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*Review Article*

# Plastics in Pharmaceutical Practice and Related Fields. Part II

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[Contents for Part I of this review appeared in the January issue; THIS JOURNAL, 52, 1(1963).]

## Leaching

A CONSTITUENT which migrates from a plastic material into a drug system or into a biological system may, for our purposes, be headed under the term *leaching*. In a résumé of this subject, it might be convenient to consider plastic devices or items in two categories. The first of these are plastic materials which can be shaped or composed into a device without the addition of other ingredients. These may be referred to as *pure* plastics, keeping in mind that pure will mean a material composed of only the polymer or copolymer. The second class or category can be called *compounded plastics*, and these materials will be composed

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of the polymer or copolymer with the addition of other ingredients.

**Pure Plastics.**—The pure plastics should present few problems to the pharmaceutical or medical practitioners in regard to leaching. That there never may be problems, however, is too much to expect even from the so-called pure plastics. The reason will become obvious when it is mentioned that often ingredients are added in very small quantities to stabilize or impart a specific property to the plastic. Since these ingredients are in very small quantities, they often are not revealed as being in the plastic. Other ingredients, such as mold release agents, or even contaminants, can become part of the plastic during the history of manufacture of the particular item. For example, it has been found that when used plastics are reground in a worn-out machine, trace metal contaminants can appear in the final plastic item. On occasions, there may be the possibility of using several pure plastic materials from different sources. Usually, these plastics are formed in pellet or powder form for convenience of use to the manufacturer of the plastic item. One supplier may add a stabilizer to his pellets or powder, which is not added to the material from the second supplier. Other situations could be revealed which would strongly suggest that the pure plastic is not in reality as pure as is believed. These trace amounts of other ingredients could cause some problems to either a drug system, to blood, or to a biological system. In the past few years reports, unfortunately not well documented, showed certain unusual results when plastic Petri dishes were employed in a laboratory (79). A change to another plastic dish, from another company, produced results which were more in keeping with the behavior of the organism.

Untoward problems may arise with the pure plastics when colorants are added to the formula. Even though these colorants might be in relatively small concentrations, the particular dye might migrate into a solution and cause a toxic effect. An example of this was seen by Autian and Brewer (80) in the development of new plastic-hubbed hypodermic needles. They noted that certain of the formulations would release a constituent to saline solution which, when injected into the mice, would cause death. Further investigation of this problem revealed that certain of the colorants could cause the toxic response.

**Compounded Plastics.**—As has been indicated in the first portion of this review, certain advantages may be gained by the addition of other ingredients to a polymer material. Perhaps the most important property to be gained is flexibility which, of course, would seem to be requisite for tubings which are to be used either to collect body fluids or to transfer drug solutions, blood, and other liquids into the body. The plastic which has found the most use as tubing material is polyvinyl chloride. A properly formulated polyvinyl chloride contains a plasticizer, stabilizing agent, antioxidant, and perhaps other ingredients such as a colorant. Often the final material is composed of 40 to 60% of the other ingredients, primarily of the plasticizer. The presently used polyvinyl chloride tubings for various purposes in medical practice may represent a great many formulas, without the actual formulation being revealed. This, of course, is regrettable since information of this type would prove exceedingly helpful to those who are interested in evaluating the merits of a particular polyvinyl chloride device.

One wonders how much thought was given to the use of compounded plastic materials for those devices which are to have contact with various drug systems or body tissues. The very prospect of migration of one or more ingredients from the material to a solution or tissue would seem to preclude the use of these materials until satisfactory tests are first performed. It is to the credit of several responsible firms that proper evaluations were first conducted prior to the introduction of these items to medical practice. One must, however, always be alert to the possibility of untoward reactions or problems when compounded plastics are employed.

Autian and Kapadia (81) noted that various polyvinyl chloride tubings used for medical purposes would release a constituent to several solvent systems employed in parenteral preparations. A revealing study was made by Thomas and Lagrange (82) on the leaching characteristics of several plastic materials. They exposed these materials to sodium chloride injection and to dextrose injection for a period of time and found that the polyvinyl chloride released a significant quantity of one or more ingredients to the solution. On further analysis, they found that a plasticizer and a stabilizer were the leached constituents. Hemolytic studies revealed that an organo-tin compound, used as the stabilizer, caused the reaction while the plasticizer showed no ill effect on the cells. The question of toxicity due to leaching from plastics was brought to the attention of Meyler, Willebrands, and Durrer (83), who observed

an unusual reaction during a heart perfusion study. The event was noticed directly after plastic tubings were substituted for the conventional glass. In this particular instance, the plastic tubing was a brand of polyvinyl chloride which released a constituent to a perfusion liquid, which in turn caused a cardiotoxic response to an animal heart. Further study of the problem led to the conclusion that the plasticizer was not the culprit, but rather a stabilizer used in the formulation of the plastic tubing.

A recent study in the author's own laboratory should be of interest to the reader for it does demonstrate that even several of the present tubings might cause a toxic effect, if not properly used. In this particular study, a number of unit packaged tubings (most were of the vinyl type) used for various purposes in hospitals were obtained. Many of these tubings were labeled as sterile, pyrogen free, and several indicated that they had been animal tested. Samples of these tubings were implanted into the muscles of rabbits, as suggested by Brewer and Bryant (84), and after from 3 to 7 days they were sacrificed and the area of the implants morphologically examined for any tissue response. Several of these tubings revealed a striking effect upon the tissue which could not be easily overlooked. Gas chromatographic techniques indicated that a number of components would be released to a solvent system composed of alcohol-water systems. Up to this writing, the actual component causing the toxic effect has not been found, but it appears that it may be due to one of the stabilizers. There appears to be little published information on intravenous, subcutaneous, and intramuscular toxicity of the various plasticizers, stabilizers, and antioxidants currently being used in the formulation of polyvinyl chloride tubings. It should be mentioned, however, that most of these ingredients have passed the requirements under the new food additive amendment and are considered nontoxic compounds. But, one should keep in mind that these tests include oral feeding tests and not tissue study tests. This last statement should perhaps be taken with some seriousness since it should dispel the idea that "FDA Approved," at the present time, means that the particular plastic device has been approved by the FDA. Rather, it should be noted that the ingredients used in the device have been approved for a food packaging application, not for a medical application.

From what has been said on leaching, it will be obvious that the solvent can have an appreciable influence on the migration of an ingredient from the plastic to the liquid phase. Further complications can develop when one or more solutes are present in the solvent. One example may illustrate this point. A polyvinyl chloride sheet was exposed to various concentrations of benzalkonium chloride (85). The results indicated that the cationic agent was sorbed by the sheet, but during the sorption process an ingredient or ingredients was being released to the solution. Some thought should also be given to the pH of the solution since experimental evidence has demonstrated that the rate of release might be somewhat dependent upon the hydrogen ion concentration of the surrounding liquid.

### Sorption

**Introduction.**—When a solution is in contact with a solid phase, both the solvent and solute molecules will be striking the solid surface. If the conditions are optimum, both types of molecules may be adsorbed to the surface of the solid. Normally with "nonreactive" materials the quantity of molecules, either solvent or solute, will be negligible and for all practical purposes it may be assumed that no adsorption has taken place. On the other hand, if the chemical structures of the components making up the solid phase are of such a nature that they can electrically attract a molecule in the solution with comparative ease, a situation may exist (depending upon the total surface area of the solid phase exposed to the solution) where a significant quantity of the solute might be removed from the solution. With plastic materials there is usually not only surface attachment, but actual penetration of the solute molecules which in turn come into contact with particular attraction sites in the polymer. In fact, it may be assumed that the greatest extent of uptake of the solute from a solution would be a consequence of the solute penetrating and diffusing into the plastic. This of course, without describing any mechanism of interaction, is exactly what occurs with most dyes in both the natural and synthetic yarns. Drug uptake or binding to a particular plastic can be considered as following one of the many postulated mechanisms for dye-yarn interaction. In general, the interaction is a physicochemical phenomenon, directly related to the chemical structure of the drug and the particular physical and chemical properties of the plastic. A number of other factors will materially affect the uptake and it is well to mention the more important ones:

concentration of solution, particular solvent system, other agents in the solution, pH of the solution, temperature, time of contact, quantity of plastic exposed to solution, purity of plastic, and possible changes in the plastic material after exposure to solution.

To prevent confusion, the term *sorption* will be used in this section to indicate that both adsorption and absorption are taking place, even though one may predominate. The terms *uptake* and *binding* will be used with the understanding that both terms may refer to either equilibrium or nonequilibrium conditions.

