

## Chapter I

### General Background

#### Introduction

The application of coating to tablets, an additional step in the manufacturing process, is usually based on several reasons (Porter, 1981 a; Porter and Bruno, 1990; Seitz, Mehta and Yeager, 1986) such as improving the esthetic qualities, the appearance or the pharmaceutical elegance of the products, masking unpleasant taste and odor of the drug, improving product stability by protection the drug from its surrounding environment (particularly air, moisture and light) or by separation of incompatible ingredients, and facilitating handling particularly in high speed filling/ packaging lines. In addition, it is also applied in order to control or modify drug-release characteristics as in acid-resistance enteric coated products by protecting the drug from the gastric environment of the stomach, sequential drug release or repeat-action products by incorporating another drug in the coating, and in sustained-release products.

Tablet coating generally can be classified into three distinct groups (Porter, 1981 a) : sugar coating, film coating and compression coating. For historical reasons, perhaps sugar coating is the method most frequently used; however, sugar is rapidly superceded by film coating because of its greater flexibility, faster process times, and greater overall process efficiency.

Film coating involves the deposition of a thin, but uniform, membrane of a pharmaceutically acceptable resin onto the surface of the tablets, granules or capsules. Obviously, the most important raw material in film coating is the film-forming resins, which must be able to form a coherent film on the surface of the substrate (Porter, 1981 b). The largest group of the pharmaceutically acceptable resins is probably the cellulose ethers. The most common material in this class is hydroxypropyl methylcellulose. Other useful cellulose ethers include hydroxypropyl cellulose, methylhydroxy ethylcellulose, sodium carboxymethylcellulose, methylcellulose and ethylcellulose. Besides these cellulose ethers, other chemicals namely polyvinyl pyrrolidone, polyethylene glycols and methacrylic acid-methacrylic acid ester copolymers also may be used.

Chitin is a linear biopolymer of N-acetyl-D-glucosamine having 1,000-3,000 basic residues. It is one of the most abundant polysaccharides that contain amino sugars. It may be regarded as a derivative of cellulose, in which the C-2 hydroxy groups have been replaced by acetamido residues (Budavari, ed., 1989; Lower, 1984 a).

Chitin occurs in the exoskeletons of marine invertebrates, in the cuticles of insects and arthropods as well as a cell-wall constituent of most fungi and yeasts. (Lower, 1984 a).

Chitin, an amorphous solid, is practically insoluble in water, diluted acids, diluted and concentrated alkalis, alcohols and other common organic solvents, but soluble in concentrated mineral acids, in which it usually becomes degraded or hydrolysed, as hydrochloric acid, sulphuric acid, 78-97% phosphoric acid and in anhydrous formic acid (Lower, 1984 a).

Despite the use of several species, chitin itself has never been found to alternate in chemical composition. However, there are substantial variations in solubility, molecular weight, acetyl values, specific rotation among chitins of different origins and prepared by different methods. Therefore, adjustments during processing may be required to make an end product of constant quality (Budavari, ed., 1989; Skaugrud, 1989).

Chitin is slowly N-deacetylated by strong alkalis, but without the destruction of its polymeric chain, at an elevated temperature over a controlled period of time to give an inhomogeneous mixture of partially deacetylated products, collectively described as chitosan, a linear polymer of D-glucosamine (Lower, 1984 b; Skaugrud, 1989, 1991).

Chitosan is soluble in diluted organic acids. Acetic acid is commonly used as a reference, but other organic, as well as mineral, acids can be used successfully (Lower, 1984 b). For practical purposes, chitosan is however, regarded as insoluble in sulphuric acid and phosphoric acid. Compared with the more common organic acids, the solubility in inorganic acids seems to be more limited with regards to the concentration ratio chitosan/acid (Skaugrud, 1989, 1991).

Chitosan is a cationic polymer and a cationic polyelectrolyte (Lower, 1984 b). Consequently, the compatibility with cationic and nonionic polymers is good, while multivalent anions will easily crosslink with chitosan to form gels and precipitates (Draget, Varum and Smidsrod, 1992; Skaugrud, 1989, 1991). Another aspect of chitosan is its ability to readily form complexes with various materials (Dutkiewicz and Tuora, 1992; Lower, 1984 b; Mireles et al, 1992; Skaugrud, 1989, 1991; Takahashi et al, 1990; Takayama et al, 1990).

Turning to its rheological properties, due to the high molecular weight and the linear unbranched structure of the molecule, chitosan behaves as a pseudoplastic material showing decreasing viscosity at increased shear (Skaugrud, 1989, 1991).

Not only similarity in molecular structure (as illustrated in Figure 1) and some physicochemical properties to cellulose, but chitin and chitosan polymer are also regarded as physiologically safe (biocompatible and biodegradable) (Lower, 1984 a) and especially inexpensive compared with any other polymers. These advantages result in many efforts to utilize chitin, chitosan and their derivatives in many fields.

Chitin, chitosan and/or their derivatives have been reported to be useful as auxiliary substances widely used in pharmaceutical technology. In tablet technology, some investigators applied them as an direct-compression diluent (Knapczyk, 1992, 1993; Sawayanagi, Nambu and Nagai, 1982 a, 1982 c) and a tablet binder (Upadrashta, Katikaneni and Nuessle, 1992). Some utilized them to enhance dissolution properties and/or bioavailability of many practically insoluble drugs by various techniques (Imai et al, 1991; Sawayanagi, Nambu and Nagai, 1982 d, 1983 a, 1983 b; Shiraishi et al, 1990).

