

Film Coating Theory and Practice

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Recent theory and developments relating to the formation and modification of synthetic polymeric films are discussed in relation to the pharmaceutical uses of such films in dosage form development. Fundamental mechanical and physico-chemical properties of films as affected by plasticization, solvent effects, polymer chemistry, film additives, and other factors are considered in relation to film dissolution, permeability, and diffusion properties.

POLYMERIC FILMS are finding an ever-increasing range of application in pharmaceutical research, development, and dosage form design. In the coating of tablets and other solid dosage forms there is presently no coating methodology that can match film coating in production capability or economy. Polymeric film coatings have been increasingly employed to coat drug particles and drug-containing pilules to produce products with a delayed or prolonged pharmaceutical action. Approximately 1000 pharmaceutical patents pertaining to polymeric materials as adjuvants, including polymeric coatings, have been issued in the last 15 to 20 years. In addition to application to all types of solid oral dosage forms, polymeric films are being employed for such diverse uses as the coating of suppositories, the encapsulation of liquids, and aerosol spray bandages. As film theory and technology continue to advance, both fundamentally and in selected pharmaceutical applications, increasing and more effective utility of polymeric films will be made by the pharmaceutical industry. The purpose of this paper is to relate some of the more recent theory and developments in film technology to pharmaceutical applications and practice.

THEORY OF FILM FORMATION

Forces in the Film.—In any pharmaceutical film coating operation in which a polymer film is being applied to a matrix, sets of forces operate between the film forming polymer molecules on the one hand (cohesion), and between the film and the substrate on the other hand (adhesion). Cohesion, also known as autohesion or self-adhesion, refers to the ability of contiguous surfaces of the same

material, at a molecular or at a supermolecular level, to form a strong bond which prevents or resists separation at the point of contact. To obtain high levels of cohesion 2 phenomena are necessary: the cohesive (autoadhesive) strength of the material, molecule to molecule, must be relatively high, and the contiguous surfaces of the film material must coalesce on contact (1). Coalescence or the disappearance of boundary layers between adjacent polymer molecular layers or surfaces is explained by diffusion theory. According to theory, movement (diffusion) of individual macromolecules or segments of macromolecules between and within film layers may occur under a variety of conditions, including during gelation, when polymers are deposited in solution over a previous polymer layer, or at elevated temperatures corresponding to a semisolid state (2). The result, if there is adequate cohesive attraction between the molecules and sufficient diffusion and coalescence, will be a restoration of the polymer structure to a uniform nonlaminated matrix at the contact zone (Fig. 1) affected by the displacement (diffusion) of whole molecules or of individual segments of the macromolecular chains. Only high polymers, owing to their molecular structure, combine sufficient cohesive strength and capacity for coalescence to produce fiber and film structures, drawn or deposited from appropriate solvents.

The significance of the degree of cohesion in film structures is fundamental to film properties. An increase in cohesion in the structure of 1 polymer to another, or of 1 analog of a homologous series to another will increase film density and compactness, may decrease porosity and permeability, decrease flexibility, probably increase brittleness, as well as affecting other film properties either directly or indirectly (3).

Controllable Processing Factors Affecting Cohesion in Pharmaceutical Film Coatings.—The factors which may increase film cohesion, polymer surface to polymer surface, not all of which are readily controllable in the typical pharmaceutical film coating operation include: increased surface contact time (4), increased contact temperature (5), increased contact pressure (4), coat thickness, and control of coat solution or coat dispersion concentration, degree of polymer solvation, and viscosity. Increased coat-contact temperature,

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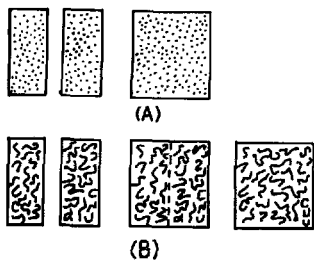


Fig. 1.—Schematic representation of the coalescence of (A) low molecular weight liquids, and (B) high polymers in a polymeric film structure.

time, or pressure all promote cohesion by promoting molecular diffusion at the contact boundaries.

Temperature.—Temperature is directly related to autohesion; indeed, the temperature dependence of cohesion is a proof of the diffusional basis of the process. As the contact temperature increases, the cohesive strength of the contiguous polymer surfaces increases over a definite temperature interval along an exponential curve, not unlike the exponential dependence of diffusion rate on temperature observed for low molecular weight materials (7). This exponential increase in diffusion rate with temperature is due to the increased thermal motion of complete polymer chain molecules or fractions of such molecules, and is probably secondarily related to decreased polymer, polymer gel, or polymer film density. That a more cohesive film generally results from the application of a warm coating solution to a warm substrate is well known to those skilled in coating technology. There are, of course, limits to the amount of heat which may be advantageously used, as excessive heat may cause premature spray drying of the coat, slipping and peeling of the coating as it approaches its melting or glass point, or the development of pinholes in the coat caused by solvent evaporation under high localized vapor pressure through a case-hardened film surface. It is also well known that an increased temperature generally greatly facilitates adhesion between polymer film and substrate, with the temperature effect probably eliciting the same phenomena as in cohesion (promoted diffusion).

