

CHAPTER I

INTRODUCTION



Polymers have been used in pharmaceutical formulations for several reasons including protection of dosage form against environmental hazards and for hiding bad taste, odour or appearance. The application widely studied today is sustained release dosage forms by coating technique.

Single polymer is normally used in the polymer coating technique. It is not recommended to use blended polymer system because of the possible incompatibility of two polymers and the different glass transition temperatures of the polymers. However, when formulating modified-release film coated oral dosage forms, it is unlikely to meet the objectives set for final product by using only one single polymer (Chang and Robinson, 1990; Amighi and Moes, 1995).

The blending of similar structure of polymers has been widely found in pharmaceutical dosage forms, such as Eudragit[®]L100 with Eudragit[®]S100 (Bodmeier and Paeratakul, 1993), Eudragit[®]RL100 with Eudragit[®]RS100 (Chang and Hsiao, 1989; Bodmeier and Paeratakul, 1993), and Eudragit[®]RL30D with Eudragit[®]RS30D (Bodmeier and Paeratakul, 1990a, 1994a). On the other hand, the blending of different structure of polymers can hardly be found. There were only a few researches. Phuapradit et al. (1995) mixed Eudragit[®]RL100 with cellulose acetate in various ratios. When higher proportion of Eudragit[®]RL100 was used, the permeability of films was increased. The higher proportion of Eudragit[®]RL100 could also influence reduction of tensile strength.

Coowanitwong (1997) studied propranolol hydrochloride pellets coated with mixed polymers between ethylcellulose and Eudragit[®]RS100. The mixed films had

intermediate release patterns when compared to those of pure films. The higher the portion of Eudragit[®] RS100 the smoother the surface.

Because the glass transition temperatures of many of the polymers used in film coating are in excess of the temperature conditions experienced in the typical coating process, it is often necessary to modify the properties of the polymer. This modification allows the final coating to better withstand the conditions to which it will be subjected in the typical coating process. One of the appropriate modification involves the process of plasticization. Plasticizers reduce the glass transition temperature of amorphous polymers and impart flexibility. Both type and amount of the plasticizers can influence and change the film properties. Too high amount of plasticizer may result in too soft of the polymer film and can start problems in coating process. To decrease these problems, some dispersed solids should be added in order to reduce tackiness of the film (Porter and Bruno, 1990).

During dissolution studies or in biological fluids, water will come in contact with, and diffuse into and across the polymeric films or coatings. The existence of the plasticizer in the coating under these wet conditions will primarily depend on its solubility in water and affinity for the polymer. Water soluble plasticizers could leach from the polymeric coating, possibly changing its characteristics (Bodmeier and Paeratakul, 1992).

The resulting polymer coating is often characterized with respect to permeability and morphological and mechanical properties. The mechanical properties of dry polymer films are significantly affected by the thermomechanical properties of the polymer, such as glass transition temperature or softening temperature, and by film additives. The selection of analysis and testing methods of polymers is important because each method can assist in the selection of the most suitable coating formulation.

In the present study cellulose derivatives and poly (methacrylic acid) esters in both organic and aqueous systems were used to study the mixing of two different polymer structures. Ethylcellulose and Eudragit[®]RS100 were employed as the organic solution while Surelease[®] and Eudragit[®]RS30D were used as the aqueous coating dispersions by using propranolol hydrochloride as a water soluble model drug.

Many investigations have already studied physico-chemical and mechanical characteristics of pure films by using various types and levels of plasticizers. However, the type and level of plasticizers affecting blended polymers from aqueous and organic systems have been studied by only a few researchers. Moreover, the studies of the effect on film characteristics by varying ratios of mixed films were still not well understood. For that reason, the study of blended polymers between cellulose derivatives and poly (methacrylic acid) esters with various types and quantities of plasticizers can be worthy for improving film properties.

Objectives of the study

1. To study the physico-chemical and mechanical properties of mixed polymers prepared from casting method between ethylcellulose and ammonio methacrylate copolymer type B.
2. To assess the physico-chemical and mechanical properties of plasticized blending films subjected to elevated level and types of plasticizers.
3. To investigate dissolution characteristics of propranolol hydrochloride from blended films in pellet form.
4. To study the potential correlation between mechanical properties and permeability performance of the mixed polymers.
5. To predict optimal ratio of mixed polymers in order to obtain good performance characteristics of films.

Literature Review

1. Film Coating

Synthetic polymers are major constituents of film coatings that can be applied rapidly and economically. The evolution led to film forming polymers, which quickly gained significance owing to improvements in spraying technique and perfection of the corresponding equipment. A large number of suitable polymers enable the manufacture of pharmaceutical dosage forms with controlled release of the active ingredient.

Film coatings consist mainly of polymers, which are applied to the cores in the form of solutions or dispersions in which other excipients are dissolved or suspended. After drying of the solvents or dispersing agents, the polymer and other excipients remain on the cores as a coherent, uniform film. The other excipients may account for up to 60% of the coating layer, depending on the pigment-binding capacity of the polymers (Bauer et al, 1998).

Pharmaceutical film-coating formulations consist of organic solutions and aqueous dispersions. Organic solution produces good results but suffers from serious drawbacks such as pollution, fire and safety hazards. However, the technique is still widely used and probably always will have an application where specialised polymers are used for coating. With the advent and successful use of aqueous film coating over several years, many initial difficulties and preconceptions have disappeared and a most useful pharmaceutical production process has resulted (Hogen, 1982).

It has been well established that the mechanisms of film formation from organic solutions and aqueous dispersions are different. In the case of coatings applied from organic solutions, initial evaporation of the solvent leads to an increase in the

concentration of the solution, resulting in increased viscosity of the sprayed film-layer, which eventually brings the polymeric chains in close proximity. Further evaporation of the solvent results in the formulation of dense polymeric network providing the coating layer. An organic solvent-based coating formulation entails molecular dispersion of the plasticizer in the polymer, a condition which maximizes intermolecular interaction and effective plasticization.

In contrast, the mechanism of film formation from aqueous polymeric dispersions involves an entirely different sequence of events. This process involves deposition of the plasticizer-softened polymer spheres from an aqueous polymeric in the form of film on the substrate. During drying, water evaporates from the aqueous dispersion, resulting in concentration of the dispersed polymer spheres, which are moved into close contact with one another. This behavior eventually leads to the coalescence of the spheres due to deformation facilitated by capillary forces that are developed in the process and existence of appropriate thermal conditions. Consequently, aqueous polymeric dispersions must be processed at temperature in excess of the glass transition temperature of the polymer or plasticized polymer (Parikh, Porter, and Rohera, 1993a: 525).

The significant ingredients used in film coating are polymers, plasticizers and additives. All of these ingredients can influence the film characteristics.

2. Polymers

A polymer is a large molecule built up by the repetition of small, simple chemical units. The repeat unit of the polymer is usually equivalent to the monomer, or starting material from which the polymer is formed. In the majority of film coating formulations, the polymer is the major ingredient. Consequently, this material will have the greatest impact on the final properties of the coating.

Polymers have various chemical types and grades. When selecting a polymer for film coating, it is thus necessary to define this material in terms of chemical structure, molecular weight, and molecular distribution because molecular weight characteristics of the polymer have a significant effect on coating properties. Nowadays there are numerous commercially synthetic polymers which have found wide ranging uses in pharmaceutical formulations.