But almost all of the investigators employed them in various forms of oral controlled drug delivery systems, especially in matrix tablets (Acarturk, 1989 a, 1989 b; Adusumilli and Bolton, 1991; Akbuga, 1993; Kawashima et al, 1985; Nigalaye, Adusumilli and Bolton, 1990; Sawayanagi, Nambu and Nagai, 1982 b), polymer matrix containing molecular dispersed solid drug (Hou et al, 1985; Miyazaki et al, 1988 a, 1988 b; Miyazaki, Ishii and Nadai, 1981), and microcapsules

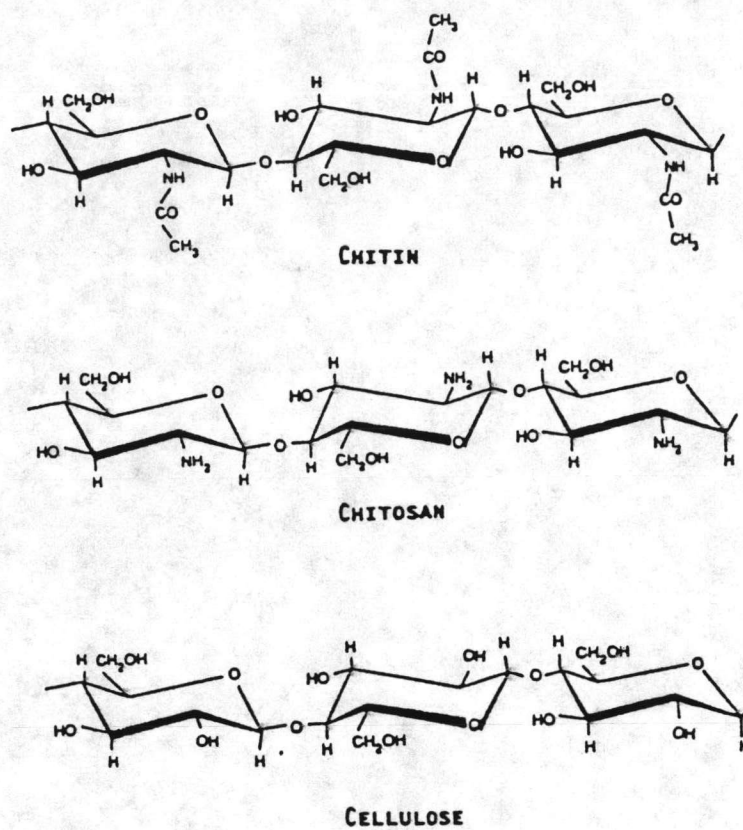


Figure 1 Chemical structure of chitin, chitosan and cellulose

(Bodmeier, Oh and Prammar, 1989; Bodmeier and Paeratakul, 1989; Goskonda and Upadrashta, 1993; Kawashima, Handa, Kasai, Takenaka and Lin, 1985; Kawashima, Handa, Kasai, Takenaka, Lin and Ando, 1985; Tapia, Buckton and Newton, 1993; Thanoo, Sunny and Jayakrishnan, 1992).

Takayama et al (1990) examined chitosan as a controlled bioadhesive drug delivery system prepared by interpolymer complex formation with anionic polymer. Others prepared chitosan gel by molecular aggregation through chemical modification (Hirano, Kondo and Ohe, 1975; Hirano and Ohe, 1975), or as chitosan membranes, blended with other polymers (Hasegawa et al, 1991; Kim et al, 1992; Nakatsuka and Andrady, 1992; Qurashi, Blair and Allen, 1992 a, 1992 b). Some also used it as a stabilizer in liposome formulations (Onsoyen, 1992).

In addition, there were some attempts to prepare chitosan free films as a drug delivery system (Kanke et al, 1989; Miyazaki et al, 1990) and studied their mechanical properties (Averbach, n.d.; Kienzlesterzer, Sanchez, Karalekas et al, n.d.; Kienzlesterzer, Sanchez and Rha, n.d.). Nevertheless, no feasibility study on the application of chitin and chitosan as tablet coating film formers has been reported.

Therefore, this investigation was aimed to study the feasibility to apply chitin and chitosan as film formers in sustained-release film coated tablets. In the examined system, the rate limiting step of drug release is its diffusion through membrane barriers, and subsequently the drug should be highly water-soluble (Longer and Robinson, 1990). Propranolol HCl is a very highly water-soluble drug (1 in 20) (Moffat, 1986). It also has short plasma half life, about 2-6 hours (Moffat, 1986); consequently, it must frequently be taken in order to achieve its therapeutic effects. It was thus used

as the model drug in the dosage unit of 80 mg. The properties of chitin and/or chitosan coated tablets were compared with those of selected cellulose derivatives coated tablets. Some mechanical and physical properties of the films were also examined.

#### Objectives of the Study

(1) To develop propranolol HCl sustained-release film coated tablets using chitin and/or chitosan as film formers, compared with cellulose ethers.

(2) To develop chitin and/or chitosan film coating formulations based on aqueous systems.

(3) To study physical properties of chitin and/or chitosan coated tablets compared with those of cellulose derivatives coated tablets.

(4) To study some mechanical and physical properties of chitin and/or chitosan cast films compared with those of cellulose derivatives cast films.

(5) To utilize chitin and/or chitosan, which were refined from the waste products, in pharmaceutical technology.