It has already been demonstrated that plastic materials are composed of crystalline regions, dispersed throughout amorphous regions. Under the discussion on permeation of gases, the point was clearly emphasized that the penetrant molecule probably could not travel through the crystalline region, but must find passageway in the amorphous zone. Solute molecules in a solution differ not from the picture given for the gas molecules and it may be assumed, except in unusual instances, that these molecules (solute) can travel or diffuse only through the amorphous zone where they become affixed to a particular site in the polymer.

One general method of studying solute-plastic interactions is by the measurement of the quantity of solute taken up at equilibrium by a plastic material at a constant temperature and pressure. The resultant data may then be fitted to one of two basic expressions. The first of these is the empirical relationship of Freundlich (86), which may for this purpose be written as

$$\log q = \log k + 1/n \log C \qquad \text{(Eq. 13)}$$

where $q$ is the quantity of drug or other chemical agents sorbed by a specified quantity of plastic, $k$ and $n$ are constants, and $C$ the equilibrium concentration of the agent in the solution. The second, based upon kinetic considerations by Langmuir (87), may be depicted as shown below

$$\frac{1}{q} = \frac{1}{kSC} + \frac{1}{S} \qquad \text{(Eq. 14)}$$

where $k$ is constant and $S$ may be considered as the theoretical saturation value of solute which will be sorbed by the plastic. A plot of $1/q$ *vs.* $1/C$ will produce a straight line from which the intercept, $1/S$, may be found (see Fig. 9).

Often it is highly desirable to express in a quantitative manner the affinity of a particular drug or agent for a plastic material. In this

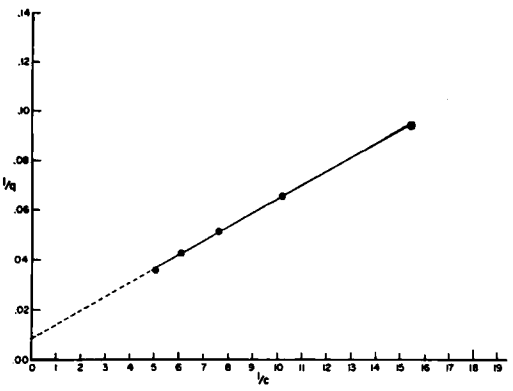


Fig. 9.—A Langmuir plot of sorption data of salicylic acid by nylon at 41.5° C. [From: Kapadia, A. J., Guess, W. L., and Autian, J., "Sorption and Diffusion Studies of Salicylic Acid in a Nylon Sheet," to be published].

instance recourse has been made to the partial molar-free energy or chemical potential ($\mu$). For example, it should be clear that if the chemical potential of a solute in one phase is greater than the potential in a second phase, there will be a driving force moving the solute molecules from the higher to the lower phase. At equilibrium, both chemical potentials would be equal and the driving force would be reduced to zero. It is possible to express the chemical potential of solute as (88)

$$\mu = A + RT \ln a \qquad \text{(Eq. 15)}$$

where $A$ is a constant, dependent upon the temperature and pressure but independent of composition, $R$ and $T$ the usual symbols for the gas constant and absolute temperature, while $a$ is the activity of the solute. By comparing the chemical potential in any given state to that in a standard state, represented as follows

$$\mu^o = A + RT \ln a^o \qquad \text{(Eq. 16)}$$

and subtracting this last equation from the previous one will give

$$\mu - \mu^o = RT \ln a/a^o \qquad \text{(Eq. 17)}$$

Now if in the standard state $a^0$ is given the value of unity, Eq. 17 will reduce to

$$\mu = \mu^o + RT \ln a$$

If we now consider a drug or solute distributed between a liquid phase (in solution) and a solid phase (plastic), we can write the expression depicting the conditions in both phases as

$$\mu_l = \mu_l^o + RT \ln a_l \quad \text{(for liquid phase)} \qquad \text{(Eq. 18)}$$
$$\mu_s = \mu_s^o + RT \ln a_s \quad \text{(solid phase)}$$

but at equilibrium

$$\mu_1 = \mu_s$$

or

$$-\Delta\mu^o = RT \ln a_s/a_1 \qquad \text{(Eq. 19)}$$

If it is assumed that the solute forms an ideal solution in both phases, activities may be replaced by concentration or

$$-\Delta\mu^o = RT \ln C_s/C_1 \qquad \text{(Eq. 20)}$$

The difference in standard chemical potential ($\Delta\mu^o$) may now be considered as the quantitative measure of the tendency of a drug or solute to move from its standard state in a liquid to its standard state in the plastic. Furthermore, this standard chemical potential may be taken as the affinity of the drug or other agent toward a particular plastic.

Equation 20 is based upon ideal conditions, a state which is often difficult to attain in practice and for this reason other more complex expressions have been developed for the evaluation of the affinity. It also appears that each particular plastic material might require a separate equation. Gilbert and Rideal (89) were one of the first to formulate a mathematical expression which could be applied to a practical situation; in this case the interaction of mineral acids with insoluble fibrous materials. Others have since used the Gilbert and Rideal equation directly, or have modified it, to fit their particular needs. Vickerstaff reviews a number of these expressions, based upon the postulated mechanism of interaction, and the reader should refer to his text for further information (90).

Little, if any, data have been published on the affinities of various agents to plastic materials, but considerable data exist for various dyes and textile material (90). Unfortunately, some of these data are in error due to the collection of results at conditions other than at equilibrium. It would seem, however, that the standard chemical potential could be used to indicate the affinity of a drug to a specific plastic material if and when such information becomes of sufficient interest to those in the pharmaceutical or research field.

Negligible uptake or sorption will be noted, at least by conventional analytical means, for a number of drugs and plastic materials. For example, with our present information it can be assumed that little sorption will occur with those plastic materials which do not have polar sites, the possibility of high uptake or sorption are minimal and often not easily discerned unless very large surface areas are exposed to the solution. Significant sorption will, however, be seen for those hydrophilic plastic materials (nylon, cellulose, acetates, etc.) which will permit the diffusion of the solute. As might be anticipated, the physical and chemical properties of the solute will also be a determinant for sorption for it appears likely that the interaction between a solute molecule and the polymer is one of an electrical nature, whether it be one of ion-ion type, dipole-dipole, ion-dipole or through secondary valence forces, such as Van der Waals' forces, or perhaps a combination of these.

In order to represent the sorption process in a simple manner, Fig. 10 is presented. Here it may be seen that a drug molecule, $D$, is in solution in contact with a polar plastic material. The parallel lines in the plastic material represent the crystalline zone or region, while the lower lines attempt to portray an amorphous region in the same plastic. Sites for possible interaction in the polymers are shown by the dots. When the solute molecules are placed into the solvent, one or more will diffuse toward the surface of the plastic and become adsorbed. When most of these surface sites are filled, there will be sufficient energy to permit these solute molecules to penetrate the surface and to travel or diffuse into the amorphous zone of the plastic where new binding sites become available. When all available sites are filled, equilibrium has been reached and sorption attained at one specific temperature and pressure. In most instances it will be correct to assume that the rate determining step of the sorption process is the diffusion of the drug in the matrix of the plastic and if this is the case, then special emphasis must be placed upon the diffusion constant or coefficient.

**Diffusion.**—In reviewing, even briefly, aspects of diffusion in insoluble materials such as plastics, it will be necessary once again to allude to some of the work of dyers and colorants in the textile industry, since this group by far has been concerned to a greater degree and depth in this facet of research than perhaps any other single group.

The usual experiments which have been utilized for the study of diffusion of solute molecules in insoluble polymeric materials may be divided into two general types: studies under a steady-state condition, and studies under nonsteady-state conditions.

Perhaps the simplest method of evaluating the diffusion coefficient of a solute in a plastic is to set up an experiment under the steady-state condition. In one compartment a known

solution of the particular solute is placed, while in the other an equal quantity of water. At repeated intervals, the water compartment is measured for solute which has permeated through the film. The data are then plotted as concentration of drug or agent appearing in the water compartment against time. The curve will initially curve, but after a steady-state condition is reached, a linear relationship will be observed from which the diffusion coefficient may be calculated using the familiar time-lag equation already given under permeation

$$D = \frac{l^2}{6\tau} \qquad \text{(Eq. 21)}$$

where $l$ is the thickness of the film and $\tau$ the time lag or the point where the straight portion of the curve crosses the time axis (see Fig. 4).