To modify the film coating system, one method that can be used is the blending of existing film-formers with other materials which may or may not be polymeric. The spectrum of such materials includes other film-formers, plasticizers, fillers/pigments and water-soluble additives. This approach has become more important as a result of the current slow rate of discovery of new film-forming materials for pharmaceutical use (Billmeyer, 1984; Okhamafe and York, 1987; Porter and Bruno, 1990).

2.1 Blending of polymers having similar structures

The use of two polymer blends which have similar structure is always found in pharmaceutical film coating. The composition can be separated into major component and minor component. Then minor component usually acts as pore forming agent and increases permeability of film formulation. Moreover, the minor component can be added to improve other properties of the film so the use of polymer blends may offer a wide range of applications for the film coating formulations. The most popular polymer that has been used as pore forming agent is hydroxypropyl methylcellulose. Many researchers have employed this polymer and mixed it with another polymer as demonstrated below.

Blends of ethylcellulose with hydroxypropyl methylcellulose (HPMC) are widely used in the formulation of sustained drug release film coatings. The water

insoluble ethylcellulose is usually chosen as the matrix and the water soluble HPMC as the minor component. The drug is released through pores created in the film coating by the dissolution of the dispersed phase. Sakellariou and Rowe (1995) had blended ethylcellulose with HPMC and founded that only the systems containing more than 60% w/w HPMC achieved complete leaching. HPMC retention was indicated for all systems with ethylcellulose as the major component.

Other research projects using the ethylcellulose/HPMC composite film had been investigated and the same result was observed. The rate of drug delivery was controlled by the water permeability of the membrane which increased with the amount of HPMC and the osmotic pressure (Hjartstam and Hjertberg, 1998).

Further studies were influenced on coating process by adding water soluble polymer (HPMC) in Aquacoat[®] and Eudragit[®]NE30D. The ethylcellulose dispersion containing the soluble ingredients led to a very permeable film which was unable to control the release of the drug (Vecchio et al., 1998).

Not only cellulose derivatives but also methacrylic ester copolymers have been mixed together to develop pharmaceutical formulations. As example, acrylic polymer in the form of aqueous dispersions like neutral ethylacrylate-methylmethacrylate copolymer (Eudragit[®]NE30D) and anionic methacrylic acid copolymers (Eudragit[®]L30D, L100-55, L100 and S100) can be mixed together without major difficulties (Lehmann, 1989).

The effect of different ratios of Eudragit[®]RS and RL on the release rates of theophylline was evaluated by many researchers (Chang and Hsiao, 1989; Amighi and Moes, 1995; Dyer, Khan and Aulton, 1995; Rafiee-Tehrani and Sadegh-Shobeiri, 1995). Eudragit[®]RS/RL pseudolatexes can be mixed in any proportion one with the other, which the higher the ratio of Eudragit[®]RL the faster the release of any

medicine. The effect of this mixing is due to readily permeability to water of Eudragit[®] RL type.

2.2 Blending of polymers having different structures

There are a few numbers of reports on the case of blending distinguishable structures of polymer to produce controlled release product. Rafiee-Tehrani and Sadegh-Shobeiri (1995) prepared the solutions of Eudragits (L100, S100, L100 + S100, RL100, RS100, RL100 + RS100), ethylcellulose and Eudragit[®] RS100 + ethylcellulose in acetone, by using dibutyl phthalate as plasticizer. They described that combination of cellulose ether derivatives and methacrylate ester co-polymer (Eudragit[®] RS100) in this investigation demonstrated predictable and suitable sustained release characteristics. Moreover, ethylcellulose and the mixture of ethylcellulose and Eudragit[®] RS100 (1:1) exhibited better linearity of drug release in comparison with other formulations.

The addition of Eudragit[®] RL100 to cellulose acetate (CA) and ethylcellulose containing dibutyl sebacate increased the permeability of the resulting membrane. The effect was more pronounced in the case of the ethylcellulose membranes. A significant increase in membrane permeability was observed when greater than 40% of Eudragit[®] RL100 was added to CA membrane because of a substantial increase in the microporosity of the resulting membrane. Moreover, the addition of Eudragit[®] RL100 to CA membrane containing dibutyl sebacate caused a significant decrease in the tensile strength, percent elongation and modulus of elasticity, thus providing weaker and softer membranes (Phuapradit et al., 1995).

Sridevi et al. (1995) developed metronidazole-loaded strips for the local therapy of periodontitis by using polymethyl methacrylate (PMM) in combination

with ethylcellulose and dibutyl phthalate as plasticizer. While pure PMM released the drug at a slower rate, the desired prolongation of metronidazole release was achieved by incorporating the drug in a combination of PMM and ethylcellulose. The incorporation of ethylcellulose in PMM led to the formation of a heterogeneous system, where diffusion of the drug took place from the interparticular pores and channels.

Blended polymers between ethylcellulose and Eudragit[®]RS100 or Eudragit[®]RL100 were studied by Coowanitwong (1997) in various ratios of polymers. At the identical ratio, Eudragit[®]RS100 gave more retardent property on drug release than of Eudragit[®]RL100. When different portions of ethylcellulose with Eudragit[®]RS100 were compared, the higher portion of ethylcellulose, the slower of drug release profile. From surface morphology by SEM, the higher portion of Eudragit[®]RS100 could give much smoother surface.

The other researchers also used two layers of coating with different structures of two polymers. Lin and Ayres (1992) studied calcium alginate bead as core carriers of 5-aminosalicylic acid by coating another layer of one polymer on the surface of another polymer coated beads. Formula with 4% Aquacoat[®] in the inner layer and 6% Eudragit[®]L30D in the outer layer provided sufficient protection against 2-hr acid treatment and a more sustained release pattern compared to the others.

In the same technique, Venkatesh and Sanghavi (1994) prepared pindolol coated pellets by using hydroxypropyl methylcellulosephthalate (HPMCP 55), Eudragit[®]S100, ethylcellulose and Eudragit[®]RS100. Coating of pellets using retardant polymers namely ethylcellulose and Eudragit[®]RS100 could control the drug release in pH 7.2, but did not control in pH 1.2. Therefore, top coating of these pellets with further coat of HPMCP 55 or Eudragit[®]S100 resulted in control of drug flux in pH 1.2.

Furthermore, Govender, Dangor, and Chetty (1995) had studied the ability of hydroxypropyl methylcellulose (HPMC) to modify the release characteristics. HPMC inclusion in the Eudragit[®] RS30D film coating increased release rates due to its hydrophilic nature which promoted the formation of pores and cracks on the polymer films.

As for the blends of polymer solutions, care must be taken when aqueous polymeric dispersions are mixed, especially when ionic interactions are expected. Furthermore, additional special attention is required when using latex aqueous dispersions stabilized by different emulsifier systems and/or having different pHs (Amighi and Moes, 1995).

2.3 Film formers

2.3.1 Ethylcellulose

Ethylcellulose is the cellulose molecule with a chain of beta-anhydroglucose units joined together by acetal linkages. Each anhydroglucose unit has three replaceable hydroxyl groups which are substituted to the extent of 2.25 to 2.60 ethoxyl groups per unit (or 44 to 50 percent ethoxyl content) structure of ethylcellulose can be found in Figure 1.