Contact Pressure and Contact Time.—Contact pressure is not a readily controllable factor in the typical pharmaceutical film coating application. Contact time refers to the duration during which a newly deposited polymer film layer is "setting-up" and the polymer molecules, wholly or in part, are capable of diffusion and orientation. Reasonably rapid solvent evaporation rates are sought in most film coating applications to facilitate rapid coating. However, solvents which flash off prematurely not only may lead to spray drying of the atomized coat solution, but may produce noncohesive films due to a premature immobilization of the polymer molecules in the film structure prior to molecular orientation, as well as to poor diffusion of the polymer molecules between molecular layers in the film.

Film Coat Thickness.—Cohesive strength of films is commonly expressed as the peeling strength, represented as the work of ergs/cm.², required to separate bonded layers of film (5). The cohesive film strength (peeling strength) has been found to increase as a zero-order function of film thickness up to some fixed value, dependent on polymer film chemical class, after which the cohesive strength is constant with further increases in thickness.

Coat Solution Concentration, Solvation, and Viscosity.—Viscosity, hence polymer solvation and solution concentration, are of great importance to the self-adhesion of high polymers. At low viscosity or at high polymer solvation levels self-diffusion should be promoted. On the other hand, at low viscosities most coating solutions will be very dilute, coating times will be unduly long, and it will be comparatively easy for a selected deposited film component forming the bond to separate from the bulk of the previously homogeneous film substrate. Consequently, an intermediate viscosity will usually result in the highest cohesive strength (6). The viscosity at which the deposited coating solution gels will also affect cohesive strength, and this will be a function of the solvent or mixed solvent system used and the rate of desolvation and stereochemical displacement of the polymer from the solvent during evaporation.

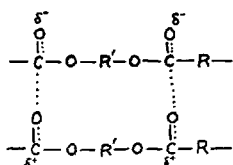
Formulation Factors Affecting Cohesion in Pharmaceutical Film Coatings.—The formulation factors primarily affecting cohesion in pharmaceutical films include polymer chemistry (stereochemistry and functionality) and polymer structural properties (molecular order and crystallinity in the film), solvent effects, the presence of added dispersed solids, and plasticization.

Polymer Chemistry.—The shape of polymeric molecules exerts a strong influence on cohesion in films, since molecular shape largely determines both the diffusibility of a macromolecule or its individual branches or segments, and the strength of its interlacing areas. Macromolecules with a regular structure, provided they are not in a strongly crystalline state, should be more diffusible than molecules with a highly irregular stereochemical structure (8, 9). Branched molecules in which the branching does not greatly hinder diffusion may have a greater cohesive strength than non-branched equally noncrystalline polymers, based on a firmer anchoring of such macromolecules in the diffusion layer. In a homologous series, lower molecular weight fractions exhibit a greater cohesion, and show a greater change in cohesion strength with temperature changes (5). In strongly polar polymers, self-adhesion by diffusion is insignificant, due to the minimal flexibility and fixed order of the macromolecules caused by the intermolecular forces holding the polymer chains in a fixed form. Proteins and celluloses are examples of such polymers exhibiting minimal molecular diffusion, proteins tending toward a helix, and celluloses having a rigid ring structure chain backbone. In crystalline polymer structures, the cohesion between ordered polymer molecules may greatly exceed that possible by the diffusion process in amorphous polymers (10).

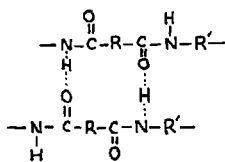
The theory of cohesion in polymer films is complex and may involve the concepts both of diffusion and ordered structure. The cohesive strength of the crystalline-amorphous polymers used pharmaceutically is related to the presence, concentration, location, and relative polarity of polar groups along the polymer chain, regularity of chain structure, branching, molecular weight, and molecular weight distribution.

Polymer Structural Properties (Molecular Order and Crystallinity).—A highly ordered, crystalline polymer represents a polymer system of maximum

cohesive structure (compactness) and cohesive strength (represented by crystal strength). The intermolecular forces which promote cohesion, particularly hydrogen bonding, also promote crystallinity (11). While polar groups diminish molecular self-diffusion, strongly polar groups or hydrogen bonding groups (such as $-\text{OH}$ and $-\text{COOH}$ groups of substituted celluloses, $-\text{COOH}$ groups of pendant carboxyl containing linear polymers such as acrylics, or $-\text{CO}-\text{NH}-$ groups of polyamides or polypeptides), if they are regularly distributed along the chain, will produce a distinct tendency for the formation of laterally ordered chains (structure I). The closer the polar groups



(A)



(B)

I

The lateral order arrangement (crystalline centers) in films. A, Polyester chains laterally ordered by dipole interaction forces. B, Polyamide chains laterally ordered by hydrogen bonding forces.

are to one another along the chain and the better their lateral fit, the more pronounced will be their effect to promote crystallinity (12, 13). Regardless of the factors promoting molecular order, it is extremely doubtful that any polymer is 100% crystalline, due to the molecular weight distribution found in polymer systems and imperfect chemical and stereochemical repeating molecular structures (14).