## Literature Reviews.

During approximately the past two decades, film coating of pharmaceutical solid dosage forms has become increasingly popular for a variety of reasons. The coating materials, which consist mainly of synthetic or natural polymers, have been applied as solutions in organic solvents. However, with the development of efficient coating machinery and the promulgation of stringent government regulations concerning the use of organic solvents, because of their explosion hazard, toxicity and expensive nature, the pharmaceutical industry has been forced to eliminate these solvents from the coating formulations and explore alternative coating systems. (Ghebre-Sellassie et al, 1988). The most commonly used methods to eliminate organic solvents are presented in Table 1 (Chang and Robinson, 1990).

### I. Aqueous-soluble Cellulosic Polymers.

The most commonly used aqueous-soluble cellulosic polymers which will be further mentioned consist primarily of hydroxypropyl methylcellulose, methylcellulose, and hydroxypropyl cellulose.

#### Method of Solution Preparation.

Preparation of aqueous polymer solutions can give rise to problems. Adding cellulose polymer directly to water with only minimal agitation usually results in formation of partially solvated "lumps" that can take a long time to dissolve. Alternatively, high-shear mixers may effectively break up the lumps, but in turn can



Table 1 Common Methods to Eliminate Organic Solvents from the Coating Process.

Method	Function	Examples of coating materials	Comments
Compression coating	Compressible materials	Sugars, hydroxypropylmethylcellulose, polyvinyl alcohol	Totally eliminates organic solvents, it is not well accepted by pharmaceutical industry owing to complicated mechanical operation and formulation problems.
Aqueous solution	Water-soluble film formers	Methylcellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose	Film formers giving solutions of low viscosity are the most suitable for use. Totally eliminates organic solvents, but unsuitable for controlled drug release.
Mixed organic aqueous system	Enteric materials	Polyvinyl acetate phthalate, carboxymethylethylcellulose, hydroxypropylmethylcellulose acetate phthalate.	Partially eliminates organic solvents. May be suitable for enteric coating, but not practical for controlled drug release.

Table 1 Common Methods to Eliminate Organic Solvents from the Coating Process. (Cont..)

Method	Function	Examples of coating materials	Comments
Alkali salts	Enteric materials	Shellac, hydroxypropylmethyl-cellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate.	To form gastric fluid resistant coatings, a volatile neutralizing agent ammonium hydroxide or morpholine, is preferable to neutralize the enteric materials. The method totally eliminates the need for organic solvents.
Hot melts	Materials with low melting points	Hydrogenated oil, wax, solid polyethylene glycol	Organic solvents can be eliminated completely. However, organic solvents may be needed to thin the hot melts, in some cases. Heating devices such as steam jackets or heating tape is needed for the spraying system to avoid solidification of the

Table 1 Common Methods to Eliminate Organic Solvents from the Coating Process. (Cont..)

Method	Function	Examples of coating materials	Comments
Aqueous dispersions of waxes and lipids	Waxes and lipids	Castor wax, carnauba wax, Cutina HR, Hoechst Wax E, Durkee 07	coating material. Ladle process may be more practical, less troublesome. Totally eliminates organic solvents. Aqueous dispersions of waxes and lipids may not be superior to hot melt coating.
Coating emulsions	Almost all water - insoluble polymers	Cellulose acetate phthalate, hydroxypropylmethylcellulose	Partially eliminates organic solvents. Still in their infancy as pharmaceutical coatings.
Latex dispersions	Almost all water - insoluble polymers	Ethylcellulose pseudolatex, Eudragit RL/RS pseudolatex, Eudragit E-30D latex	Totally eliminates organic solvents. Latex dispersions usually have low viscosity and a high solids content.

generate foam that can take quite a while to dissipate. Both annoyances will be minimized if the solution is made up ahead of time and then allowed to stand overnight (Porter, 1981 b).

To produce the aqueous polymer solutions, the polymer powder is first dispersed in about one-third the total quantity of water as hot water (80-90° C), in which the polymer will not be soluble, preventing the formation of "slimy lumps". Mixing/agitation should continue until all particles are thoroughly wetted. The remaining water can then be added as cold water or preferably as iced water to obtain the proper temperature with minimum agitation. On a production scale, moderate agitation is better than vigorous agitation while the powder is being added to the hot water, since severe foaming may be caused by vigorous agitation and may be persistent. If followed, this procedure permits coating solutions to be prepared with minimum of waiting (Dow Chemical Company, n.d.; Nippon Soda, n.d.; Porter, 1981 b).b

#### Mechanism of Film Formation.

Film structure is a key factor in determining the performance of any polymeric coating. Consequently, understanding the process of film formation with any polymeric system can help provide insight into how the final coating will behave (Porter, 1989).

Generally, film formation from an aqueous or organic solvent solution of a polymer involves conversion of a viscous liquid into a visco-elastic solid. Based on the solvation process itself, the particles involved are individual polymer molecules, extended as long chains and separated from each other only by molecular distances in

the solvent. As solvent rapidly evaporates, the coating liquid will increase in concentration and contract in volume and hence increment in the viscosity. Further loss of solvent at a slower rate is now controlled by the diffusion rate of solvent through the polymer matrix. Then, concentration of the polymer in the coating increases to the point where the extended polymer chains ultimately become immobilized (the so-called solidification point). As the remaining solvent is gradually lost (beyond the solidification point) resulting from the slow diffusion of residual solvent through the "dry" coating, the gelled solution forms a continuous film and produces a three-dimensional dried gel or xerogel network (Banker and Peck, 1981; Porter, 1989; Porter and Bruno, 1990).

From a structural standpoint, the quality of the final dried coating is very much determined by the initial interaction between the polymer and the solvent, and the volatility of the solvent system used. Maximum interaction between the polymer and the solvent (often determined by cohesive energy densities, or solubility parameters), typically results in maximum chain extension of the polymer such that interaction between the polymer chains in the resultant dried coating will also be high (yielding a film with good mechanical properties). Volatility of the solvent will play a large part in determining the tendency of the polymer solution to partially "spray dry" during application, resulting in the formation of a very porous coating (Porter, 1989).