Ethylcellulose is soluble in a wide variety of solvents, thus making it easier to use when solution application is desirable. Among the useful solvents are the esters, aromatic hydrocarbons, alcohols, ketones and chlorinated solvents. Its solubility is dependent upon the ethoxyl content. The addition of 10-20% of a lower aliphatic alcohol to solvents, such as ketones, esters and hydrocarbons, can improve the solubility.

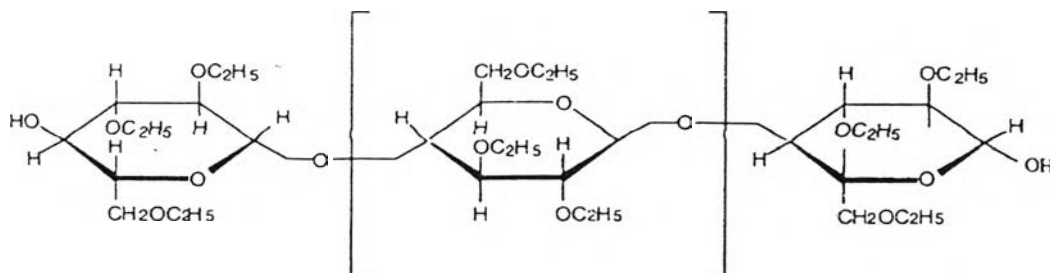


Figure 1 The molecular structure of ethylcellulose with complete ethoxyl substitution

Ethylcellulose is resistant to alkalis, both dilute and concentrated, and to salt solutions. It is more sensitive to acidic materials than are cellulose esters. However, the material can withstand dilute acids for a limited period of exposure. In most formulations of ethylcellulose resins, 5-30% plasticizer (based on the total solids) is sufficient to produce a satisfactory film flexibility. Ethylcellulose is available as an aqueous polymer dispersion for use in film coatings (Rekhi and Jambhekar, 1995).

Surelease[®] is a 25% w/w dispersion prepared by a phase inversion in-situ emulsification technique, fully plasticized polymeric dispersion of ethylcellulose that provides reproducible drug-release profiles. It is a complete, ready-to-use system. Surelease[®] is composed of the following ingredients.

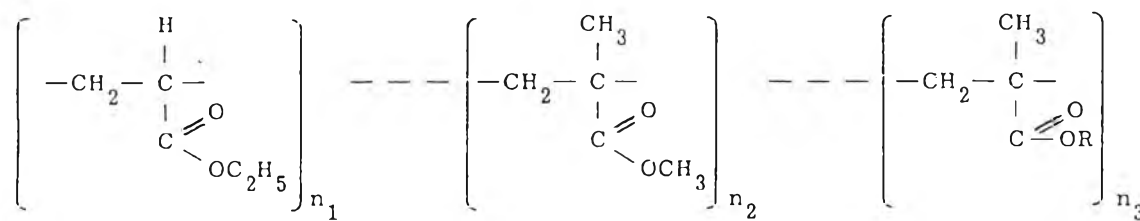
- Ethylcellulose. It forms a relatively impermeable barrier. Due to its water insolubility, it has been finely dispersed in the Surelease[®] system
- Dibutyl sebacate or fractionated coconut oil and oleic acid. These ingredients are the plasticizers for the Surelease[®] system. In the manufacturing process they are incorporated within the dispersed polymer particles to achieve a consistent and effective plasticizer level.

- Ammoniated water. Ammonia is used to stabilize the dispersed polymer and as the vehicle for the system. It imparts a characteristic ammonia odor to the product.
- Fumed silica. This ingredient is added to facilitate the application of Surelease[®]; it is an antiadherent.

The combination of these ingredients through a unique, patented manufacturing process forms a milky liquid dispersion with a characteristic ammonia odor. The Surelease[®] system is virtually ready to use. Gentle agitation may be required to redisperse any settlement that has occurred. To facilitate ease of spraying, the solids content should be reduced from 25% to 15% by the addition of distilled water. Dissolution profiles are unaffected by pH (Moore, 1989).

2.3.2 Ammonio methacrylate copolymer type B

Polymethacrylates are film coatings and matrix structures based on polymeric methacrylates. The introduction of hydrophilic quaternary ammonium groups by copolymerization with trimethylammonioethyl methacrylate chloride (TAMCI) modifies the permeability of methacrylic ester copolymers. The commercial products of methacrylic ester copolymers type B are Eudragit[®] RS100 and Eudragit[®] RS30D. The structure of Eudragit[®] RS is presented in Figure 2. Eudragit[®] RS is based on poly (ethylacrylate – methylmethacrylate – trimethylammonioethyl methacrylate chloride) copolymers with the ratios of 1:2:0.1. The TAMCI copolymers are produced by bulk polymerization and are commercially available as solid granules (Eudragit[®] RS100) and used in sustained release formulations in the form of organic coating solutions or as milled polymer powder for direct compression into matrix tablets.



Methacrylate ester copolymers

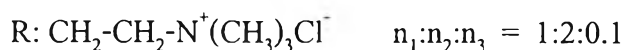


Figure 2 The molecular structure of Poly (ethylacrylate, methylmethacrylate) trimethylammonioethyl methacrylate chloride

Eudragit[®]RS100 can be soluble in isopropanol and ethanol in combination with acetone or methylene chloride; also in methanol, chloroform, trichloroethylene, ethyl acetate and glycol monotetrachloride. It is insoluble in petroleum ether or light petroleum and can swell in aqueous media. The amount of water absorbed depends on the pH of the solution and the type of Eudragit[®].

Eudragit[®]RS30D is prepared by direct emulsification of the solid bulk polymer in hot water without any additive to a stable aqueous dispersion. The formation of a latex-like aqueous dispersions is obviously caused by the hydrophilic ammonium groups. The commercial aqueous dispersions with 30% polymer content contain 0.25% sorbic acid as a preservative but no emulsifier. The addition of 10-20% plasticizers is necessary to reduce minimum film forming temperature of both Eudragit[®]RS100 and Eudragit[®]RS30D.

The addition of plasticizer, which is usually a nonionic substance, is no problem. A plasticizer of some water solubility such as triacetin and triethyl citrate can be added directly to the latexes; freely water soluble or even hygroscopic substances like PEG and sorbitan esters should be dissolved in water and added as 20-35%. Water insoluble plasticizer can be emulsified in water using some latex-compatible emulsifier and mixed with the latex for some time in which the hydrophobic plasticizer will reach equilibrium distribution between the water and polymer phases of the latex. The compatibility of latexes with water soluble polymers and the miscibility of different latexes must be checked in each individual case (Lehmann, 1989).

3. Plasticizers

Many polymer materials that are used in film coating tablets and beads display brittle properties under normal ambient temperatures and humidity conditions, the incorporation of a plasticizer is necessary to obtain an effective coating without any defects. Plasticizers are also added to polymeric solutions and dispersions to modify the thermal and mechanical properties of polymers. The addition of plasticizer may lower the melt viscosity, the glass transition temperature (T_g), or the elastic modulus of the polymeric material with the magnitude of the effect being dependent on the degree of interaction between the polymer and the plasticizer (Gutierrez-Rocca and McGinity, 1993, 1994).