Typical noncrystalline polymers include those in which an irregularity of structure occurs, as in copolymers of two or more dissimilar monomer constituents, and in polymers having atactic configurations (a random sequence in the branching of substituents about the polymer chain). There are a few exceptions of atactic polymers such as poly(vinyl alcohol) which do crystallize. This is because certain groups such as CH_2 , CHOH , CF_2 , and $\text{C}=\text{O}$, are small enough to fit into the crystal lattice of the polymer structure. However, most atactic polymers, such as poly(vinyl acetate), due to their stereoirregularity, are noncrystalline and have never been crystallized (15).

The nearly limitless gradations between substantially completely crystalline polymers and truly amorphous polymers are typical of the great majority of pharmaceutically significant polymers which are composed both of distinct crystalline and amorphous phases. Such polymers commonly possess some features leading to disorder, such as atactic configuration, irregular substitution, or bulky side groups which space the individual linear macromolecules apart from each other, plus features leading to an ordered structure, such as a rigid chain or polar substituents. Thus, in addition to having a given chemical molecular structure or range of structures, polymeric fibers and films also have what is termed a fine structure (16) or a supermolecular structure (14). This struc-

ture describes the relative co-existing ordered-disordered lateral position or placement of the linear polymer chains or groups of chains in the particular polymer structure, and relates to the general over-all crystallinity of that structure (Fig. 2). The relative degree of molecular chain order to disorder in a film varies with such factors as the method of film application, the solvent system from which the film was cast, and the stresses in the film; and affects such physical properties as film strength, solubility, and miscellaneous mechanical properties (14). The toughness and rigidity of films are favored by a high chain order (14). Crystallinity, independent of molecular weight, is the single effective determinate which is directly related to film stiffness and yield point, and also affects film permeability, flexibility, and brittleness (17-19). In general it is more difficult to correlate the physical properties of a polymer film to a lateral order parameter (crystallinity) for derivatives of a parent polymer, such as cellulose derivatives, than for the parent polymer itself, *i.e.*, cellulose (14).

Solvent Effects (Solvation).—Pharmaceutical polymeric film coatings, almost without exception, are applied to the substrate from colloidal solution in an organic solvent system. During the dissolution of a macromolecular substance, the cohesive forces between the solute macromolecules are neutralized by unions with the solvent molecules (solvation). The more crystalline a polymer, the greater the intermolecular cohesive forces, and the more difficult it will usually be to dissolve such a polymer.

The polymers used in pharmaceutical film coating and other operations, so as not to be inert in the human gastrointestinal tract, are generally polyfunctional polyelectrolytes, containing an aliphatic polymeric nonpolar carbon chain with polar substituents along the chain. Depending on the aqueous pH at which the functional groups ionize and on the rate of ionization, the coating polymer may produce a fast, an enteric, or a prolonged disintegrating or dissolving coating. Polymers which are completely aliphatic (polyethylene), substantially crystalline (pure cellulose), or which contain only nonionizable functional groups or a very high proportion of such groups to ionizable groups (highly esterified carboxyl containing polymers) will be insoluble in water regardless of pH.

The functionality of the polymer also relates to solution properties and to film characteristics. As the functional groups on a linear polymer become ionized during dissolution, the charged groups will repel each other, producing a stretching of the poly-

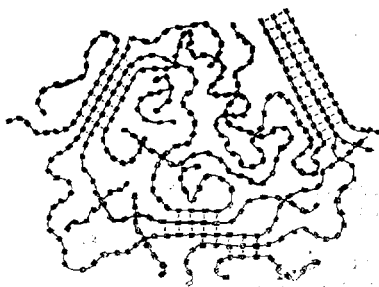


Fig. 2.—The fine structure or supermolecular structure illustrating the laterally ordered (crystalline)-disordered (amorphous) placement of linear polymer chains in a film matrix.

mer chain. The greater the degree of dissociation and the more extensively the chain is charged, the more the chain will uncoil. Simultaneously, the solvation effect, or the interaction between the charged polymer molecules and the molecules of the polar solvent, will increase with the increasing charge on the chain. With increased solvation there will usually be a viscosity increase due to the envelop of solvent surrounding each chain more effectively, keeping the chains from coming into contact and aggregating, and due to the extended configuration and greater spatial requirements of the more completely solvated system.

Polar solvents (Table I) tend to be solvents for polar substances including macromolecular poly-electrolytes (Table II), and nonpolar solvents are generally poor solvents for such polymers. A given polymer is most soluble in solvents that best match the polymer or its solvated derivative in cohesive energy density (Tables I and II) (20). Solubility properties of colloidal macromolecules in organic solvents are complex and depend on chemical, electrical, structural, and steric effects, which lead to mutual interactions between solute and solvent.