#### Hydroxypropyl Methylcellulose.

The polymer is prepared by reacting alkali-treated cellulose

first with methyl chloride to introduce methoxy groups and then with propylene oxide to introduce propylene glycol ether groups. The resulting products are commercially available in different viscosity grades (Seitz, Mehta and Yeager, 1986; Wallace, 1990).

Hydroxypropyl methylcellulose closely approaches the desired attributes of an ideal polymer for film coating. Unlike many cellulose products, it dissolves readily in water in all proportions and is limited in concentration only by viscosity. Some types are also soluble in a number of binary organic-water solvent systems, providing a unique combination of organic and water solubility (Wallace, 1990). It is stable in the presence of heat, light, air and moisture. It forms clear, tough, flexible films that are excellent barriers, especially useful in the coating of tablets and other pharmaceutical forms. The films tolerate the presence of colorants and other additives. They are resistant to chip and abrasion, and stable to a wide range of biochemical or enzyme systems. They dissolve completely in the gastrointestinal tract at any biological pH providing good bioavailability of the active ingredients (Nagai, Sekigawa and Hoshi, 1989 ; Seitz, 1988 ; Wallace, 1990).

Seitz (1988) and Seitz, Mehta and Yeayer (1986) suggested that films prepared with this polymer generally will need another polymer or plasticizers to improve their binding to tablet surfaces and avoid the problem of bridging or filling of tablet intagliations investigated by various researchers (Kim, Mankad and Sheen, 1986 ; Rowe, 1982 ; Rowe and Forse, 1980 a, 1980 b, 1981). Nagai, Sekigawa and Hoshi (1989) also discussed other problems arising during the aqueous coating of hydroxypropyl methylcellulose.

Hydroxypropyl methylcellulose of low viscosity grade, produced by depolymerization of higher viscosity hydroxypropyl methylcellulose, is commonly used in film coating. Commercially available brands widely used are Pharmacoat (Shin-Etsu Chemical Co., Ltd., Japan) and Methocel E (Dow Chemical Co.) (Nagai, Sekigawa and Hoshi, 1989).

Banker et al (1981) evaluated hydroxypropyl methylcellulose as pharmaceutical film coatings from completely water based systems. The coating results, applied in the Wurster tower, were excellent. Unpigmented coatings generally had shorter disintegration time than pigmented coated tablets and were much less prone to undergo increasing in disintegration time upon storage. But the pigment formulations clearly had a tendency to the lower moisture uptake, as compared to the coated tablets containing no pigment. They also observed no change in hardness and color intensity with any coating after aging.

Maffione et al (1993) investigated the possibility of using high viscosity grades of hydroxypropyl methylcellulose (Methocel<sup>®</sup> K 4 M and Methocel<sup>®</sup> K 15 M) as a film forming agent in a conventional coating process. They could solve the technical problems encountered in terms of poor sprayability and time consuming operation. The release profile of coated tablets showed a characteristic lag-time, increasing as a function of the amount of the coating layer and hydrophilic nature of the plasticizer. This could be exploited for the design of delayed-release dosage forms.

Since higher viscosity grade polymers produce better films, lower viscosity grade materials permit higher solids loading, even

though they produce technically weaker films. Thus, a compromise has to be reached, often to the detriment of the properties of the final film (Porter, 1981 b ; Seitz, 1988).

Hydroxypropyl methylcellulose was also utilized as the overcoating once the drug pellets were coated to the desired coating level with ethylcellulose coating dispersion to eliminate the tackiness usually observed during curing stage (Harris, Ghebressellassie and Nesbitt, 1986) and as the effective film-coating additive to modify the *in vitro* dissolution release rate of ethylcellulose-coated theophylline granules (Li et al, 1990).

#### Methylcellulose

The polymer is made by reacting purified cellulose with methyl chloride in the presence of caustic soda (Wallace, 1990). It swells in cold water and produces a clear to opalescent, viscous colloidal dispersion. Highly substituted, low viscosity grades of methylcellulose are preferred for film coating (American Pharmaceutical Association and Pharmaceutical Society of Great Britain, 1986).

Wan and Prasad (1990) studied the swelling of composite disintegrant-methylcellulose films. They noticed that methylcellulose films swelled rapidly on contact with water. The swelling rate decreased with increasing in the viscosity of methylcellulose. Disintegrants such as Polyplasdone<sup>®</sup> and Ac-di-Sol<sup>®</sup> when presented in the methylcellulose film buffer the swelling action of methylcellulose. This swelling properties of methylcellulose films were also related to the disintegration time of the methylcellulose film coated tablets.



### Hydroxypropyl Cellulose.

This material is manufactured by treatment of cellulose with sodium hydroxide, followed by a reaction with propylene oxide at an elevated temperature and pressure (Seitz, Mehta and Yeager, 1986 ; Wallace, 1990). The propylene oxide can be substituted on the cellulose through an ether linkage at the three reactive hydroxyls present on each anhydroglucose monomer unit of the cellulose chain. The etherification takes place in such a way that hydroxypropyl substituent groups contain almost entirely secondary hydroxyls. The secondary hydroxyl present in the side chain is available for further reaction with the oxide, and chaining-out may take place. This results in the formation of side chains containing more than one mole of combined propylene oxide (American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, 1986).