To be effective, a plasticizer molecule must interpose itself between the polymer chains and interact with the forces holding the chains together, thereby weakening the polymer intermolecular attractions and increasing the polymer's free volume. They form a secondary valence gel with the polymers, in which the plasticizer molecules are not firmly localized. Instead, a dynamic equilibrium of interactions is established between plasticizer and polymer segments, as well as between the polymer segments and the plasticizer molecules themselves. The plasticizer molecules augment

the flexibility of the polymer chains by pushing chain segments further apart or altering the average chain conformation through molecular effects. The glass transition temperature of the system decreases as a result of the increased segmental mobility, and the film becomes pliable polymers under conventional film-coating conditions.

As far as polymeric film coatings are concerned, these effects can be achieved by either *external plasticizing*, i.e. adding suitable substances to the coating formulations, or *internal plasticizing*, i.e. copolymerization with softening monomers of greater chain length.

The basic requirements of plasticizer are permanence and compatibility. Permanence dictates that the plasticizer has a low vapor pressure and low diffusion rate within the polymeric film, a requirement that favors high molecular weight plasticizers. Compatibility, on the other hand, demands that the plasticizer be miscible with the polymer and exhibit similar intermolecular forces to those present within the polymer (Porter and Bruno, 1990; Bauer et al., 1998).

Not only one type of plasticizer is able to be mixed with polymer but also secondary plasticizer. Different secondary plasticizers were added to self-adhesive Eudragit[®]E100 films. Secondary plasticizers with a low molecule weight and a solubility parameter similar to that of Eudragit[®]E100 polymer and triacetin were compatible. The results indicated that PEG 200, propylene glycol, diethyl phthalate, and oleic acid could serve as a secondary plasticizer to improve the transparency, flexibility, and adhesion of Eudragit[®]E100 film (Lin, Lee, and Lin, 1991).

Effective plasticization is critical when using aqueous polymeric dispersions in order to ensure that sufficient free volume exists at normal processing temperatures to facilitate coalescence of the polymeric particles into a continuous film.

For practical and economic reasons, a plasticizer selected for pharmaceutical purposes will decrease the T_g of the film forming polymers even at low levels. This lowering of the glass temperature depends on the type and quantity of plasticizer. For binary, homogeneous mixtures it can be calculated in the first approximation from the following equation:

$$\frac{1}{T_g} = \frac{W^1}{T_g^1} + \frac{W^2}{T_g^2}$$

T_g = the glass transition temperature of the resulting coating

T_g^1, T_g^2 = the glass transition temperature of polymer and plasticizer, respectively

W^1, W^2 = mass fractions of polymer and plasticizer in the mixture, respectively

The effectiveness of plasticizers in the coating formulation depends on further factors, e.g. other excipients, solvent systems, application method, etc. (Porter and Bruno, 1990; Bauer et al., 1998).

3.1 The different types of the plasticizer

Plasticizer can be divided into water-soluble and water-insoluble plasticizers. A potential disadvantage of water-soluble plasticizers is their leaching from the coating after contact with dissolution or physiological fluids. The release kinetic will vary because of this change in film composition, the systems are therefore difficult to be controlled accurately.

Bodmeier and Paeratakul (1992) had studied the leaching of triethyl citrate as a function of Eudragit[®] RS/RL ratio. The two dispersions between Eudragit[®] RS30D and Eudragit[®] RL30D were mixed in various proportions. The higher proportion of quaternary ammonium groups in Eudragit[®] RL films resulted in faster hydration and leaching of the plasticizer. The release rate constants initially increased rapidly with

increasing proportion of Eudragit[®]RL30D, but levelled off at concentrations above 60% of Eudragit[®]RL30D. In the part of water insoluble plasticizers or lipophilic plasticizers, they could remain in the coating and assure more constant conditions during the entire release (Lin et al., 1991; Siepmann, Paeratakul, and Bodmeier, 1998).

It is well known that different plasticizers, at the same concentration level, will affect the T_g and hence the mechanical properties to a different extent. The effect of the various plasticizers was investigated by many researchers. Bodmeier and Paeratakul (1994a) studied the influence of water soluble plasticizers and water insoluble plasticizers on dry and wet films. Dry Eudragit[®]RS30D films plasticized with water soluble plasticizers had higher elongation and lower puncture strength values, while films prepared with the water insoluble plasticizers had lower elongation and higher puncture strength values. However, wet Eudragit[®]RS30D films plasticized with water insoluble plasticizers were significantly more flexible than the corresponding wet Eudragit[®]RS30D films plasticized with the water soluble plasticizers.

Three different plasticizers were used in cellulose acetate film by Schultz, Tho, and Kleinebudde (1997). All of these plasticizers were triethyl citrate, diethyl phthalate and tributyl citrate representing increasing lipophilicities. Membranes containing a more lipophilic plasticizer had a lower water permeability leading to a decrease in water flux. The reduced water penetration resulted in a prolonged swelling time and a decreased release rate after membrane perforation. However, there was no difference in mechanical properties between the three plasticizers used due to the hydrophilicity and high water permeability of cellulose acetate.

Phuapradit et al.(1995) had prepared cellulose acetate membrane and ethylcellulose membrane by using dibutyl sebacate, triethyl citrate and triacetin as plasticizers. The results of mechanical deformation studies indicated that triacetin had a greater potential for partitioning into the cellulose acetate polymer than did triethyl

citrate or dibutyl sebacate. Dibutyl sebacate had a greater potential for partitioning into the ethylcellulose polymer than did triethyl citrate or triacetin. The ethylcellulose membrane containing dibutyl sebacate which it was more hydrophobic than the other two plasticizers so a hydrophobic drug, like theophylline, would have a greater partitioning into the ethylcellulose membrane.

Hutching, Clarson, and Sakr (1994) had considered the relative effectiveness of plasticizers and even classes of plasticizers to influence maximum stress of Aquacoat[®] film. They concluded that the maximum stress values which were obtained for the di-acid esters and for the fatty acid/alcohol classes were generally lower than those obtained for the citrate esters and triacetin. This observation may be correlated with molecular structure as both the di-acid esters and for the fatty acid/alcohols are long chain molecules while the citrate esters and triacetin are branched.

Molecular weight of plasticizers also has influenced mechanical properties and miscibility of polymer. This experiment was prepared by blending various molecular weight of polyethylene glycol with Eudragit[®]E100 film. A lower molecular weight of plasticizers resulted in greater plasticizing action to reduce tensile strength and to increase film elongation, independent of whether the plasticizer was hydrophilic or hydrophobic. Moreover, plasticizer of low molecular weight should be more efficient owing to its larger surface areas as compared with the same plasticizer of the higher molecular weight. Thus, the plasticizing efficiency of plasticizers may be related to the size and amount of the plasticizer molecules and the number of the interchain bonding sites in the polymer (Lin et al., 1991).

3.2 The amount of the plasticizer.

Experiments should be performed to determine the most favorable proportion of plasticizer. Too low levels of a plasticizer may result in incomplete or a

discontinuous film. On the other hand, too high proportion of plasticizer may result in seed agglomeration, sticking, and poor fluidization problems during coating by fluidized bed coater caused by excessive softening of the polymer film. The levels of the plasticizer had influenced the film characteristic as described below (Chang and Robinson, 1990).