Even though the steady-state condition has much to be desired in evaluating diffusion coefficients, often it becomes impossible to use this method and one must therefore turn his attention to experiments where nonsteady-state conditions exist. Under the nonsteady-state conditions, where the concentration of the solute in the plastic is continually changing, Fick's second law is applicable or

$$\frac{dC}{dt} = D\frac{d^2C}{dx^2} \qquad \text{(Eq. 22)}$$

where $C$ is the concentration, $D$, $t$, and $x$ are terms already defined. It is not, however, possible to solve for $D$ in the above equation directly and hence recourse must be made to other mathematical expressions which are in themselves special cases dependent upon the experimental design. These special cases, for convenience, may be divided into two broad categories: for "finite solutions" (or where the concentration of the drug in the solution does not appreciably decrease over the time period of the experiment), and for "infinite solutions" (or where the concentration of the drug in the solution does decrease over the time period of the experiment). Each of these categories may be further divided into the particular geometry of the plastic (*i.e.*, plane sheet, cylinder, or sphere) and whether the diffusion coefficient is constant or varied over various concentration ranges of the solute in the plastic. Representa-

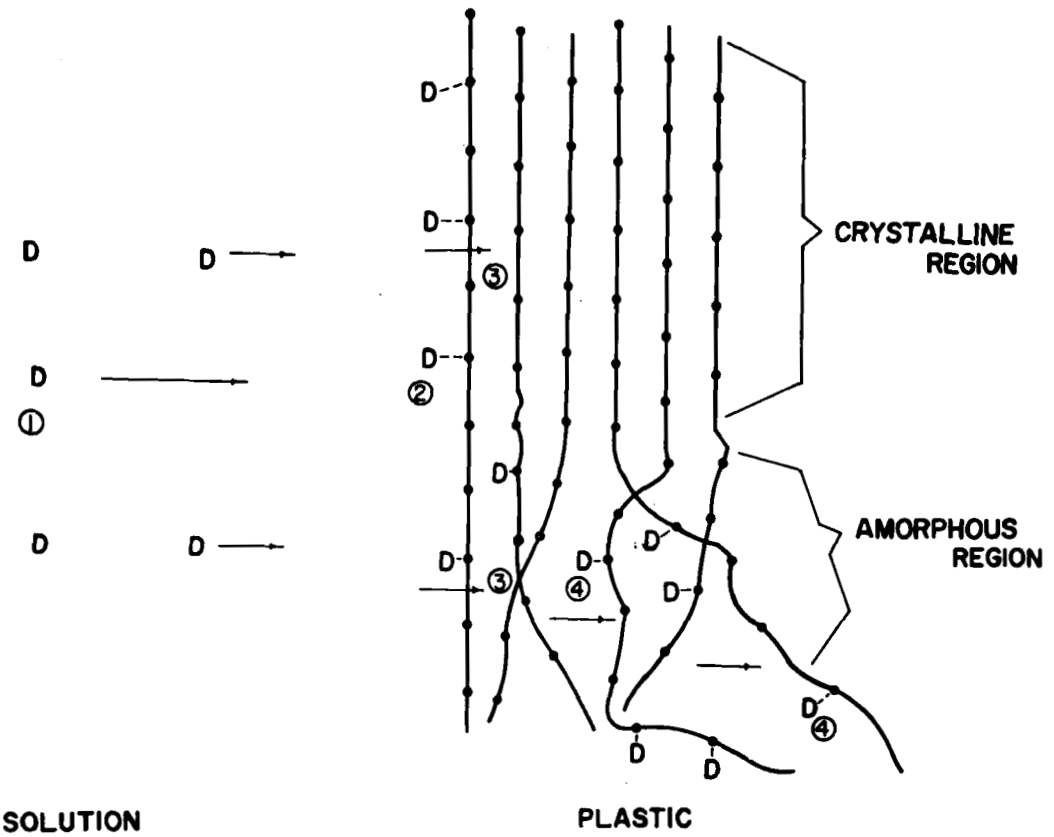


Fig. 10.—A schematic model showing sorption of a drug by nylon. D = drug molecule; -- = polymer chain; and • = binding sites in polymer.

tive mathematical expressions will be given for several of these special cases in the section to follow, but for more details the reader should become familiar with several texts on the subject of diffusion, in particular the books of Barrer (91), Jost (92), and Crank (93).

Perhaps the most work in the past for the calculation of diffusion coefficients has been based upon the "infinite solution" and a diffusion coefficient which may be considered as constant, an assumption which may not be correct, as we will learn later. For simplicity also, the plane sheet has most often been employed, even though the cylinder and sphere have received attention. For the most part, the mathematical expressions or methods have been derived for use with data collected from sorption studies.

McBain (94), as early as 1909, used an expression which apparently was borrowed from previous investigators on heat transfer problems to evaluate $D$ from adsorption data. The equation may be stated as

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\left(e^{-\pi^2 Dt/l^2} + \frac{1}{9}e^{-9\pi^2 Dt/l^2} + \frac{1}{25}e^{-25\pi^2 Dt/l^2} + \ldots\right) \quad \text{(Eq. 23)}$$

where $M_t$ is the concentration of drug or agent taken up by a sheet in time $t$, $M_\infty$ is amount of the drug or agent taken up at equilibrium, and $l$ is the thickness of the sheet. Hill in 1928 (95) used a nearly similar equation to calculate the diffusion of oxygen into muscle tissue and this particular equation has since been suggested for calculation of diffusion into cylinders.

Neal and Stringfellow (96) used Eq. 23 for the first time to calculate the diffusion coefficient of a dye in cellulose from absorption-time data. Crank and Henry (97) presented an expression following an infinite series as shown above for calculating $D$. This expression follows

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \times e^{-D_o\pi^2(n+1/2)^2 t/l^2}, \ldots \quad \text{(Eq. 24)}$$

For simplicity it is best to find a suitable value for $t/l^2$ for which $M_t/M_\infty = 1/2$ or

$$\left(\frac{t}{l^2}\right)_{1/2} = -\frac{1}{\pi^2 D_o} \ln\left\{\frac{\pi^2}{16} - \frac{1}{9}\left(\frac{\pi^2}{16}\right)^9\right\}, \ldots \quad \text{(Eq. 25)}$$

which may be reduced to

$$D_o = 0.04939/(t/l^2)_{1/2} \ldots \quad \text{(Eq. 26)}$$

Equation 26 can be used rather conveniently to find $D$. A sorption-time experiment is run from which $t$ at 50% sorption is found. Since $t$ and $l$ (thickness) are known, $D$ may be calculated. Up to this point it has been assumed that the diffusion coefficient was a constant and not dependent upon concentration in the plastic. Recently this has been found not to be the case for many systems and it has been surmised that (97, 98) values for $D$ using the above equations are actually average values and should be indicated as such or designated as apparent diffusion coefficients. Crank and Park (99), using Eq. 26 as a starting point, developed a method of evaluating $D$ as a function of concentration. These same authors have also found that desorption studies may also be used for the calculation of $D$ and that if both are considered, a better approximation for $D$ (than by either sorption or desorption) is possible.

In the past also, it has usually been necessary to run sorption experiments in such a manner that the concentration of the drug or agent in the solution would remain nearly constant. This problem has now been overcome by the development of newer mathematical expressions for "finite solutions" or for those cases where there is a decrease in the concentration of solution over the time period for equilibrium to be reached. Crank (93) gives full treatment to these methods in his excellent text on the mathematics of diffusion.

Since McBain's equation, a great many other equations of the same general type have evolved for both "infinite" and "finite" solutions. These usually have followed an infinite series which might be represented by the general expression (100)

$$\frac{M_t}{M_\infty} = 1 - A.e^{-BK} - C.e^{-FK} - G.e^{-HK} \ldots \quad \text{(Eq. 27)}$$

where $A$, $B$, $C$, etc., are numerical constants of known values and $K$ is equal to $Dt/l^2$ for a plane sheet (or if for a cylinder $l$ can be considered as the radius). The task of solving equations of this type are rather formidable and quite time consuming. Fortunately, the task has been simplified by preparing theoretical values of $M_t/M_\infty$ for various values of $K$. From these tables it becomes an easy task to evaluate the apparent diffusion coefficients, as is now described. First, a sorption experiment is run at a specified temperature and the data plotted as $M_t/M_\infty$ *vs.* the square root of time. If the diffusion is of a Fickian nature, a straight line relation will result.

Now a theoretical plot is made of $M_t/M_\infty$ *vs.* the square root of $K$ from data taken from

the appropriate table. This relationship will also result in a straight line. From the experimental curve at a definite $M_t/M_\infty$ value, the appropriate $t$ is found. In an identical manner and at the same $M_t/M_\infty$ value, $K$ is deduced. Since $K = Dt/l^2$ and since the values for $K$, $t$, and $l$ are now known, it is a simple calculation to find the diffusion coefficient.