Hydroxypropyl cellulose is soluble in water below 40°C (insoluble above 45°C), gastrointestinal fluids and many polar organic solvents, similar to hydroxypropyl methylcellulose. This polymer is extremely tacky as it dries from a solution system and may be desirable for a subcoat, but not for a color or gloss coat. The polymer yields very flexible films. It is usually not used alone, but in combination with other polymers to improve the film characteristics. (Seitz, Mehta and Yeager, 1986).

Banker et al (1981) evaluated hydroxypropyl cellulose as plasticized film coatings applied from a totally aqueous system. They obtained elegant coatings of the polymer from both employing either clear or pigmented polymer solutions and utilizing either pan or air suspension coating methods. Compared with hydroxypropyl

methylcellulose, the hydroxypropyl cellulose coated tablets were somewhat softer, probably reflecting the more flexible film. Other effects on the tablet properties were similar to those obtained with hydroxypropyl methylcellulose as previously described.

Lindberg and Jonsson (1972) also described an attempt to correlate tablet bed temperature with the occurrence of tackiness in the automatic film coating of tablets with hydroxypropyl cellulose.

In addition, at least one supplier (Shin-Etsu Chemical) has available a low substituted pharmaceutical grade of hydroxypropyl cellulose (L-HPC). Whereas hydroxypropyl cellulose is highly substituted and readily soluble in water and other solvents, L-HPC is hardly soluble in these solvents. In water, for example, it absorbs water and swells, aiding its use as a tablet binder and disintegrant (Wallace, 1990).

## II. Aqueous-insoluble Cellulosic Polymer.

Although hot melts and wax emulsions currently are being investigated as possible alternatives to eliminate the solvents, an extensive effort has been devoted to the development of water based coatings. At present and in the foreseeable future, latex or pseudolatex coatings appear to be the best choice to eliminate solvent based coatings for controlled drug release (Chang and Robinson, 1990; Ghebre-Sellassie et al, 1988).

### Latexes and Pseudolatexes.

A true latex is prepared by polymerization of a monomer or monomer blend, normally emulsified in an aqueous medium with the aid of anionic or non-ionic surfactants (Onions, 1986 a).

Pseudolatex is physically indistinguishable from a true polymer emulsion or latex. The water-based, true latexes are limited to synthetic polymers with liquid-insoluble monomers that may be emulsified into water. On the other hand, pseudolatexes can be prepared from any existing thermoplastic, water-insoluble polymer by mechanical methods of virtually converting it into a colloidal aqueous dispersions (Banker and Peck, 1981; Onions, 1986 a).

Both latex and pseudolatex are or may be colloidal dispersions, containing spherical solid or semisolid particles less than 1  $\mu\text{m}$  in diameter, with narrow particle size distribution. Both are very fluid even at polymer concentrations of 20-40 %, and both systems form films by the same mechanism (Banker and Peck, 1981).

Aqueous polymeric dispersions and polymeric colloidal systems have many advantages over other polymeric solution systems, the most important of which may be its high solids content and low viscosity (Banker and Peck, 1981 ; Onions, 1986 a).

The low viscosities of pseudolatex dispersions and the high concentration of polymers they may contain in comparison to other polymer solutions indicate a number of further advantages in use (Banker and Peck, 1981 ; Onions, 1986 a). Most important, less energy is required to remove water during coating, simply because water is only a dispersion medium and does not solvate the polymeric beads (Ghebre-Sellassie et al, 1988). Therefore, the tablets are exposed to less heat during coating and less time is required for coating.

### Methods of Pseudolatex Preparation.

Several techniques, including emulsion solvent evaporation, phase inversion, and solvent change, can be employed to prepare suitable pseudolatex dispersion systems. Each method has advantages and disadvantages, based upon ease of preparation, pseudolatex stability, convenience of use, film properties, and economics (Chang, Hsiao and Robinson, 1987; Chang and Robinson, 1990).

#### 1. Emulsion-solvent Evaporation Technique.

The technique involves emulsification of an organic polymer solution in water. After continuous stirring, the solvents evaporates and rigid polymer microspheres are formed. The procedure for preparing pseudolatex is essentially the same as that described later (figure 2). The polymer emulsion, with small droplets below the resolution limit of the optical microscope, can be accomplished by subjecting the crude emulsion to a source of energy such as ultrasonic irradiation or by passing the crude emulsion through a homogenizer or submicron disperser. The polymer solvent is normally stripped from the emulsion at elevated temperatures and pressures to leave a stable pseudolatex. If foaming is not a problem, the solvent may be removed under reduced pressure.

#### 2. Phase Inversion technique.

The phase inversion technique involves a hot-melt or solvent gelation of the polymer, which is then compounded with a long-chain fatty acid such as oleic acid, lauric acid, or linoleic acid, using conventional rubber-mixing equipment such as an extruder.