The importance of triethyl citrate as a plasticizer for Eudragit[®]RS30D had been reported by Govender et al. (1995). Increasing the plasticizer concentration enhanced the deformation and coalescence of the polymer spheres. The surface of these films showed an improvement in the smoothness and continuity which resulted in the slower in vitro drug release.

By reducing the plasticizer levels, the permeability of the film is remarkably augmented because of incomplete coalescence. The higher level of the plasticizer has an accelerating effect on the speed of film formation. Schmidt and Niemann (1993) had manifested that low release rates were easily obtained from Eudragit[®]RS30D films with 20% plasticizer at a coating level of 4%.

The similar trends were obtained. These results were presented by Bodmeier and Paeratakul (1994b) and Schultz et al. (1997) that the higher the level of plasticizer the lower the drug release. Nevertheless, the increase in permeability of Eudragit[®]RS30D could occur at higher amount of plasticizer. Bodmeier and Paeratakul (1990a) studied the effect on drug release by using different levels of triethyl citrate. The increase in release rate constant at high triethyl citrate concentration more than 30% could happen by the leaching out of the water soluble plasticizer.

The effect of different types and levels of plasticizers on the thermal and physico-mechanical properties of Eudragit[®]L was studied (Gutierrez-Rocca and McGinity, 1994). For the water soluble plasticizers, triethyl citrate and acetyl tributyl

citrate, there was a decrease in the Tg and elastic modulus when plasticizer was included in the film at the 10% level. No further decreases were found in the Tg and elastic modulus as the plasticizer increased from 10-30%. The longer elongations seen with the water soluble plasticizers indicated a higher affinity for these compounds to diffuse into and interact with Eudragit[®] L, thereby increasing the mobility of the polymeric chains. The puncture strength decreased and the elongation increased with increasing plasticizer concentration with dry film were more studied by Lin et al. (1991) and Bodmeier and Paeratakul (1993).

3.3 Properties of plasticizers in experiment

3.3.1 Dibutyl phthalate

USPNF : Dibutyl phthalate (reagent)

- Formula : $C_6H_4(COOC_4H_9)_2$

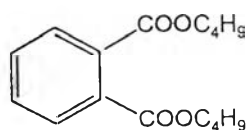


Figure 3 Chemical structure of dibutyl phthalate

- M.W. : 278.35
- Mp : -35 °C, bp : 340 °C, density : 1.049 ; solubility in water 0.04 g/100 ml, miscible with lower alcohols and dichloromethane.
- Produced by esterification of phthalic anhydride.

3.3.2 Triethyl citrate

USPNF : Triethyl citrate

- Formula : $C_{12}H_{20}O_7$

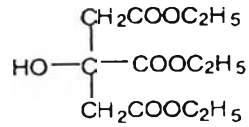


Figure 4 Chemical structure of triethyl citrate

- M.W. : 276.3, bp : 288 °C, density : 1.135-1.139; almost colorless, oily liquid with a faint, pleasant esterlike odor; miscible with alcohol, ether and chloroform.

3.3.3 Glyceryl triacetate

USPNF : Triacetin

- Formula : $C_9H_{14}O_6$

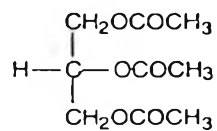


Figure 5 Chemical structure of triacetin

- M.W. : 218.03, bp : 258-259 °C, density : 1.16; clear, odorless liquid; soluble in water (7%) and miscible with ethanol, ether and chloroform; hydrolyzes slowly in the presence of water with formation of acetic acid and methanol.
- Produced by acetylation of glycerol.

4. The Additives

By the incorporation of pigments and insoluble fillers, permeability and drug release of a film coating may be affected. There are a number of studies on the permeability of additives or pigments in the pharmaceutical coating formulations. Many additives such as talcum, magnesium stearate, surfactant can lead to modification of any polymer characteristics.

Magnesium stearate was incorporated into Eudragit[®]RS30D formulation to reduce the inherent tackiness and therefore overcome processing difficulties associated with this polymer. The slower in drug release with larger quantity of magnesium stearate was possibly due to the hydrophobic nature which inhibited hydration of the polymeric membrane and thus retarded the release of medicine (Govender et al., 1995).

Talcum or silica likewise was added in order to reduce the tackiness and the permeability of the Eudragit[®]RS pseudolatex film. The dissolution rate was quite different from expectation. Chang and Hsiao (1989) concluded that the enhancement of dissolution rate by inclusion of dispersed solids may be due to an increase in porosity and heterogeneity of the membrane.

The influence of talcum on the properties of cellulose acetate film was studied by Schultz et al. (1997). At low concentration, talcum reduced the water permeability of film coating materials. Exceeding the critical pigment volume

concentration (CPVC), voids were created resulting in an increase of water permeability. The CPVC is the specific value for each type of film so raising amount of talcum over CPVC may cause the creation of water permeation enhancing voids. Furthermore, the amount of talcum had no significant effect in the mechanical properties of swollen films.

The other additive that can influence on polymer is surfactant. The pH-dependent drug release from ethylcellulose pseudolatex (Aquacoat[®]) beads was caused by the presence of the anionic surfactant, sodium lauryl sulfate and a co-surfactant, cetyl alcohol. Drug release increased with increasing concentration of sodium lauryl sulfate while an increase in the amount of cetyl alcohol resulted in a significant decrease in drug release (Bodmeier and Paeratakul, 1991).

Citric acid and urea were established as suitable plasticizers for hydroxypropyl methylcellulose and polyvinyl alcohol that could observe from the reduction of T_g. The fall in the higher transition temperature was due to the additives, with many hydrogen bonding groups strongly interacted with the polymers. Interposition of additive molecules between adjacent polymer chains generally enhances segmental mobility and hence the fall in the glass transition temperatures (Okhamafe and York, 1988).

Maul and Schmidt (1995) reported that platelet-shaped pigments or fillers reduced bisacodyl release from pellets coated with Eudragit[®]L30D, independent of their chemical constitution and the polarity of their surfaces. Coarse platelets demonstrated a greater effect than finer ones. Additionally, coatings with spherical titanium dioxide and red iron oxide needles had no barrier effect or led to an increase in permeability depending on their concentration within the coating.

Furthermore, the active ingredient can influence the film property. Salicylic acid and chlorpheniramine maleate could exert a plasticizing influence when

incorporated into the acrylic resin films (Eudragit[®]RSPM and Eudragit[®]RLPM). The T_g decreased progressively with increased drug loading of either salicylic acid or chlorpheniramine maleate (Jenquin et al., 1990, 1992). Moreover, when PEG 400 was incorporated into salicylic acid-containing films, PEG 400 could result in reduction of the tensile strength and increment of the percent elongation. The presence of PEG 400 had a toughening effect on the acrylic resin films. These findings demonstrate that not only the type of polymer/plasticizer but also the type of drug significantly influences the characteristics of the films (Jenquin et al., 1992).

5. The Glass Transition Temperature

The glass transition temperature (T_g) is found in all amorphous polymers and in amorphous regions of partially crystalline polymers. The T_g of the latter is independent of the degree of crystallization but the magnitude of the transition decreases with an increase in crystallinity with the result that the transition becomes difficult to detect in highly crystalline polymers (Ford and Timmins, 1989).

