, this may not be the case.

TABLE VII.—VAPOR AND LIQUID PERMEABILITY OF MARLEX 50^a AT 80° F.^b

Chemicals Used	Vapor Permeability ^c	Liquid Permeability ^c
Amyl alcohol	0.353	0.268
Ethylene glycol	0.669	0.873
Acetic acid	0.940	0.993
Aniline	1.09	1.27
Ethyl alcohol	1.26	1.77
Oil of peppermint	1.36	1.75
Butyric acid	1.54	3.61
Benzaldehyde	2.45	3.92
Methyl salicylate	3.39	3.92
Methyl ethyl ketone	4.12	8.05
Amyl acetate	5.54	6.75
Diethyl ketone	7.67	7.67
Ethyl valerate	8.11	9.69
Butyraldehyde	9.86	12.58
Ethyl acetate	13.7	13.7
<i>n</i> -Butyl ether	19.3	34.3
Butyl iodide	52.04	112.72
Heptane	54.0	69.7
Butyl chloride	69.63	86.05
Butyl bromide	76.15	113.19

^a Trademarked name for Phillips' high density polyethylene. ^b Martinovich, R. J., and Boeke, P. J., "Technical Information on Marlex," Sales Service Lab., Phillips Petroleum Co., Bartlesville, Okla., Oct. 1957, p. 2. ^c Expressed in Gm.²/24 hr./100 in.² mil thickness.

Results of studies have also revealed that formulations containing volatile ingredients might change, when stored in plastic bottles, because one or more of the ingredients are passing through the walls of the container (77). Often the aroma of cosmetic products becomes objectionable due to preferential transmission of one of the ingredients, or the taste of medicinal products changes for the same reason (78). The plastic container may also have an influence upon the physical system making up the product. For example, certain water-in-oil emulsions cannot be stored in the hydrophobic plastic bottles, since there is a tendency for the oil phase to migrate and diffuse into the plastic.

Heise, Parlman, and Pinsky (73, 74) have done considerable noteworthy work on plastic containers and have made a number of suggestions on how to select a particular container for a general type of product. Even more noteworthy, however, is the series of tests their group has developed to help interested parties evaluate the merits of a container. They include the following tests (74): environmental stress-crack test, using Igepal CO-630 water solution,

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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