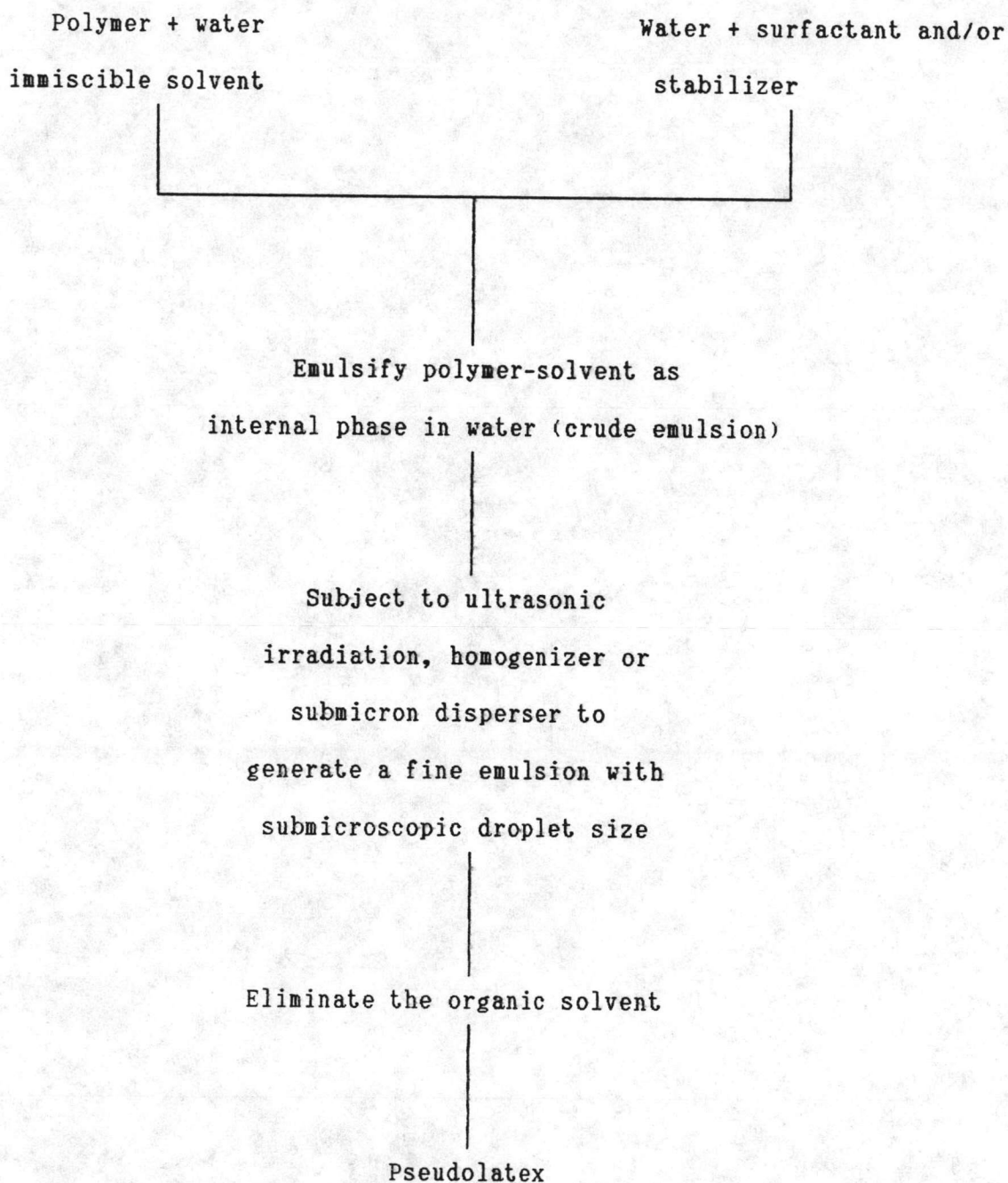


Figure 2 Schematic process for emulsion-solvent evaporation technique.

When the mixture is homogeneous a diluted solution of an alkali is slowly added to the mixture to form a dispersion of water in polymer. Upon further addition of aqueous alkali under vigorous agitation, a phase inversion occurs and a polymer in water dispersion is produced (figure 3).

### 3. Solvent Change and Self-dispersible Technique.

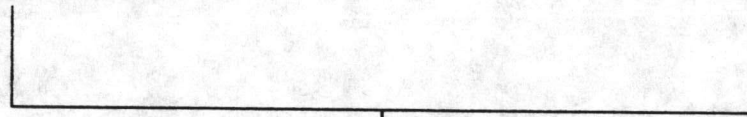
An ionic water insoluble polymer, which may be generated by acid-base treatment or chemical introduction of functional groups such as ammonium groups, phosphonium groups, or tertiary sulfonium groups, may be self-dispersible in water without any need for additional emulsifier. Generally, the polymer is first dissolved in a water-miscible organic solvent or in a mixed water-miscible organic solvent system. The pseudolatex can then be obtained by dispersing the polymer solution in deionized water into the polymer solution under mild agitation. The organic solvent(s) is subsequently eliminated from the aqueous-organic solution to leave a stable pseudolatex (figure 4). The absence of emulsifiers has several interesting consequences such as stability to heat and mechanical shear, and dilutability with organic solvents. Table 2 lists the general features of commercially available pseudolatex-coating systems for controlled drug release.

### Mechanism of Film Formation.

Films are formed from aqueous polymeric dispersions (or pseudolatexes) by a completely different mechanism to those obtained from polymeric solution. In the liquid state, the polymer is present

Hot melt or solvent  
gelation of polymer

Long chain fatty acid,  
such as oleic acid.



Mix thoroughly to form  
homogeneous mixture

Add a dilute solution of an  
alkali slowly into the mixture

Water in polymer dispersion

Further incorporation of  
aqueous alkali

Polymer in water dispersion  
(pseudolatex)

Figure 3 Schematic process for phase inversion technique.