At low enough temperatures, all amorphous polymers exist in a glassy state where no large-scale molecular motion can take place, and while in the glassy state, polymers are characterized by their hardness, stiffness, and brittleness. As the temperature is raised, polymers undergo a transition, known as the glass transition temperature, T_g , where they change from a glass to a rubbery elastomer or flexible plastic. This transition takes place over a narrow temperature range and corresponds to the onset of segmental motion of long segments of the polymer chain, which is brought about by the availability of sufficient thermal energy to overcome intermolecular interactions.

As a consequence of this transition, the polymer undergoes an abrupt change in properties. Among these are coefficient of expansion, permeability, heat content,

refractive index, and hardness. Thus, in designing a controlled-release device, it must be known whether at use, the polymer will be above or below its glass transition temperature.

The glass transition temperature, also known as the second-order transition, is a characteristic of a particular polymer structure, and its value is closely related to intermolecular forces and chain stiffness. Thus, because above the T_g segmental motions of polymer chains take place, it follows that very flexible polymers, where free rotation about bonds along the polymer chains is possible, will in general have low T_g values. For this reason, poly (dimethyl siloxane), in which virtually unrestricted rotation takes place between the silicon-oxygen bond, has one of the lowest T_g values known (-123°C).

Clearly, the onset of segmental motion of polymer chains will also depend on the magnitude of intermolecular forces because no motion of polymer chains can take place until enough thermal energy is available to overcome those forces. Consequently, polymers with strong intermolecular interactions will tend to have high T_g values (Heller, 1987: 167-168).

Changes in the T_g of one polymer usually affect different film properties. Adding plasticizer can generally lower T_g because plasticizer enhances segmental mobility of polymer. In another way, adding pigment can generally reduce polymer chain mobility which manifests as an increase in T_g . Moreover, modifications to the polymer that increase the presence of polar groups, hydrogen bonds, and other factors that enhance the intermolecular forces tend to raise T_g (Okhamafe and York, 1987; Heller, 1987).

T_g is dependent on molecular weight of polymers. Derbin et al. (1996) founded that the T_g increased from 27°C for the molecular weight of Poly DL-lactic

acid of 3,500 (PLA) to 57 °C for the highest molecular weight PLA of 553,000. However, the differences in T_g became progressively less significant as the molecular weight increased from 92,000 to 553,000, reaching a plateau at 57-58 °C. As the polymer molecular weight increased, there were fewer chain ends which had less free volume than the same number of atoms in the middle of the chain. The decrease in free volume gradually reached a limit as the molecular weight increased because of chain entanglements. In the same manner, the energy required to produce the excess free volume, as reflected by the T_g, also reached a limiting value.

Polymer-polymer compatibility may also be evaluated from T_g data. If the two polymers in a binary film system are compatible, one T_g, lying between the T_g's of the individual polymers in the blend, is observed. For partially compatible polymers, two T_g's are detectable if the compatibility limit is exceeded: one for the blend and the other for the polymer which is in excess. Moreover, the glass transition spread or width for partially compatible polymer blends increases as the content of the second polymer is raised until just before incompatibility sets in (Okhamafe and York, 1987).

6. Thermal Analysis

Thermal methods are especially appropriate for study of interactions in film coating formulations. Unlike the other methods, the nature of the specimens used solid films rather than liquid film solution. Moreover, the data received from thermal methods generally supply a more quantitative characterization of interaction processes.

Several researchers have addressed the importance of the T_g of a polymer used for film coating, since many knowledges of the T_g are a good indicator of the polymer's behavior under ambient and coating conditions. A number of studies involving thermal techniques report the measurement of glass transition temperature by

differential scanning calorimetry, thermomechanical analysis, and torsional braid analyzer.

6.1 Differential Scanning Calorimetry (DSC)

In differential scanning calorimetry, an average-temperature circuit measures and controls the temperature of sample and reference holders to conform to a predetermined time-temperature program. Experimentally, measurements are made by either recording and integrating the temperature difference or recording the energy necessary to establish zero temperature difference between a substance and a reference material against either time or temperature as the two specimens are subjected to identical temperature regimens. A hypothetical thermogram is depicted in Figure 6 (Billmeyer, 1984; Radebaugh, 1992).

The T_g is evident as a small endothermic rise and is represented by the midpoint of the rise measured from the extension of the pre- and post-transition baselines, i.e. when the transition assumes half the value of this change.

Many polymers exhibit a small endothermic peak at their T_g . This effect is due either to a bulk stress relaxation in the system or to a free volume effect at the molecular level. In the latter case, the post-transition baseline is extrapolated through the peak to determine the T_g (Ford and Timmins, 1989). In order to investigate the T_g , many researchers used DSC to check the physico-chemical properties of film (Entwistle and Rowe, 1979; Porter and Ridgway, 1983; Hutchings et al., 1994; Gutierrez-Rocca and McGinity, 1994; Maarschalk, Vromans, et al., 1998).

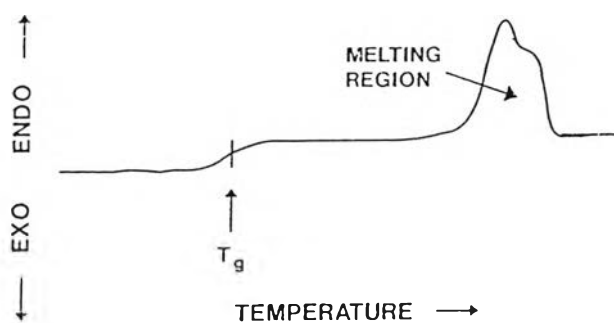


Figure 6 A typical DSC thermogram, where T_g is the glass transition.

The soft acrylic polymer dispersion (Eudragit[®]NE30D) could be blended with the hard acrylic polymers (Eudragit[®]RS30D, S100) in order to decrease the softening temperature or the minimum film forming temperature of the combined film and consequently, to improve their film forming properties. The thermograms of the blends by DSC are characterized by two individual glass transition temperatures unlike what is usually observed with blends of totally miscible and compatible polymers which are characterized by only one intermediate transition temperature. Regarding these results, Amighi and Moes (1995) concluded that the use of the soft acrylic polymer did not have any effective plasticizing effect on the T_g of the hard acrylic polymer. Therefore, the films obtained from blends were heterogeneous as they contained a continuous phase of the soft polymer in which was embedded uncoalesced latex particles of the hard polymer.

Thermograms of the blending film containing Eudragit[®]RS100, Eudragit[®]E and indomethacin were carried out by DSC to control the T_g of polymers and the physical state of indomethacin after two and three years of storage. The appearance of two separated peaks corresponding to the enthalpic recovery of the polymers was observed after three years of storage. Lovrecich et al. (1996) suggested

that the polymer mixture produced a slow phase separation. Nevertheless, no indomethacin peak was detected.