Copolymers present a special solubility problem,

TABLE I.—RELATIVE POLARITY AND INTERMOLECULAR ATTRACTION OF COMMON ORGANIC SOLVENTS AND WATER

Solvent Class	Solvent Examples	Dielectric Constant of Solvent (70)	Cohesive Energy Density of Solvent, cal./ml. ^a
Water		78.5 ^b	551.1
Glycols		35-50 ^b	...
	Glycerol	42.5 ^b	...
	Ethylene glycol	37.7 ^c	...
	Propylene glycol	35.0 ^c	...
Alcohols		15-30 ^b	...
	Methanol	32.6 ^b	210.3
	Ethanol	24.3 ^b	163.4
	1-Propanol	18.3 ^b	...
	<i>n</i> -Propanol	20.1 ^c	147.5
	1-Butanol	17.8 ^c	...
	<i>n</i> -Butanol	17.1 ^b	131.8
Ketones		10-20 ^b	...
	Acetone	20.7 ^b	98.5
Ethers, esters, aliphatic, and chlorinated hydrocarbons		0-10	...
	Dichloromethane	9.1 ^c	...
	Ethyl acetate	6.0 ^b	83.0
	Chloroform	4.8 ^c	85.4
	Dichloroethylene	4.5 ^c	...
	Ethyl ether	4.3 ^c	54.1
	Trichloroethylene	3.4 ^c	...
	Carbon tetrachloride	2.2 ^c	73.6
	<i>n</i> -Hexane	1.9 ^c	52.4

^a The cohesive energy densities were calculated from latent heats of vaporization and molecular volumes at 20°. C.E.D. is a measure of the intermolecular attraction and molecular cohesion of a substance and is particularly useful in predicting solvent power for polymers. (See Reference 72). ^b Dielectric constants determined at 25°. ^c Dielectric constants determined at 20°. As the dielectric constant decreases, the relative polarity, solvent to solvent, decreases. With a decrease in temperature the dielectric constant increases, and a polar organic solvent may become a better solvent for a polar polymer.

TABLE II.—RELATIVE POLARITY AND SOLUBILITY PARAMETERS (COHESIVE ENERGY DENSITY) OF POLYMERIC MATERIALS

Polymer or Polymer Class	Dielectric Constant (60 cycle) (71)	Cohesive Energy Density, cal./Gm. (73)
	Nonpolar	
Polyethylene	2.3	62
Polystyrene	2.5-2.7	75
Acrylates	3.4-3.6	85
Polyvinyl chloride	3.2-3.6	90
	Intermediate Polarity	
Polyvinyl acetate	...	85-95
Acrylics	3.5-3.8	95
Ethylcellulose	3.2-4.0	...
Polyamides	4-5	...
Cellulose acetate	3.5-7.5	130
Cellulose acetate phthalate	3.5-6.4	...
Cellulose nitrate	6.7-7.3	110
	Polar (soluble in water and polar organic solvents)	
Polyvinyl alcohols	Carboxyvinyl polymers	
Maleic acid copolymers	Hydroxyethyl celluloses	
Polyvinyl pyrrolidone	Carboxymethyl celluloses	
Polyethylene glycols	Methylcelluloses	
	Gelatin	

since virtually all pharmaceutically employed copolymers contain a substantially nonpolar comonomer plus a polar comonomer. Examples of such copolymers, with the nonpolar component given first are: styrene, vinyl alcohol or acrylic acid copolymers; ethylene, maleic anhydride or acid copolymers; acrylate, acrylic acid copolymers.

The solubility of copolymers is generally low in solvents for either homopolymer, but may be high in mixtures of these solvents wherein maximum solvation and extension of the polar and nonpolar comonomer units occur in a polar-nonpolar mixed solvent system. A single solvent of intermediate polarity will not usually be as effective for such copolymers or for a mixture of 2 or more homopolymers which differ widely in polarity as the mixed polarity compound solvent system.

Not only the degree of substitution (D.S.) and the polarity of substituents, but also the space requirements of substituents, may affect the solubility properties of some polymers. The water solubility of cellulose has been related to the wedging apart of the cellulose ring structure chains by the substituent groups to bare the remaining hydroxyls for hydration (21). Bulky substituent groups, being more effective in wedging the chains apart, enable water solubility to occur at lower degrees of substitution. Methylcellulose is soluble at D.S. 1.3 (22, 23), ethylcellulose at D.S. 0.7, and sodium carboxymethylcellulose at D.S. 0.3 (24). Solubility of cellulose in organic solvents stems from a predominance of alkyl ether substituent groups over the remaining hydroxyl groups.

As a rule, maximum coating solution solvation and polymer chain extension will produce the most superior films showing the greatest combined strength and cohesiveness. Since solvation and polymer chain extension is reflected in the viscosity of the sol, viscosity provides a useful control measure to (a) compare the relative effectiveness of various solvents for a particular polymer or polymer system, and (b) appraise the adequacy of solvation and chain extension of a polymer system in a given solvent according to formulation and method of preparation prior to film application. Other physical methods have been used to measure solvation making use of birefringence measurements, vapor pressure data, heats of solution, and infrared absorption spectra (25-27), but the usefulness of such measurements varies with the polymer structure, and the results are often difficult to interpret. As a control procedure of the polymeric sols used in film coating operations, viscosity remains the most simple and direct, although empirical, method of comparing solvation.