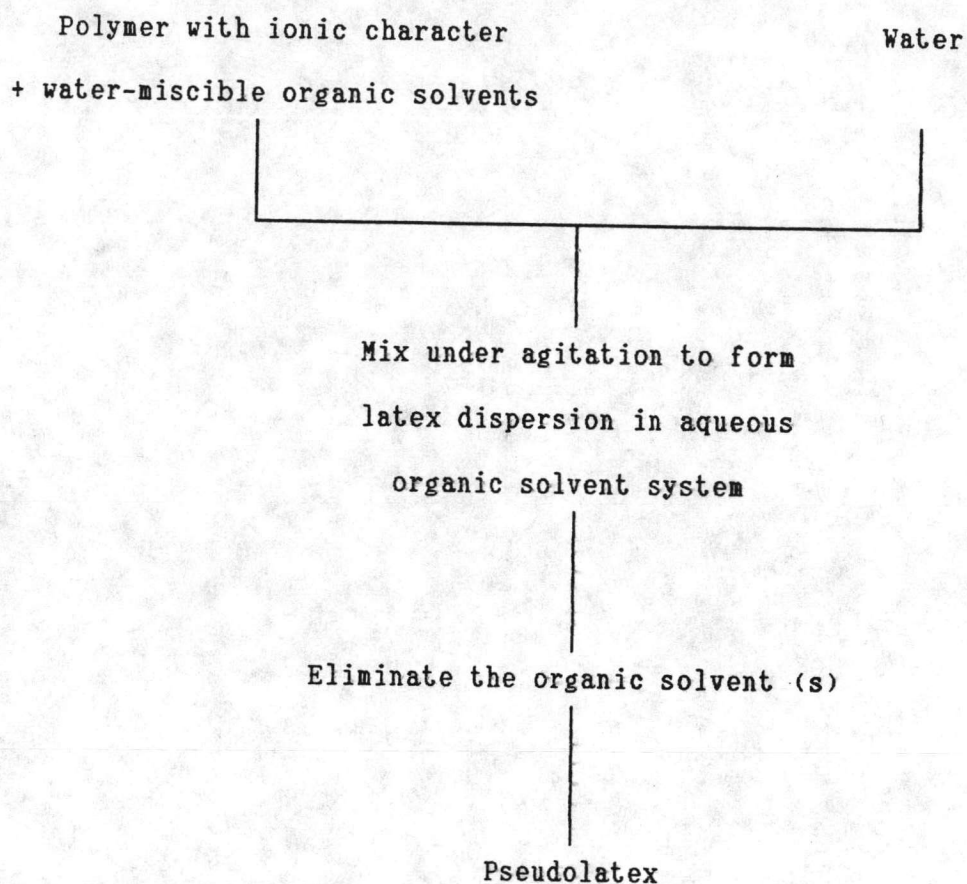


Figure 4 Schematic process for solvent change and self-dispersible technique.



Table 2 General Features of Pseudolatex Coating Systems for Controlled Drug Release.

Latex system	Method	General features
Aquacoat (F.M.C. Corp.)	Emulsion-solvent evaporation	Unplasticized ethyl cellulose dispersion. Contains sodium lauryl sulfate and cetyl alcohol as stabilizers. 30% w/w solid content.
Surelease (Colorcon, Inc.)	Phase inversion	Fully plasticized ethyl cellulose dispersion. Contains oleic acid, dibutyl sebacate, fumed silica, and ammonia water, 25% w/w solid content.
Eudragit RS30D and RL30D (Rohm Pharma)	Solvent change	Unplasticized poly (ethylacrylate, methylmethacrylate, trimethyl-ammonioethylmethacrylate-chloride) dispersions. Contains no emulsifier. 30% w/w solid content.

as discrete particles in aqueous suspension. To form a continuous film, these polymeric particles must come closely together, deform and ultimately fuse together. At the same time, the vehicle (water) must be removed (Porter, 1989).

The actual mechanism is quite complex and many competing theories exist to explain the process. In simplification, as a latex dries and water rapidly evaporates, the latex particles are forced nearer and nearer together until they begin to contact one another closely. The water film surrounding the latex particles shrinks, thus providing a high surface tension that drives the particles still closer together. Strong driving forces must be present to overcome the inherent hardness of the polymer spheres, causing the polymeric particles to deform and coalesce; electrostatic repulsive charges must also be present. As water evaporates, the capillary forces (between particles) resulting from high interfacial tension between the polymer and water and from the surface tension between water and air, provide the main force for overcoming the electrostatic repulsion. Film formation then occurs by coalescence as the boundaries between the adjacent latex particles disappear and movement of polymer molecules across the interfaces between the particles occurs (Banker and Peck, 1981 ; Porter, 1989 ; Porter and Bruno, 1990).

Coalescence of latex particles may be facilitated by the addition of an appropriate plasticizer, one that should be capable of diffusing itself into the latex beads. This will soften the beads and reduce their melting or transition temperature; thereby, reducing their resistance to deformation. Such plasticizers should not separate during film formation and should tend to become a permanent component

of the film. The resulting structure helps the pseudolatex to produce denser, less-permeable films, higher-gloss films, and films of higher mechanical strength (Banker and Peck, 1981).

Whether the specific requirements for film formation are met or not depends upon the deformability and hence the chemical composition of the polymer. The polymeric spheres must deform sufficiently under the existing stresses to achieve a continuous and permanent film. In addition, the rate of water withdrawal should not outpace the rate of deformation of the polymer particles. Otherwise, film integrity will be greatly impaired. Other factors which accelerate, retard or even inhibit film forming are relative humidity and, particular, temperature. Water evaporates slowly at lower temperatures and would theoretically provide better film forming conditions. However, as the temperature drops, the polymeric particles start to harden and their resistance to deformation increases. (Ghebre-Sellassie et al, 1986).

#### Ethylcellulose Pseudolatex.

Currently, there are two marketed aqueous polymeric dispersions of ethylcellulose, that are manufactured using different processes, and these dispersions are intended for used as film coatings for modified-release products.