Hyppola, Husson, and Sundholm (1996) measured the T_g of ethylcellulose films with differential scanning calorimetry although it was very difficult because of too weak signal. However, the results of the DSC measurements gave very similar information to the tensile tests about the efficiency of the different plasticizers. Dibutyl sebacate and Myvacet[®] (acetylated monoglycerides) were the two most efficient plasticizer grades. In some of the samples, two glass transitions were observed : one at the right temperature and another one at the temperature corresponding to the T_g of ethylcellulose. These could be seen at films plasticized with 10% triethyl citrate, diethyl phthalate and triacetin. It seemed that some of the polymer was probably not plasticized so the system was biphasic.

The T_g of different copolymers was also determined by DSC. Copolymers with different T_g 's were synthesized by free radical copolymerization of methylmethacrylate (MMA) with lauryl methacrylate (LMA). Effects of LMA on copolymer film properties could act as plasticizer on the polymer chains. The reduction of T_g was happened when the proportion of LMA monomer was augmented (Maarschalk, Zuurman et al., 1997).

6.2 Thermal Mechanical Analysis (TMA)

Thermal mechanical analysis measures the deformation of a sample under a nanoscillatory load as a function of temperature is changed at a programmed rate. Deformation can be followed in the penetration or expansion modes. Figure 7 presents typical TMA data obtained using the expansion and penetration modes. Softening point (T_s) indicates the point whereat the polymer softens prior to melting and normally lies between glass transition temperature (T_g) and melting point (T_m). At

T_s , polymer chain mobility is so high that some intersegmental bonds are fractured and as a result, the polymer matrix is more porous and resistance to penetration becomes low. Hence, the application of the penetration mode can detect this point by rapid penetrating to film samples with probe. T_g usually can measure in the expansion mode. At T_g , the rigid polymer chains become more mobile that can cause increasing the void volume. This is manifested as a thermal expansion of the film coating which displaces the expansion probe (Okhamafe and York, 1987; Radebaugh, 1992).

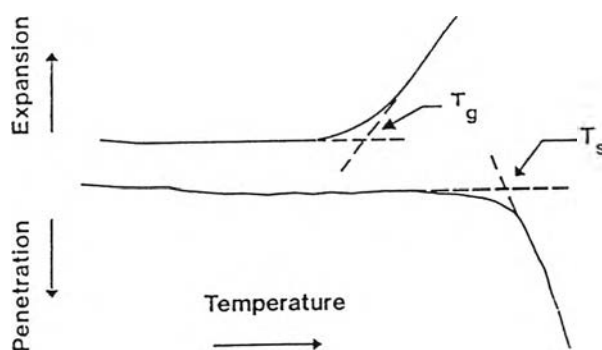


Figure 7 Typical TMA thermogram illustrating the expansion and penetration modes, where T_g is the glass transition temperature and T_s the softening temperature.

Thermomechanical analysis studies have been used previously to study the mechanical properties of pharmaceuticals and excipients, including films. TMA techniques were used by Derbin et al. (1996) to further examine the effects that plasticizer had on the characteristics of Aquacoat[®] films (ethylcellulose pseudolatex). They concluded that the addition of plasticizers reduced the onset of softening values of the ethylcellulose pseudolatex films. The extent of the reduction varied with the choice of plasticizer, greatest reductions being observed with triethyl citrate.

Both DSC and TMA in penetration and expansion mode were used to examine interaction between aqueous-based hydroxypropyl methylcellulose and

polyvinyl alcohol and water-soluble additives. There were some conflicting data because of different measuring procedures. In DSC, the samples were pretreated to remove moisture and so their thermal history different from that of TMA samples. This probably also explains, in part why the T_g obtained from DSC was always lower than the corresponding T_g from TMA studies. Nonconformity of DSC and TMA T_g values could also partly be due to the possible existence of a time lag between the endothermic process at glass transition, which is monitored in DSC, and the actual change in free volume which TMA measures.

6.3 Torsional Braid Analysis (TBA)

The method employed to determine the T_g of the various formulations is the torsional braid pendulum originally invented for following the rigidity changes accompanying the curing of polymer. This is a dynamic mechanical technique which measures the response of a polymer-impregnated glass fiber braid to a sinusoidal stress as a function of temperature.

To study the plasticizing efficiency of the dialkyl phthalates when added to ethylcellulose. This plasticizing efficiency had been evaluated by measuring the T_g of formulations using the TBA. In conclusion, diethyl phthalate was the best plasticizer and it lowered the T_g of the ethylcellulose very close to 60 °C when using 30% w/w concentrations (Rowe, Kotaras, and White, 1984).

Sakellariou, Rowe, and White (1988) employed TBA in the study of the relatively difficult phenomena of leaching/retention of soluble components in blends with an insoluble component. They found that hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl cellulose (HPC), cellulose acetate phthalate and PEG 6000 exhibited considerable interactions with ethylcellulose as they all showed retention at low ethylcellulose contents. Furthermore, hydroxypropyl methylcellulose (HPMC),

HPC and HPMCP blends with ethylcellulose exhibited effective dispersion of the soluble component in ethylcellulose matrix, as they all showed retention at blend compositions with high ethylcellulose contents.

A torsional braid analyser was also used for dynamic mechanical spectra of the blends ethylcellulose and HPMC. The phase separation was also confirmed by the presence of two transitions in the TBA spectra corresponding to the glass transition temperatures of the two polymers (Sakellariou and Rowe, 1995).

7. Tensile Testing

Lowering of the T_g alone, however, cannot be used as a sole prediction of the final coating performance or response to changes in the applied stress or strain. Mechanical testing such as tensile testing can be a useful guide in predicting not only the film coating characteristic but also in comparing the effect of plasticizers in film samples as a function of formulation compatibility, type and level (Gutierrez-Rocca and McGinity, 1994).

Traditionally, stress-strain testing in the tensile mode has been a popular and widely used mechanical test for polymeric films. The tensile test is practical, and analysis of its data is relatively straightforward. In the development of a film coating system, the evaluation of free films has been established as a valuable tool, since it can be readily used to characterize and evaluate the fundamental properties of the coating (Li and Peck, 1989; Parikh, Porter, and Rohera, 1993b).

There remains a method for preparing film samples, either to cast the polymer solution onto a flat surface or to spray it from an atomiser. Cast methods have been widely used for the preparation of polymeric films from organic solution or

aqueous dispersion. Several researchers had employed this technique (Arwidsson and Johansson, 1991; Lin and Ayres, 1992; Hjartstam and Hjertberg, 1998).

Casting is a preferable method for producing films, when the aim is to study elementary properties of the polymer formulation, although sprayed films would be more realistic when one thinks of real pharmaceutical coatings. Cast films are reproducible because environmental factors affect the film preparation less than with sprayed films. Isolated films are a good way to screen formulations and to select the best one for further studies (Hyppola et al., 1996). For aqueous latex and pseudolatex dispersions, however, polymeric particles will trend to settle during the drying process in the cast method, which will lead to uneven film formation (Obara and McGinity, 1995).

Free films prepared by a spray method provide a better simulation of the coating process such as the experiments of Hutchings et al., 1994 and Schultz et al., 1997. The comparison of mechanical properties of free films between cast and spray techniques was recently reported and the spray technique was found to provide more reproducible results for each polymer (Obara and McGinity, 1994). Although the spray method will generate a film that more representative of that formed during film coating, numerous technical problems must be circumvented in order to prepare reproducible film.