This graphical method using appropriate tables has had great use, particularly in evaluating the diffusion of dyes in textiles. Since very little published work is available for the diffusion of drugs in plastics, only one example will be cited to demonstrate the ease with which these tables can be used. The particular case will be the work of Kapadia, *et al.* (101), who studied the diffusion of salicylic acid in nylon. Their particular experiment was of the "finite solution" type, using a plane sheet.

Sorption studies were conducted at various temperatures and a plot was made of $M_t/M_\infty$ *vs.* $\sqrt{t}$ as shown in Fig. 11. For each temperature the total amount of drug removed from the solution at equilibrium was found and equated to a per cent value. From Bertheir's table (see Fig. 12) and at the appropriate total per cent uptake

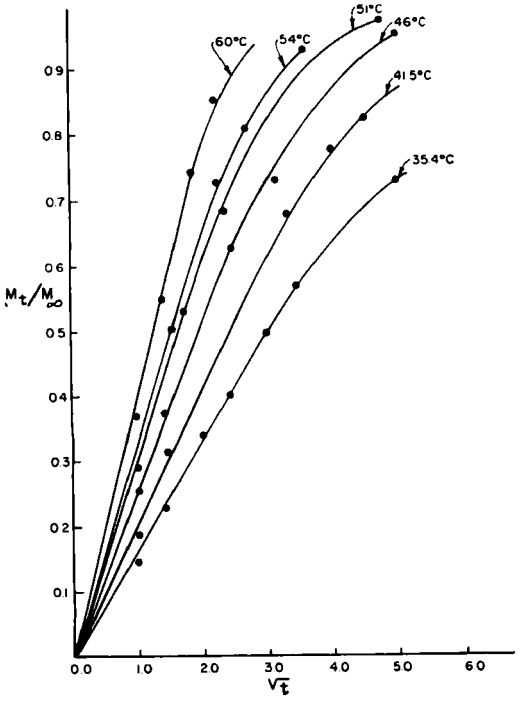


Fig. 11.—Fractional uptake of salicylic acid *vs.* square root of time at various temperatures. [From Kapadia, A. J., Guess, W. L., and Autian, J., "Sorption and Diffusion Studies of Salicylic Acid in a Nylon Sheet," to be published.]

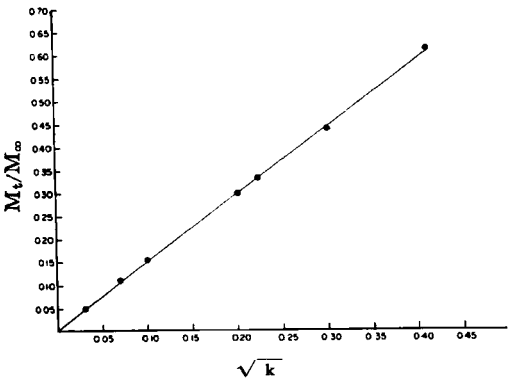


Fig. 12.—Theoretical plot of fractional uptake *vs.* the square root of $K$ at a total per cent uptake of 45.8. $K$ is taken from Berthier's table for a plane sheet. [Berthier, G., *J. Chim. Phys.*, **49**, 527(1952).]

TABLE VIII.—APPARENT DIFFUSION COEFFICIENT OF SALICYLIC ACID IN NYLON AT VARIOUS TEMPERATURES[a]

| Temperature, °C. | $D$, cm.²/sec. |
|---|---|
| 35.4 | $8.97 \times 10^{-10}$ |
| 41.5 | $1.26 \times 10^{-9}$ |
| 46.0 | $2.08 \times 10^{-9}$ |
| 51.0 | $2.73 \times 10^{-9}$ |
| 54.0 | $3.86 \times 10^{-9}$ |
| 60.0 | $5.91 \times 10^{-9}$ |

[a] Kapadia, A. J., Guess, W. L., and Autian, J., to be published.

(at equilibrium), corresponding $K$ values for each $M_t/M_\infty$ were used to draw a theoretical curve as shown in Fig. 12. In the manner already described, or by the method of slopes, the apparent diffusion for each temperature was calculated. These values are included in Table VIII.

Some remarks should be made in regards to the variable diffusion coefficients. Even though expressions have been developed for calculating these values as a function of concentration in the plastic, it becomes a bit more complex to arrange the experiment where accurate values of the concentration in a particular point of the plastic can be measured. McGregor, Peters, and Petropoulos in recent publications point out some of the fallacies inherent with previously used methods for studying the variable diffusion coefficients and recommend a microdensitometric technique for more accurate values of these constants (102–104). For extremely accurate work and where fundamental knowledge may be needed in regards to the diffusion of a drug into a solid material, the method of McGregor, *et al.* (102), may hold great promise. The exact technique, however,

will undoubtedly pose some problems which may be difficult to overcome in certain laboratories.

Mention might also be made of the advantage of using radiotracer techniques in diffusion studies. For example, Hayashi (105) has found this method as a very fast method for determining the diffusion of surface-active agents in nylon. Briner, *et al.* (106), have employed a liquid scintillation method for measuring the diffusion of certain agents in plastics. The radiotracer method makes possible the evaluation of diffusion in a substrate, which might not be feasible by the use of conventional analytical methods and it undoubtedly is a method which will receive greater attention in the very near future.

**Mechanism for Sorption and Factors Influencing the Process.**—*General.*—It has been pointed out in this review, and demonstrated experimentally in many instances, that diffusion of the solute in the matrix of the plastic is the rate determining step in the overall process of sorption. Here it should not be implied that little importance is attached to those instances when only surface adsorption occurs, but rather to indicate that when both adsorption (at surface) and absorption are taking place, most likely the quantity of solute adsorbed is insignificant to the amount absorbed. That serious consequences might arise when a very potent drug or an extremely active biological agent is adsorbed on the surface of a plastic, even in microquantities, is certainly not to be minimized and good pharmaceutical practice demands an appreciation of this fact.

The question now arises as to how best depict a mechanism for sorption of an agent by a plastic material. This task has presented a formidable obstacle to numerous conscientious investigators and it appears now that no one mechanism can describe all of the sorption process for all the varieties of plastic materials. In fact, often a number of theories can be used to describe the same interaction between a solute and a plastic. With our present knowledge, one must be content to accept certain, rather broad, generalities on the mechanism of sorption and then to turn his attention to a number of factors which may influence the sorption process.

Even though the uptake of a solute from a solution onto and into a plastic material is a sorption phenomenon, it should be clear that the chemical structure of both the solute and the polymer (making up the plastic) are the determining factors for sorption to occur. A second consideration, which can play a rather large role in the sorption process, is the physical condition of the particular plastic material. Here reference is made to the available regions in the plastic which will permit entrance and travel to the solute molecules, for without these passageways the solute will react only at the surface of the material. All other factors, such as pH, solvent systems, concentration of solute, presence of other ingredients in both the solution and plastic, and temperature only diminish or accent the magnitude of sorption.

*Effect of Structure.*—In considering structural relationship and uptake of drugs by plastic, one soon recognizes that little available literature has been compiled on this subject by the pharmaceutical and medical professions, the obvious reason being that sorption of a drug is highly undesired, and all efforts will be expended to prevent such an incident from occurring. One must, therefore, dip into the literature of other disciplines, in particular the textile group, to learn of the influence of the structure on uptake of chemical agents, primarily those which are used for dying of yarns (90). Other related data may be sifted from extensive work in the biological field on the binding of various agents to proteins (107–110) and protein-like compounds and recent contributions from the physical pharmacists on binding of drugs with macromolecules used in pharmaceutical systems (111–114). Data from the textile industry seem to be most closely related to our particular interest because textiles both chemically and physically resemble the plastic materials which are used in pharmacy and medicine and because textiles are solid materials, whereas the polymeric materials of the biochemists and the physical pharmacist have been primarily of the water-soluble type.

The greatest bulk of substrates investigated by the textile group has been those yarns which can be either of the cellulosic type (cotton, cellophane, cellulose acetate) or the polyamide type (silk, wool, and nylon). From these two types of materials and with the addition of other information, an attempt will be made to view certain structure features of the solute molecules which give rise to the interaction (and of sorption) between an agent and a polymeric material.

One important feature of a dye molecule is its ionic charge which can arise from such functional groups as the sulfo and carboxyl radicals for acidic dyes and from cationic quaternary

ammonium groups in basic dyes (115). The presence of this electrical charge, positive or negative, can cause either an interaction to take place or conversely can prevent an interaction. Other forces beside the ionic type for attracting and binding solute molecules to a polymer have also been recognized and it appears that the particular substrate will have a further influence on which force or combination of forces will support the interaction. For example, wool (a polyamide-like material) seems to have the ability of attracting any type of solute molecule, which will ionize in solution, while for substrates such as cellulose acetates or certain of the polyesters (Orlon), little uptake will be noted for those solute molecules which are in ionic form (115).