Plasticization.—A plasticizer is defined as a substantially nonvolatile, high boiling, nonseparating substance, which when added to another material changes certain physical and mechanical properties of that material. Plasticizers (28-31) are added to polymeric substances for a variety of reasons, but they are especially necessary adjuncts to most polymeric films in order to reduce brittleness, improve flow, impart flexibility, and increase toughness, strength, tear resistance, and the impact resistance of the film coating. The mechanism by which the plasticizer achieves these changes is theorized to be a decrease in the cumulative intermolecular forces along the polymer chains

(reduction in cohesion), which generally produces a decreased tensile strength, a lower softening temperature, and a decrease in the glass transition temperature. The plasticizer and polymer are generally thought to be held together by intermolecular secondary valence forces forming a complex or molecular aggregate (31). The lowering of the glass transition temperature below room temperature by plasticization changes a hard, brittle, glass-like material at room temperature to a soft, flexible, and tough material.

Two types of plasticization are recognized (3). External plasticization is the process, thus far described, by which a substance is added to the polymer structure and may be physicochemically associated to it, reducing cohesion in the structure to effectively extend, dilute, and soften the structure. Similar changes can be accomplished by altering the internal chemical structure of the polymer, as by copolymerization, which is known as internal plasticization. The method of plasticization employed with cellulose and other comonomer polymeric pharmaceutical films is external plasticization. Acrylic, vinyl, styrene, and other polymers which may be readily copolymerized will require little, if any, external plasticization after copolymerization.

The basic requirements of any plasticizer in a polymer system are compatibility and permanence. To be compatible the plasticizer must be miscible with the polymer, indicating similar intermolecular forces in the 2 components. The most effective plasticizers will generally resemble most closely in structure the polymers they plasticize. Thus, water-soluble cellulose ethers (retaining a high ratio of hydroxyls to such ethers) are best plasticized by hydroxyl containing compounds such as glycerin, glycols, and other hydroxy containing compounds. Substantially aliphatic nonpolar polymers are best plasticized by chemically similar materials such as non-solvent oils. However, since the intermolecular forces in nonpolar polymers, such as polyethylene, are low, it is difficult to find a plasticizer for such materials. Likewise, since the intermolecular forces of strongly crystalline polymers are so high, plasticizers cannot be found with adequately high intermolecular forces to satisfy such polymers and be compatible with them. Effective plasticization is, thus, usually limited to amorphous polymers or to amorphous-crystalline polymers in which the crystalline phase is not predominant.

It cannot be emphasized too strongly that the total film coating formulation of polymer-plasticizer-solvent, plus other components, such as insoluble additives or surfactants to promote spreading, must be considered as primarily affecting, in consort, the nature and properties of the film that is formed. Thus, in considering the 3 fundamental elements of polymer-plasticizer-solvent, not only must the polymer and plasticizer be compatible and the polymer be effectively solvated in the solvent, but the plasticizer must approximately match the solubility properties of the polymer in the solvent system used. In simple systems, since the polymer and plasticizer probably possess common functional groups, solvents can usually be readily selected in which the components are equally readily soluble, thereby preventing premature plasticizer or polymer separation during film dep-

osition and drying. In compound systems in which two or more polymers differing in polarity and chemical type are used with one or more plasticizers in a mixed solvent system, the problem of compatibility becomes complex. If a satisfactory mixed solvent system may be formed which is an azeotrope, the problems of changes in solvent composition during evaporation and premature separation of film components during drying will have been overcome. In nonazeotropic mixed solvent systems, drastic changes in solvent composition during drying with accompanying heterogeneous film component separation may be avoided if solvents can be selected which have somewhat similar vapor pressures at the film-drying temperature.

The permanence requirement of plasticizers in pharmaceutical operations is very important, since it relates to the physical and mechanical stability of the film with time and under stress environmental conditions. External plasticizers, which are physicochemically associated with the polymer by miscibility and by primary or secondary forces, may not readily be leached out of the film matrix and may resist losses by evaporation. The use of the higher molecular weight plasticizers of an effective plasticizer series, which have a lower vapor pressure and lower diffusion rate in the film matrix, will produce a plasticized film of greater permanence. The plasticity of an unmodified as well as of a plasticized polymer film is related to the chemical composition of the polymer (and plasticizer) and to the arrangement, stereochemistry, and forces acting between the chain macromolecules, including intermolecular and internuclear distances, and to the effect of the regularly interposing plasticizer molecules within the molecular polymeric network. These relationships and effects will dictate the proportion in which the plasticizer must be used to produce the desired film properties. Cellulosic polymeric films commonly require 30 to 60% plasticizer, relative to polymer weight for adequate plasticization. Less rigid polymers and copolymers will rarely require the addition of more than 10–20% of an external plasticizer.