Stress-strain testing is usually done by measuring continuously the force developed as the sample is elongated at constant rate of extension. The generalized stress-strain curve for polymer films or plastics shows in Figure 8 (Billmeyer, 1984). Each of these parameters can be explained as described below.

Tensile strength or breaking stress is the maximum stress applied to a point at which the film specimen breaks. Tensile strength can be computed from the

applied load at rupture and the cross-sectional area of fractured film. Higher values of tensile strength of the films are desirable for abrasion resistance.

$$\text{Tensile strength} = \frac{\text{Load at failure}}{\text{Film thickness} \times \text{Film width}}$$

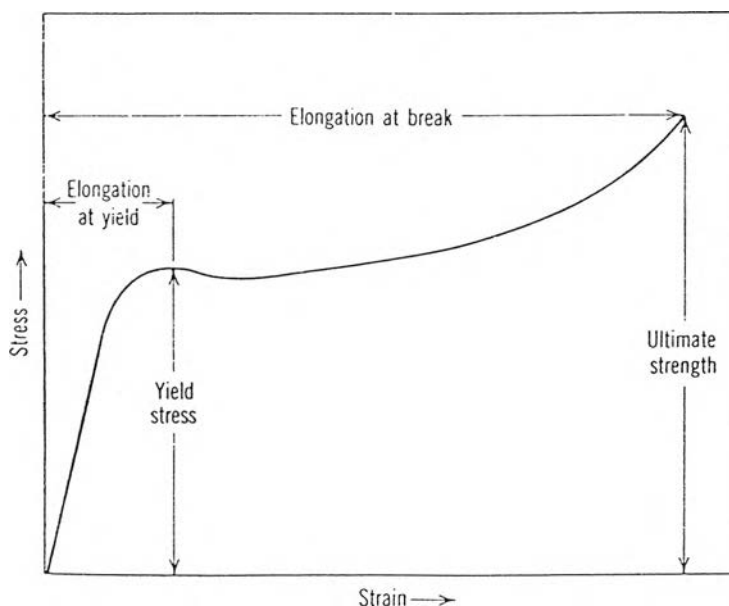


Figure 8 Generalized tensile stress-strain curve

Elongation (strain) at break is a measure of the ductility of the film. Strain is a non-dimensional quantity. It is calculated as the change in the length at the time of sample failure of the films divided by the original length expressed as a percent.

$$\text{Strain at break} = \frac{\text{Length of sample}}{\text{Original length of sample}} \times 100$$

Elastic modulus or Young's modulus is a measure of the stiffness and rigidity of the film. It is the ratio of applied stress and corresponding strain in the region of approximately linear elastic deformation. It can be computed from the slope of the

linear portion of elastic deformation on the load-time profile, cross-head speed, and film dimensions.

$$\text{Elastic modulus} = \frac{\text{Slope}}{\text{Film thickness} \times \text{Film width} \times \text{Cross-head speed}}$$

Area under curve is a function of the work done (force x displacement) in breaking the film and is representative of the film's toughness. Toughness has not been defined; it is bound up with impact strength, but this is only a guide. It is much more a function of stress, elasticity (Aulton, 1982; Parikh et al., 1993b; Hutchings et al., 1994).

Figure 9 shows a stress-strain curve typical of some other classes of polymeric materials. The properties of these polymer types are related to the characteristics of their stress-strain curves in Table 1.

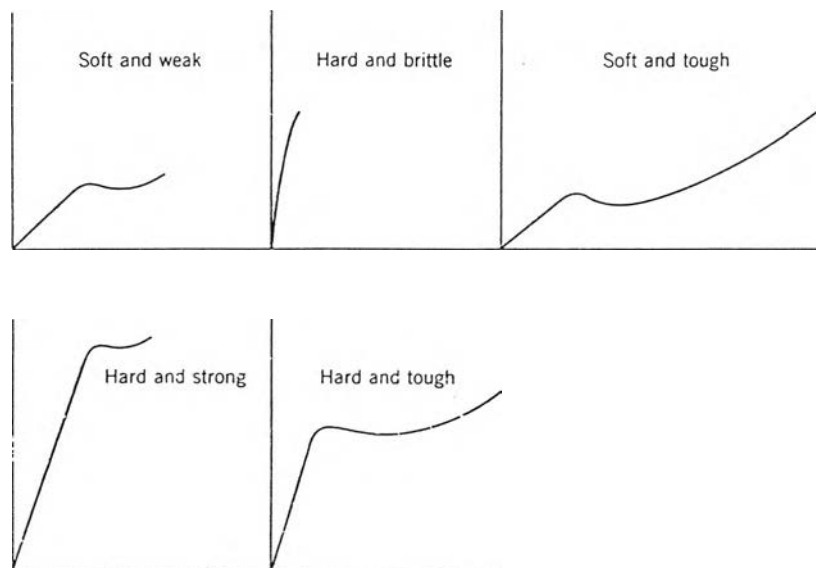


Figure 9 Tensile stress-strain curves for several types of polymeric materials
(Winding, 1961)

Table 1 Characteristic features of stress-strain curves as related to polymer

Description of Polymer	Characteristics of Stress-Strain Curve			
	Modulus	Yield Stress	Ultimate Strength	Elongation at Break
Soft, weak	Low	Low	Low	Moderate
Soft, tough	Low	Low	Yield stress	High
Hard, brittle	High	None	Moderate	Low
Hard, strong	High	High	High	Moderate
Hard, tough	High	High	High	High

As known, Eudragit[®]RS30D and RL30D are often blended to obtain films or coating with varying permeability characteristic. Bodmeier and Paeratakul (1994a) used tensile testing to compare dry and wet film properties. The puncture strength of dry films was not affected by the proportion of the polymers, while the elongation slightly decreased with an increasing fraction of Eudragit[®]RL30D. However, with wet films, the puncture strength decreased and the elongation increased with increasing proportion of Eudragit[®]RL30D.

A result of tensile testing of ethylcellulose:hydroxypropyl methylcellulose (HPMC) mixture had been studied by Hjartstam and Hjertberg (1998). A film with a higher amount of HPMC produced a membrane with a higher modulus of elasticity. This result could be either an incompatibility between the two polymers or a comparatively higher elastic modulus of the added polymer giving the admixture a higher modulus. However, after hydrating the free films in distilled water for 2 hours, the blended film had become more soft. Water acted as a softening agent and this was more pronounced in the ethylcellulose film containing more HPMC.

Tensile tests were used by Gutierrez-Rocca and McGinity (1993) to monitor the changes in physico-mechanical properties caused by the aging of acrylic films. Physical aging of both aqueous and solvent cast films resulted in a decrease in elongation or elasticity, accompanied by an increase in tensile strength because the mechanical properties of film sample changed during the exposure to dissolution media. Tensile testing was used to determine for dry and swollen cellulose acetate films (Schultz et al., 1997). From this result, the tensile strength of swollen film decreased to about 50% when compared with the dry film. Nevertheless, the elongation at film rupture was the same for dry and swollen samples.

Hyppola et al. (1996) used tensile testing and DSC to evaluate the effects of various plasticizers on ethylcellulose film. In comparison with other plasticizers, the compositions containing dibutyl sebacate and Myvacet[®] were the two most efficient plasticizer grades due to a trend of growing elongation at break. These films also showed the lowest Tg values.