It seems to be well established that for cellulose fibers, the charge on the solute is of secondary importance and the particular structure and the geometric arrangement in the molecule are the most critical points in the dyeing or sorption process. A number of investigators have indicated that the dye molecule must be linear so that it can lie parallel to the polymer chain and further, that the molecule (dye) should contain polar groups spaced at critical intervals to interact with specific sites in the cellulose polymers (116–118). Vickerstaff points out that the dye-cellulose interaction seems to favor a "lock and key" process (115).

From the great number of studies on the dyeing of cellulose, Vickerstaff has been able to set down a number of requirements which a dye should meet in order to be considered for dyeing of cellulose material. These may be stated as follows (119):

1. The molecule should be capable of assuming a linear configuration.
2. The aromatic nuclei should be capable of assuming a coplanar arrangement.
3. The molecule should contain groups capable of forming hydrogen bonds.
4. The presence of a conjugated system of double bonds, which by resonance promotes coplanarity of the molecule and probably favors hydrogen bond formation by the groups at the ends of the conjugated chain.

Favorable, but not essential, conditions are (again from Vickerstaff).

5. Widely spaced hydrogen bond-forming groups.
6. The presence of the minimum number of solubilizing groups necessary for solubility.
7. The disposition of the solubilizing groups along one side of the dye molecule and of hydrogen bonding groups along the other side.

Until recently, little work of a physical chemical nature was conducted on the uptake of surface-active agents by cellulose materials. White and associates (120–122) made an intensive investigation of the absorption of certain cationic surface-active agents by cellulosic substrates (such as cotton). They theorized that the uptake was due to two processes, namely a cationic exchange between the surface-active agent and the polymer followed by an ion-pair absorption.

The acetylation of the hydroxyl groups in cellulose gives rise to commercially important materials such as cellophane and rayon. Alteration in the structure of the original material (cellulose) by the presence of acetyl groups produces a marked difference in the sorption of various solute materials. For example, most anionic dyes will not produce good coloring of rayon material as they will on cotton (123). Several reasons have been given for the inability of cellulose acetate to behave like cellulose (124). For one reason, the hydrophilic characteristic of cellulose acetate is decreased, which in turn prevents swelling (in water) in comparison to cellulose. This affords less opportunity for certain molecules to find passage through the material. A second reason for less uptake of a solute such as the acidic dyes (or anions) is the high negative surface potential on the cellulose acetate which repels the anionic molecules. Conversely, however, the cationic molecules become easily sorbed. Giles (125) has presented an interesting discussion on effects of structure on the dyeing of cellulose acetate. In his paper, he points out that a review of studies on adsorption (including absorption) gives rise to three general mechanisms of interaction: solid solution, polar forces, and nonpolar forces. Rather than coming to the conclusion that these mechanisms are conflicting, Giles gives recognition that all three types may be true, under certain circumstances. Several other interesting points are revealed in Giles' work. For example, as the number of hydrogen donating groups increase in a particular molecule, a general increase in uptake will be noted. There are instances, however, where this rule is not followed, but these exceptions might be explainable on the internal bonding of these functional groups, preventing the hydrogen from the solute molecule to bind with a negative site in the cellulose acetate. Steric hindrance may also block hydrogen donating groups (in the solute molecule) from interacting with the polymer. Forces of attraction may also be set up between hydrogen molecules of the cellulose acetate and negative sites in the solute molecule, forming the usual

hydrogen bond. Well-documented evidence is at hand to demonstrate the effect which the hydrophobic portion of the solute molecule will have on sorption of solute molecules by cellulose acetate and, in fact, with most types of substrates (125). In general, it will follow that in a related series of solute molecules, uptake of the solute will increase with an increase in an aliphatic chain.

Very little published information, if any, has appeared in which the objective of the investigator was to study sorption of drugs by cellulose acetate. Saski (126), however, has recently undertaken such a study and has demonstrated that sorbic acid will be bound to various degrees to the plastic, both from an aqueous and from a hydroalcoholic solution. It would be reasonable to assume that other similar agents would also be sorbed by the cellulose acetate, and it will be interesting to see how structural changes in the solute molecule will alter the overall uptake.

The protein fibers (silk and wool) and the polyamide fibers and plastics (nylon) present a very old substrate (silk and wool) and a relatively new substrate (nylon). In general, the uptake of certain agents on the above mentioned substrates follow to various degrees the same pathways but since nylon is a synthetic material and since more experimental work has been conducted on this substrate, the remaining portion of the section will be devoted to nylon.

Nylon has three polar sites in the molecule. On one end of the molecule there is a carboxylic acid group while on the other there is an amine group. Dispersed throughout the chain there are a number of amide linkages. These polar sites for the main part determine the binding phenomenon. Acidic dyes (salts of the various acid dyes are actually used) will interact with the terminal amino group in the following manner (127, 128). In a pH above 3.0 the end amino group will become positively charged. This positive charge will then bind the anion of the dye. In the stated pH range (above 3.0) there appears to be little interaction at the amide linkages. The carboxylic group seems to contribute little to binding of these acidic dyes. On the other hand, weak organic acids may be bound to both the terminal amino group and to the amide linkages (in this case by hydrogen bonding). Phenol appears to be bound only through hydrogen bonding to the amide linkages since acetylation of the amino group blocks completely the binding (129). As will be seen shortly, the pH of the solution will have a great effect on the uptake of acidic compounds.

Studies in the author's own laboratory have indicated that a great many weak organic acids will be sorbed by nylon (130–132). Those already studied include phenol, salicylic acid, the parabens, sorbic acid, benzoic acid, and derivatives of benzoic acid. Not all weak organic acids are bound, however, as may be witnessed by the work of Briner, Autian, and Skolaut (133) who found that no significant amounts of acetic acid, glycine, or tyrosine were sorbed by nylon. These results give further support to the already well-emphasized fact that with our present knowledge predictions of binding or uptake can only be considered as a hazardous guess—at least with the polyamides.

Cationic agents have been studied as to uptake by nylon and it appears that these interact at the negative sites in the polymer, but the exact mechanism has not been clearly defined. Guess and group (134) noted the uptake of both dicyclomine hydrochloride and benzalkonium chloride. Others have investigated the uptake of surface-active agents of the cationic type and found these also to be sorbed (105, 135).

Steric effects and internal bond formation may reduce the uptake of a particular solute molecule by nylon (as well as other substrates). For example, it has been found that salicylic acid will be bound to nylon in very large quantities, but that acetylsalicylic acid under identical experimental conditions revealed little or no binding (13).

One cannot ignore the influence of van der Waals' forces on the overall interaction between a solute and a polyamide (125, 129, 136). Many examples may be cited to demonstrate that in those molecules which are bound to various substrates, an increase in the hydrophobic characteristic will usually increase the uptake. Practical and theoretical work must still be pursued in regard to nylon as well as to other plastic materials in regard to the influence of the structure of the solute on uptake, in particular, those molecules which resemble or are considered as drugs.

*Effect of pH.*—Sorption of a particular solute by a plastic material will not only depend upon the structure of the polymer and the solute, but may also depend upon the hydrogen ion concentration of the solution. This of course is true of those agents which might be classified as weak organic acids or weak organic bases. The polyamides (nylon) are a good substrate to illustrate an example where pH influences the

uptake of weak organic acids. A number of textile investigators have observed that acid dyes will have less tendency to be sorbed by nylon as the pH of the dye bath is increased (127, 128). Opinions have been offered as to the mode of interaction and even though there is some difference in opinion among the investigators, Peters' explanation for a number of dyes seems to be fairly well supported by experimental data.

An analysis of an actual nylon molecule would reveal that there are many more amide groups than either of the terminal end groups (carboxylic or amino). At very high pH values, the uptake of an acid dye is quite low, but as the pH decreases a sharp increase in uptake is noted which quickly reaches a fairly constant value. At a pH around 3.0–2.5, another sudden upsurge is noted which continues with further increase in uptake. This S-type of uptake curve appears to be true of most acidic dyes and weak organic acids. Peters (127) has postulated the following mechanism for the pH effect. At the high pH values the interaction of the dye (as an ion) takes place on terminal amino groups which are positively charged forming a salt-type of binding (ion-ion). This type of combination between a dye and a substrate has already been reported for wool (137). Proof that the amino groups are taking part in the interaction may be demonstrated by acetylating these groups in nylon, whereby the uptake at the high pH is decreased. As the pH is decreased, binding or uptake is increased but does reach a limiting value which is interpreted to mean that all of the amino groups have become saturated with the dye. At the lowest pH range 3.0 and below, the nitrogen of the amide group has taken on a positive charge and attracts the dye (which is still in an ionic form even at low pH values).