Plasticizer efficiency, stability, compatibility, and permanence may be evaluated by a number of semiempirical tests, including measurement of the amount of nonsolvent required to cause phase separation of each component from the polymer-plasticizer solution, viscosity studies, polymer-solvent interaction constants of the solutions, depression of the glass transition temperature, and other physical and mechanical properties of plasticized free film samples. (See under *Mechanical Properties of Films*.) Since these tests are semiempirical they will not all rate a series of plasticizers in the same order. The ultimate selection of a particular plasticizer may also depend on selected physical properties of the plasticizer, e.g., hygroscopicity (which may affect moisture uptake by the film and its effectiveness as a moisture barrier) and water solubility. Plasticizer water solubility is often important in pharmaceutical applications especially when higher plasticizer concentrations are required. A soluble plasticizer may be needed for a soluble coating, and an insoluble plasticizer may be required to produce an enteric or slow release coating.

Plasticizers having pharmaceutical applications include (15, 32): (a) phthalate esters, which account for over half of all the plasticizers used industrially; (b) phosphate esters, chiefly tricresyl phosphate, which may be restricted to topical film use; (c) adipates, azelates, oleates, and sebacates, especially useful for vinyls; (d) epoxy plasticizers produced by reacting hydrogen peroxide with unsaturated vegetable oils and fatty acids; (e) fatty acid esters from natural sources, which are also useful as extenders to reduce cost or to produce a slowly soluble coating; and (f) glycol derivatives which are particularly useful for celluloses and poly(vinyl alcohol).

Addition of Dispersed Solids.—Frequently the most expensive aspect of film coating is the cost of the organic solvent carrier of the coating polymer. Recovery systems for these solvents in the exhaust air outlets of coating equipment have been prohibitively costly to date. Depending on the molecular weight of the polymeric materials and on the viscosity produced in the organosols, 2–10% w/v of polymer is the usual range of polymer which can be applied as a coating solution. When coating powders, beads, or pills containing drug, the increased surface of the smaller particles may require that 25–100% of uncoated particle weight be added as film coating material on a dry weight basis. This means that for 1 Gm. of product to be coated from 2.5–50 ml. of coating solution may be required. In such cases solvent costs become extremely high and coating times are unduly long. To combat this problem pharmaceutical scientists have borrowed an approach of the paint industry by adding insoluble particulate fillers or extenders to the film compositions, either dispersed in the film coating polymer solution or dusted on the drug containing particles during coating. Alternate deposition of film coating polymer and dusting powder leads to the deposition of alternate polymer-powder monolayers with relatively low adhesion energies and a consequent loss of film durability (33, 34). The effects of dispersed added solids on polymer film structures, with the dispersed solids having been added from a coat solution containing suspended filler, are generally predictable according to the effect on properties wrought by a decrease in molecular order in the film. The decrease in order may result in plasticization-like effects, while the increased density and solids content in the film may actually increase film strength. Properly formulated fillers and extenders may greatly enhance film dimensional stability, impact resistance, tensile and compressive strength, abrasion resistance, and thermal stability (35, 36).

Desolvation (Gelation).—As the solvent of the applied polymer solution evaporates, an organogel commonly forms at some critical solids concentration during film formation. The most important property, which gives information about the onset of such gelation during drying, is the increase in viscosity with time at constant temperature and during increasing concentration of the colloid. Gelation involves structuration of the organosol system. In the less concentrated organosols prior to solvent evaporation, Brownian movement will be adequately intense and unhindered to keep the aggregates in a continually dispersed condition by the molecular impacts. Upon cooling or with an increasing concentration of polymer in the solution

via solvent evaporation, the power of the impacts diminishes, and the particles can stick together or form a network type of structure. If the chains are asymmetric, as are most of the pharmaceutical polymeric polyelectrolyte materials, they will be joined into a substantially random three-dimensional mesh on gelation, which will immobilize the organic solvent liquid. Another way of visualizing the gel as it forms is by desolvation of the colloidal polymeric material by evaporation of the organic solvent. Since the number of molecules of solvent per molecule of polymer decreases as evaporation proceeds, desolvation of the polymer is continuously affected, and at some point gel growth will occur, and the system will go through an organogel or semigel phase. The dry film will, therefore, represent the final stage of a gel-like aggregate resulting from the progressive evaporation of the volatile solvent.

The rate of desolvation and gelation is a primary function of the evaporation rate of the solvent or compound solvent system (37). A rather rapid rate of desolvation and gelation is usually indicated in pharmaceutical film coating operations to permit more rapid application of the coat, to reduce the duration of the tacky state of the coat during drying on continuous or intermittent application, and to promote simultaneous desolvation of the various coat components. If the coating is being applied from a spray system, the solvent must not evaporate prematurely so as to deposit a spray dried or gelatinized coating on the matrix. The major advantage of the airless spray technique is in circumventing this last problem.