Some investigators have indicated that the high rate of uptake at low pH values for the acidic dyes are in reality due to the hydrolysis of the main chain which creates new sites for interaction (138, 139). Others (127, 140) have disputed this thesis in the past but the work of O'Briain and Peters (141) sheds considerable light on the actual mechanism of high uptake at low pH values. These latter workers reveal that the acidic dyes are bound to the amide linkages either as free acids or by adsorption of the hydrogen ions to the amides followed by the dye anion. Simultaneously but much slower binding takes place with new terminal amino groups due to hydrolysis of the polymer.

Kapadia, Guess, and Autian (101) have also noted the S-type of sorption curve for salicylic acid. Figure 13 is taken from their study and illustrates the influence pH has on salicylic acid in nylon. Their postulated mechanism at the lower pH is binding of the acid to the amide linkages by hydrogen bonding since at the low pH values the salicylic acid is completely in the unionized form.

*Effect of Solvents.*—The solvent system may have an appreciable influence on the uptake of solute molecules. Several reasons have been stated for the effect of the solvent on sorption. Perhaps the most important influence the solvent can have is to swell and plasticize the plastic

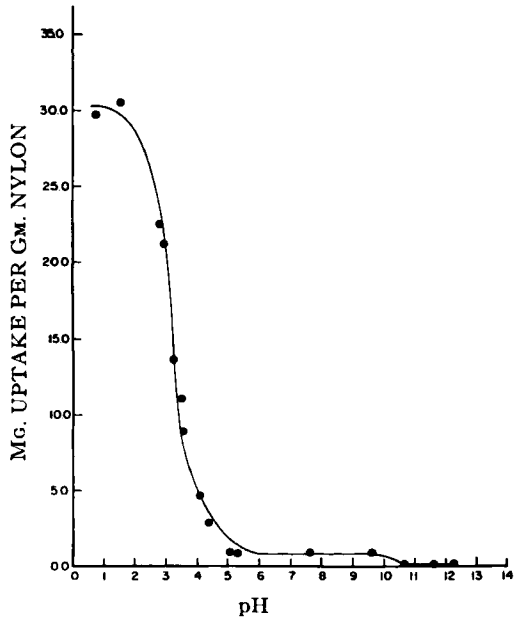


Fig. 13.—Uptake of salicylic acid by nylon at different pH values. [From Kapadia, A. J., Guess, W. L., and Autian, J., "Sorption and Diffusion Studies of Salicylic Acid in a Nylon Sheet," to be published.]

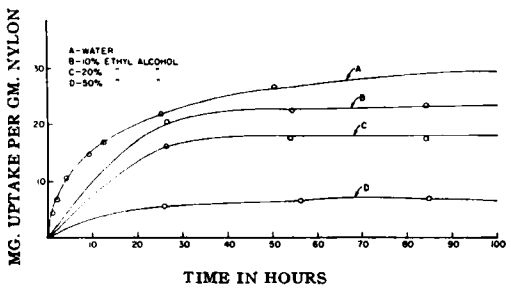


Fig. 14.—Effect of ethyl alcohol on the sorption of salicylic acid (0.15%) by nylon (41.5°C). [From Kapadia, A. J., Guess, W. L., and Autian, J., "Sorption and Diffusion Studies of Salicylic Acid in a Nylon Sheet," to be published.]

permitting more passageways to open up for the solute molecules (142). A less polar solvent system will have less tendency to swell a hydrophilic plastic material, which in turn should decrease the uptake of a solute. One example of this may be seen in Fig. 14 where various concentrations of water-alcohol systems have been used as a solvent for salicylic acid. As the concentration of alcohol increases, there is a general drop in the quantity of drug sorbed at equilibrium by the nylon. This trend may not always be followed. For example, Teulings and White (143) noted that certain dyes (dispersed dyes) would show a decrease in uptake at equilibrium in cellulose acetate up to a specific concentration and then an increase in uptake with an increase in butanol concentration. One should of course keep in mind that certain organic solvent systems may alter the structure of the particular plastic material in a manner which increases the amorphous content of the plastic. This structural change would then make available new sites for the binding of solute molecules.

*Effect of Concentration.*—Certain unusual features may be met with in regard to the concentration of a particular solute in a solution. As an illustration of this point reference is made to Figs. 15 and 16. In this particular study, the investigators were observing the uptake of several acidic drugs by nylon syringes. Figure 15 demonstrates the usual uptake curve at various concentrations when the data are plotted as bound *vs.* unbound drug (in this case sorbic acid). In like manner, the data for phenol are plotted as appears in Fig. 16. It is evident that phenol, up to a certain concentration, deviates markedly from sorbic acid. In the case of phenol, the uptake increases in a linear fashion but at a specific concentration there is a sudden increase in the uptake. This result may be attributed to the swelling and plasticizing effect which phenol will have on nylon, but apparently this influence is not felt until a critical concentration is approached (130). Other effects due to concentration, which are not as dramatic as phenol, have been observed in careful experiments of certain acidic drugs in nylon. In one particular study it was noted that the Langmuir relation would hold true for a certain concentration range, but an inflection would be seen if all the points were plotted on the curve (101). Much more information will be needed to interpret these results, but it is important to recognize that concentration effects should not be ignored in practical applications, since even slight effects might cause, on long storage conditions, unexplainable results.

Another group of compounds, which have shown unusual behavior in regard to the influence of concentration, are the surface-active compounds on solid substrates. In general, as the concentration of the solution is increased, adsorption or sorption increases in a regular manner until the critical micelle concentration is reached and a sudden increase in uptake is noted. With further increase in the concentration of the surface-active agent, the uptake

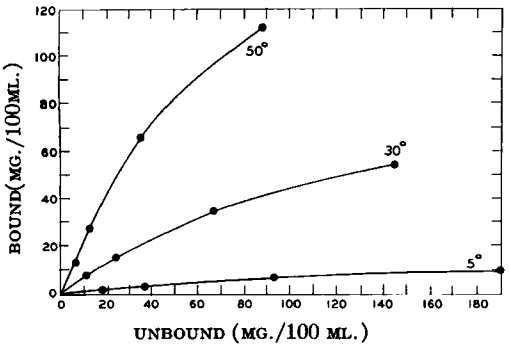


Fig. 15.—Uptake of sorbic acid by nylon syringes. [From Marcus, E., Kim, H. K., and Autian, J., THIS JOURNAL, 48, 457(1959).]

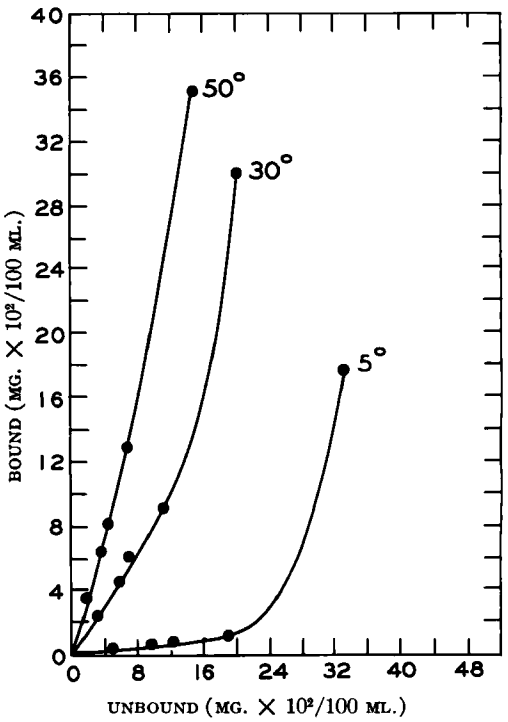


Fig. 16.—Uptake of phenol by nylon syringes. [From Marcus, E., Kim, H. K., and Autian, J., THIS JOURNAL, 48, 457(1959).]

continues until a limiting value is reached. Aickin (144) is believed to have been one of the first to note this type of behavior with surface-active agents, but since then, a great many other investigators have observed the same phenomenon on a number of unrelated substrates. Vold and Sivaramakrishnan (145) explained the sharp increase at the critical micelle concentration of surface-active agents on carbon black as being due to the binding of the surface-active agent as micelles on the substrate, rather than individual molecules. Hayashi (105), in one of his studies on nylon, postulated that below the c.m.c., the uptake was probably due to a chemical adsorption of the surface-active agent on the nylon, but at or above the c.m.c. the agent was adsorbed as micelles.