MECHANICAL PROPERTIES OF FILMS

Polymeric films possess mechanical and stress-strain (rheological) properties which are comparable to the viscosity properties of liquids. These film properties relate to such characteristics of film coatings as impact strength, flexural strength, coat stability to temperature change, peel strength, flexibility, and coat resistance to many types of environmental and physical stresses. The stress-strain properties are determined by measuring the linear expansion of standard free test film strips under increasing load forces (38). From the stress-strain curve (40) (Fig. 3) the following physical characteristics of the film samples may be determined: tensile strength, yield point, breaking strength, modulus of elasticity, plastic deformation, and other properties.

The modulus of elasticity, also known as Young's modulus, is the constant of proportionality of stress to strain, and is equal to the slope of the

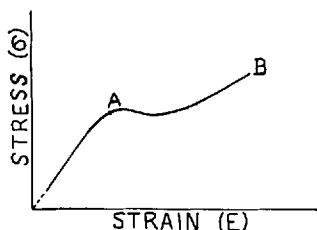


Fig. 3.—Stress (Gm. load/cm.² of surface)—strain (cm. or per cent elongation). Curve of a typical pharmaceutical thermoplastic polymer film structure. Point

A is the deformation point or the lower yield point, and point B is the breaking stress, breaking point, or the upper yield point.

straight-line portion of the stress-strain curve. This parameter is a measure of the "stiffness" of the film, or the ability of the film to withstand a high stress while undergoing little elastic deformation. The greater the slope of the curve and the higher the modulus of elasticity, the stiffer and stronger the film, and the more stress will be required to produce a given amount of deformation.

Tensile stress is the load per unit area of the original cross section at any instant, usually expressed as force/unit area (39). The maximum tensile stress during a test (A of Fig. 3) is termed the tensile strength. Point A of the stress-strain curve also represents a stress at which the film first undergoes a marked increase in strain without a corresponding increase in stress, representing permanent deformation. This stress value for a standard film sample is termed the "yield point." Sometimes the stress at the deformation point, A, is called the "lower yield point," and the stress at point B, the film break point, is called the "upper yield point." Some materials have no lower yield point since they fail or break before they deform materially. A yield strength may then be determined, which can either be the maximum stress above which the material is damaged or, in comparing a series of films, is the stress of some fixed strain.

The distance between A and B along the stress-strain curve (Fig. 3) indicates the degree of plastic deformation the sample undergoes before breaking. If the film sample has a low yield point and undergoes little deformation before breaking (the distance A to B is short), the film is weak and brittle. Lever and Rhys (40) classify polymeric materials into 4 categories according to the relative height of the yield point on the stress axis and according to the difference between the yield point and the breaking point along the strain axis.

Ordinary substances are little affected by changes in the external environment such as pressure, temperature, humidity, or physical stress, relative to their ordering or crystallinity. Polymers behave quite differently. Environmental factors may appreciably affect the mechanical properties and the stress-strain relationships of certain polymer films, especially polar polymers such as the cellulose, due to the moisture sorption and swelling of the film structure (41, 42). The effect of such moisture sorption is similar to plasticization; elongation (strain) begins at a lower stress (load), elongation is much greater for given load forces, and the presence of a yield point may not be detectable. The amount of strain (elongation) under stress (load) is also generally significantly increased with a temperature increase (43, 44). Polymer structures also tend to increase greatly in crystallinity with stress. The reasons for this difference lie in the filiform shape and the high internal flexibility of the individual molecules in the macromolecular compounds.

Stress-strain data may be used in comparing film samples as a function of formulation factors, e.g., polymer combinations used, plasticizer, solvent system or surfactant employed, the effect of dispersed solids; or the data after correlation to coat mechanical stability properties on a given substrate may provide a direct indication of coat friability resistance, impact strength, abrasion resistance, and other properties. Munden *et al.* (45)

and Utsumi (46) have recently reported the modulus of elasticity, tensile strength, and per cent elongation of plasticized and unplasticized free films. Kabre (47) reports that the plasticizer is the most important formulation factor affecting mechanical properties of films, and he compared a series of plasticizers for their effect on the mechanical properties of a cellulosic polymer system.

An important mechanical effect of polymeric films, from a pharmaceutical coating standpoint, relates to their surface friction. Hardy (48) has reported on the property of polar organic compounds lowering the coefficient of friction of rubbing solids. Langmuir reported early on the effectiveness of fatty acid films in reducing frictional coefficients (49) and also found that multimolecular layers of film did not significantly reduce the coefficient of friction beyond the reduction produced by a monomolecular film (50). The mechanism of the lowered surface friction is related to the polar film forming groups adhering to the substrate, leaving the more aliphatic and less polar polymer structure exposed to comprise a surface of lower free surface energy, with the film coating initially deposited therefore acting like a boundary lubricant (51). The problems encountered in tablet and particle film coating in conventional equipment due to the lowered coefficient of friction of the coated material, the sliding of the polymer coated contents in the coating pan, and the common necessity for baffling the coating pans is well known. As polymer coat buildup proceeds beyond the monolayer, the problem involved with slipping and sliding of the coating pan contents often diminishes. The reason for this is that as the substrate is covered and the coat builds, there is less polymer orientation to the substrate, polymer deposition in the film is more random, and there is a consequent increase in the coefficient of friction of the coating.