*Effect of Other Ingredients in Solution.*—Most practical systems, especially those which might be considered as drug systems, are composed of usually more than one solute and it becomes necessary to establish the influence of these other ingredients on the sorption process. It is known, for example, in the dyeing industry that inclusion of electrolytes will aid in the sorption process (90). Other solute molecules, which may structurally resemble the main ingredient in a solution, are apt to compete for sites in the plastic and in these instances a knowledge of the affinities would be of help in predicting which ingredient would be sorbed to the greatest extent. Possibility of interaction between the same molecules and with other molecules in the solution forming a complex or micelle will undoubtedly have an influence on the uptake, which would be extremely difficult to predict without a thorough study of the problem experimentally.

*Effect of Temperature.*—Temperature may have two effects on the sorption process. As the temperature is increased, the rate of uptake is increased, but the uptake at equilibrium is decreased. This statement is illustrated in Fig. 17 showing the effect of temperature on the uptake of salicylic acid by nylon. The fast rate of uptake at the higher temperatures is directly related to the increase in the diffusion rate. The lower equilibrium uptake is a consequence of several factors of which the increase in kinetic energy of both the solute molecules and polymer molecules plays the most decisive role. This energy appears to be sufficient to break bond formations between the solute and the polymer which were stable at lower temperatures and also appears to prevent, statistically, adequate solute orientation to the binding sites due to the increase in mobility of both the solute and the polymer. Certain anomalous results have been obtained with cationic agents and nylon. In these cases there was an increase of uptake with an increase of temperature. These values indicate another mechanism for the interaction (134) or a degradation of the polymer.

A great many of the investigated solute-polymer uptake data may be plotted to the Arrhenius equation with considerable success. Since diffusion is considered as the rate determining step, the influence of temperature on diffusion is usually employed as

$$\log D = \log D_o - \Delta E/2.303\ RT$$

where $D$ is the apparent diffusion coefficient

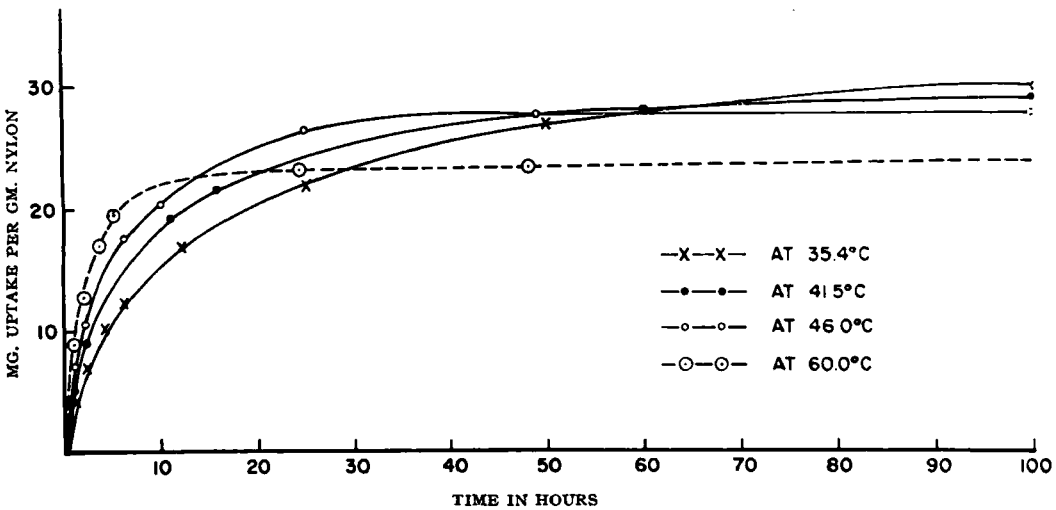


Fig. 17.—Effect of temperature on the sorption of salicylic acid by nylon. [From Kapadia, A. J., Guess, W. L., and Autian, J., "Sorption and Diffusion Studies of Salicylic Acid in a Nylon Sheet," to be published.]

$D_o$ is a pre-exponential factor indicating the value of $D$ at infinite temperature, $\Delta E$ the activation energy for diffusion, $R$ and $T$ the appropriate gas constant and absolute temperature, respectively. A plot of log $D$ *vs.* $1/T$ for salicylic acid is shown in Fig. 18 from which the activation energy for diffusion may be calculated and in this case $\Delta E$ is 20.5 Kcal./mole.

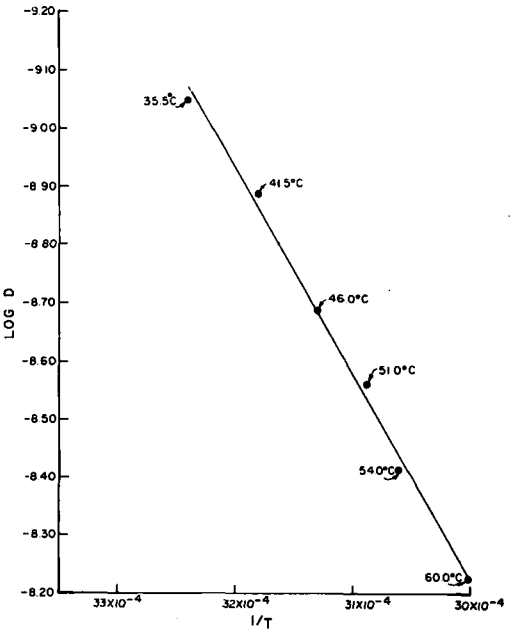


Fig. 18.—A plot of the log of D *vs.* the reciprocal of the absolute temperature for salicylic acid in nylon. [From Kapadia, A. J., Guess, W. L., and Autian, J., "Sorption and Diffusion Studies of Salicylic Acid in a Nylon Sheet," to be published.]

*Effect of Other Ingredients in Plastics.*—The discussion on sorption has dealt with a plastic which is considered composed of only the polymer, but it is known that many of the commercially available materials have various ingredients added for securing certain advantages. Sorption in these compounded plastics raised the question as to the possibility that the solute has interacted with one of the other ingredients, rather than the polymer. Reference may be made to an experiment conducted by Guess, Worrell, and Autian (85) on polyvinyl chloride used in medical practice. Benzalkonium chloride was found to be sorbed by the plastic to a significant degree, as may be noted by referring to Fig. 19. Even though no direct proof was obtained on the mechanism, it was believed that the benzalkonium chloride reacted with one of the other ingredients in the plastic formulation, since the structure of polyvinyl chloride would not suggest that this relatively nonpolar polymer would interact with a charged molecule to any appreciable extent.

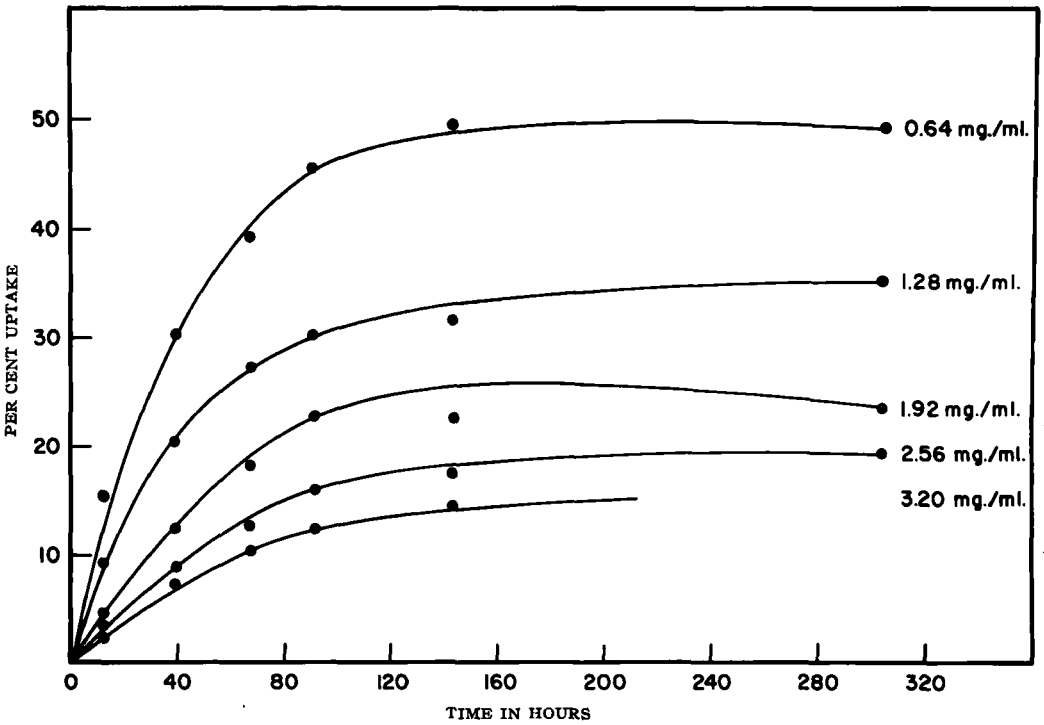


Fig. 19.—Effect of concentration on uptake of benzalkonium chloride by PVC. [From Guess, W. L., Worrell, L. F., and Autian, J., *Am. J. Hosp. Pharm.*, 19, 370(1962).]