PERMEABILITY PROPERTIES OF FILMS

The permeability of polymeric film coatings involves 3 processes of interest to the pharmaceutical scientist: (a) gas diffusion processes, notably oxygen permeation, through the film; (b) water and water vapor sorption and permeation (liquid permeation processes); and (c) dialysis processes concerned with the dialysis and permeation of soluble components across the intact or modified film.

Munden (45) found an oxygen permeability range of 10^{-4} – 10^{-3} Gm. cm./cm.² 24 hr. for the oxygen permeability through free unplasticized films. With a few exceptions, he found an inverse relationship between water vapor transmission and oxygen permeability. Water vapor permeability has been shown to be dependent on the relative polarity of the polymer (52). The more polar films tend to be more ordered and less porous, hence less oxygen permeable; while the less polar films are more porous, permitting the permeation of oxygen but not necessarily of the larger water molecules; and, being more lipophilic, the less polar films have less affinity for moisture and water sorption. Gas permeation through a completely crystalline polymer is known to be negligible. Bent (53) reports that gas permeation is proportional to the volume fraction of the amorphous phase of a film structure,

$$P = P_a X_a$$

where P_a is the permeability for the amorphous phase, and X_a is the volume fraction of the amorphous phase in the film structure.

Lamonde (54), in studying a series of substantially insoluble films, found that the addition of phthalate plasticizers increased water permeability rates with an increasing concentration of plasticizer, and with a decrease in molecular weight of the plasticizers of a homologous series at a constant concentration level. Figure 4 shows the latter relationship for Lucite 46, a 50/50 *n*-butyl/isobutyl methyl acrylate copolymer. The water permeability decrease is related to a water solubility decrease in the plasticizer as one goes up in molecular weight in a homologous series of plasticizers. Even though the difference in water solubility in the plasticizers within the series is small, the slight water sorption by the plasticizer as described by solution theory (55) promotes further sorption, frequently nonideal (56) by the film, related to a clustering tendency of the penetrant molecules in the film (57–59). The addition of other additives, such as surfactants, to a film of ethylcellulose has been reported to produce clustering centers for water sorption (60).

The relationship between the assorted formulation factors and oxygen, and water vapor or water permeability and actual stability parameters of coated products remains to be established.

Dialysis and liquid permeability properties may be important to both fast and slow releasing film coating formulations. Some present commercial pharmaceutical tablet film coatings, presumably composed of cellulose acid phthalate and polyethylene glycol, release medicament substantially completely within 1 hr. through an intact film. An obvious application with marked advantages of

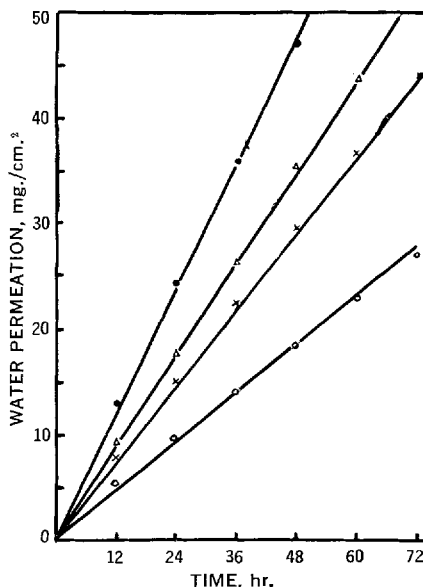


Fig. 4.—The effect of plasticizer composition (molecular weight and substitution) on the water permeability of *n*-butyl/isobutyl methacrylate (Lucite 46) copolymer films containing 15% plasticizer. Key: O, unplasticized; ×, dioctyl phthalate; Δ, dibutyl phthalate; ●, diethyl phthalate.

liquid permeable and dialyzing film coatings of controlled release rates in the sustained-release field.

Glass powder beads are reported to increase the glass transition temperature (T_g) of polyisobutylene, polyurethane (61), polystyrene, and poly (methyl methacrylate) (62), and titanium dioxide is reported to have the same effect on the T_g of other polymers (63). The increase in glass transition temperature appears to depend on the volume fraction of the filler in the system with the effect being attributed to the immobilization by adsorption of the polymer segments close to the surface of the filler particles. Carbon black did not affect the T_g of several polymers studied (64). Polar titanium dioxide as well as nonpolar fillers substantially reduce the sorption of organic vapors by poly (vinyl acetate), even at very low vapor pressures (65). The absorption isotherms of filled polymer films closely resembled that of the pure polymers below their glass transition temperatures, which also was attributed to immobilization of polymer segments at the solid surface.

As more is learned about methods of controlling the film membrane diffusion coefficients of pharmaceutical films as functions of added dispersed solids, film structure and orientation, salt concentration, ion ratios, film membrane-solution interactions (65-67), acid and base concentrations (68), and liquid boundary layer thickness (69), and according to formulation and methods of application, this physicochemical approach to controlled drug release will certainly advance, and the utility of polymeric films as more effective protective coatings may be exploited more completely.

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