### Chemical Reactivity

The term *chemical reactivity* perhaps is not the best selection of a title for a discussion of plastics, since it appears that true chemical reactions between a polymer and a specific drug or similar agent are indeed far and few between. This does not, however, exclude the effect of oxygen under certain conditions of temperature and environment in reacting with a particular polymer, leading to eventual degradation of the plastic. Chemical reactivity here will refer to visible evidence that a particular plastic material is altered, or that a change has taken place in the physical characteristic of the solution. More of this type of information is available to the product development and packaging groups, rather than available in the literature and for this reason only a few selected instances will be cited which have been seen in the author's laboratory or have been brought to his attention.

Hartop has found that certain colorations in a plastic material are probably a result of one of the additives in the plastic, rather than due to the polymer itself (146). Since even the pure plastic materials usually have an antioxidant or a stabilizer there may always be the possibility for a stain developing on the plastic with certain ingredients in a drug product. This stain may also pass into the solution, adding a color or changing the color of the product. In a series of tests on various formulations of polyvinyl chloride with a number of parenteral products, several incompatibilities were observed. No further investigation as to the causative agent was pursued, but it was noted that in several cases, even though the exact material was employed, one drug product induced a color, while a second, having the same generic title, did not (2). The results of these studies do lend support to the contention that it will be quite difficult to predict performance in a plastic package until exacting testing programs are conducted on the whole drug product.

Since there are a variety of drugs and a variety of other ingredients used in pharmaceutical systems, one must expect occasional incompatibilities in which an agent or solvent has either etched or dissolved the plastic. This problem has already been touched upon under the section on leaching, but again, deserves some comments here.

Certain ingredients in parenteral products (as for example, paraldehyde, diethyl carbonate, benzyl alcohol, and benzaldehyde) will etch and dissolve polystyrene (147). Products of an oily nature may have a dissolving or softening effect upon polyethylene. The fluorinated hydrocarbons have been found to attack polystyrene, polyethylene, and most vinyl products. Brown has stated that the attack on plastics by the fluorinated hydrocarbons decreases as the number of fluorine atoms increase in the molecule (148).

When a chemical reaction occurs and it is easily evident, the product can be removed, thereby producing no harm to the patient or embarrassment to the manufacturer. What effect minor changes may have on the plastic or solution is a question which cannot be rightly answered. These changes usually take place after the product is out in the market or in the hands of the physician or patient. It will be interesting to see what results will turn up in the near future concerning plastic containers which have had long contact with drug systems under a variety of environmental conditions.

### Alteration in the Physical Properties of Plastics

Such incidents as permeation, leaching, sorption, and chemical reactivity in regards to plastics will undoubtedly have an effect on one or more physical properties of the plastic. One of the more common observations with polyethylene bottles is the "bulging" or partial "collapse" of the container depending upon the direction of migration of a particular gas or vapor. Often this can be minimized by proper design of the container. A test which is frequently used to detect changes in physical characteristics is tensile strength measurements which may be defined as the force required to break by simple tension. As an example of the effect various liquids may have on the tensile strength of two plastic materials (polyethylene and polypropylene), Table IX is given. It will be noted that the linear polyethylene has the least ability to withstand these liquids. Surface-active agents, such as Igepal have a dramatic effect on polyethylene and, as has been stated in a previous portion of this review, Igepal is a recommended ingredient for testing of bottles. No real information is presently available as to the influence of drug systems on the tensile strength of plastics but it is suspected that certain combinations of ingredients might alter this physical property.

Temperature and changes of temperature can cause certain plastic objects to become distorted or, if the material contains plasticizers, the material may become brittle. Treatment of plastic items to various types of sterilization may alter

TABLE IX.—CHANGE IN TENSILE STRENGTH OF POLYETHYLENE AND POLYPROPYLENE ON LONG IMMERSION IN SELECTED LIQUIDS; 4 MONTHS OR MORE[a]

| Liquid | Polyethylene | | Polypropylene % Crystallinity | |
|---|---|---|---|---|
| | Low Density | Linear | 63 | 56 |
| Water | 1.8 | 0 | −1.1 | −8.6 |
| Isopropyl alcohol | 1.1 | −7.1 | −7.1 | −11.3 |
| Primol D | −8.1 | −78.0 | 10.1 | −20.0 |
| Silicone oil | −1.5 | −11.0 | 13.8 | −7.1 |
| Methylethylketone | −5.2 | −42.7 | 0 | −6.0 |
| Sodium hydroxide, 10% | −1.6 | −14.0 | 3.2 | −4.5 |
| Common salt, 10% | 2.6 | −6.5 | 0 | −9.1 |
| Acetic acid, 10% | −8.1 | 9.8 | 13.2 | −4.7 |
| Dioctyl phthalate | −6.5 | −2.3 | 5.9 | −3.6 |
| Linseed oil | −5.6 | −60.5 | 1.1 | −3.4 |
| Corn oil | 0 | −50.5 | 16.0 | −19.8 |
| Methanol | 2.2 | 2.5 | 2.3 | −7.2 |
| Igepal | −100 | −100 | 9.8 | −1.8 |

[a] Kresser, T. O. J., "Polypropylene," Reinhold Publishing Corp., New York, N. Y., 1960, p. 33.

the physical properties of the material to such a point that the device is no longer worthy of use. Preliminary reports on electron sterilization of plastic items have revealed that certain polypropylenes will take on a color while others will become brittle and break on touch (79). Ethylene oxide sterilization with certain Freons will disintegrate a number of plastic items which are used in hospitals (79).

Since pharmaceutical products are to be in contact with containers for long periods of time prediction of the behavior of the container over the history of the product will be extremely difficult without suitable testing programs. Even this approach may fail if a complete history of the container is not known. Plastic materials are also finding use in surgery where implants for the replacement of body organs or vessels are becoming more frequent. Exactly what effects the biological system will have on these plastic materials over long periods of time is a question which still needs to be answered.

## SUMMARY

Plastics are no longer a curiosity item in the practice of pharmacy and medicine. Each year which passes finds more, and often better, uses for these polymeric materials. Since at the present time there are no real controls or standards for plastic items in the medical field, each group must select their plastic material with the greatest of care. This selection must be based upon thorough testing procedures to suit the needs of the product and the market. Problems can arise from improper use of plastics and public health responsibility requires that all in the chain of distributing the plastic article, be what it may, are morally liable for any adverse consequence.

This review was an attempt to acquaint those in the pharmaceutical and closely allied fields with the opportunities which plastics offer while at the same time exposing a number of present and possible future problems. If this paper contributes in some small way to eliminating or circumventing the problems which may be associated with plastics, while kindling greater interest in developing better uses for plastics in pharmacy and medicine, the author's efforts in composing the review will be justly rewarded.

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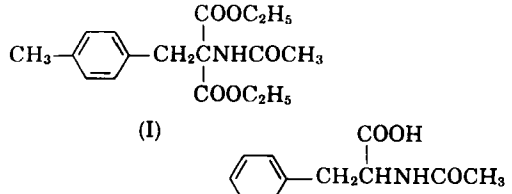
## *Research Articles*

# Methyl-Substituted Tyrosines and Related Compounds as Potential Anticancer Agents

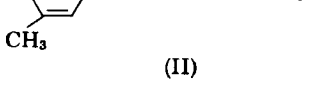
By EUGENE C. JORGENSEN and ROBERT A. WILEY†

**3,5-Dimethyl-DL-tyrosine, 3-methyl-DL-tyrosine, 3-methyl-5-iodo-DL-tyrosine, as well as synthetic intermediates and derivatives of these, have been prepared for study of anticancer activity. Preliminary tests on two members of the series against experimental tumors in mice showed a slight inhibition of tumor growth.**

THE SYNTHESIS and antitumor activity of a number of derivatives of phenylalanine, N-acetylphenylalanine, and diethyl α-acetamido-α-benzylmalonate have been reported (1, 2). The most active members of this series were diethyl α-acetamido-α-(4-methylbenzyl) malonate (I) and N-acetyl-3-methyl-DL-phenylalanine (II). Studies relative to the synthesis of analogs of thy-



(I)



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