Aquacoat<sup>®</sup> (FMC Corp., Philadelphia, Pennsylvania) is a pseudolatex of ethylcellulose in water, prepared by emulsion solvent evaporation technique. It appears as a white milky liquid with the characteristic odor of ethylcellulose. The pseudolatex contains 30% solids, 5% of which is sodium lauryl sulfate and cetyl

alcohol included as stabilizers ; their concentrations are in the range of 0.9-1.7% and 1.7-3.3%, respectively. Ethylcellulose is present in the dispersions as spherical particles in the size range of 0.1-0.3  $\mu\text{m}$ . The pH of the dispersions ranges from 4.0 to 7.0 (Ghebre-Sellassie et al, 1988 ; Harris and Ghebre-Sellassie, 1989).

Because ethylcellulose has a high glass transition temperature ( $T_g$ ) of about 120-135°C and clearly needs incorporation of a suitable plasticizer to assure the complete coalescence of the latex particles, hence the formation of a satisfactory and continuous film, before it is applied (Ghebre-Sellassie et al, 1988 ; Onions, 1986 b ; Porter, 1989).

Surelease<sup>®</sup> (Colorcon Inc., West Point, Pennsylvania) is a completely plasticized aqueous polymeric dispersion that consists of ethylcellulose in ammoniated water and is prepared by phase inversion. The product is an off-white, opaque milky liquid with a characteristic ammonia odor, in which dibutyl sebacate and oleic acid are incorporated within the dispersed polymeric system during the manufacturing process. Ammoniated water is used to help stabilize the dispersed polymer. In addition, the dispersion contains fumed silica which acts as an antiadherent and facilitates the application of Surelease<sup>®</sup> during the coating process. The total solids content of Surelease<sup>®</sup> is 25%, 70% of which is ethylcellulose. It has a pH of 9.5-11.5 (Ghebre-Sellassie et al, 1988 ; Moore, 1989).

Because Surelease<sup>®</sup> is plasticized during the manufacturing process, the coating formulations can be prepared simply by diluting the dispersion with water.

Iyer et al (1990) observed the fastest release rate with Aquacoat<sup>®</sup>-coated acetaminophen pellets, while the release rate of Surelease<sup>®</sup>-coated drug pellets and those coated with an organic ethylcellulose solution were comparably or equally slower. This was due to the degree of interaction resulting from incorporating the plasticizer with the melted polymer in Surelease<sup>®</sup> might be comparable to that occurring in the organic solution. Whereas, Aquacoat<sup>®</sup> was plasticized by mechanical means ; consequently, the degree of plasticization during the preparation of the coating formulation might be less than optimum in comparison with the other two coating formulations, and this property was bound to have adverse effects on the final film.

With ethylcellulose-coated beads, the drug release is expected to be pH-independent for drugs with pH-independent solubility characteristics. However, several studies with Aquacoat<sup>®</sup>-coated beads (Bodmeier and Paeratakul, 1991 b ; Chang, Hsiao and Robinson, 1987 ; Goodhart et al, 1984 ; Lippold et al, 1990 ; Lippold, Sutter and Lippold, 1989 ; Rekhi et al, 1989) showed a faster drug release in simulated intestinal fluid when compared to simulated gastric fluid.

Goodhart et al (1984) attributed the faster drug release to the ionization of sodium lauryl sulfate ( $pK_a = 1.9$ ). Sodium lauryl sulfate could affect the partitioning of the drug into the gastrointestinal fluids by virtue of its state of ionization under acidic or basic conditions.

In contrast, Lippold, Sutter and Lippold (1989) suggested that the presence of carboxyl groups on the polymer chain was responsible for the pH-dependent effects. Investigations on

carboxyl groups in microcrystalline cellulose and native cellulose were reported ; thus, in ethylcellulose, they can mainly be encountered in the terminal groups of ethylcellulose molecules. Supposing the existence of carboxylic groups, its dissociation and hydration may improve the permeability of the coatings.

To investigate the contributions of sodium lauryl sulfate or the polymer to the pH-dependent drug release, Bodmeier and Paeratakul (1991 b) prepared ethylcellulose pseudolatexes with varying surfactant concentrations. The release from beads coated with surfactant-free pseudolatexes was insensitive to the pH of the dissolution medium. Besides the plasticizer, the surfactant system may have a significant influence on the coalescence of the polymer particles. Although a surfactant is needed to stabilize the pseudolatex, sodium lauryl sulfate may interfere with the coalescence during the coating process. The surfactant was located at the particle surface and in the aqueous phase and repulsive forces had to be overcome during fusion of the latex particles. They clearly concluded that the presence of anionic surfactant, sodium lauryl sulfate, in the coating caused the pH-dependent drug release from ethylcellulose pseudolatex coated beads, and not the polymer.

Conversely, drug release from beads coated with Surelease<sup>®</sup> was less affected by changes in the pH of the dissolution fluid. This could be because sodium lauryl sulfate was not present in this formulation (Rekhi et al, 1989). Similar findings had been reported for theophylline beads coated with Surelease<sup>®</sup> (Chang, Hsiao and Robinson, 1987).

The *in vitro* release profile of the basic formulation coated granules, which contained ethylcellulose and dibutyl sebacate, showed that only about 85% of theophylline was released in 12 hours. Seeking to improve the dissolution rate profile of theophylline from coated granules, Li et al (1990) incorporated various additives into the film coating basic formulation. Hydroxypropyl methylcellulose altered the granules' dissolution profile most effectively. Banker and Peck (1981) also confirmed that water-soluble cellulosic polymers would probably be the most compatible with the ethylcellulose in the film. The release rate of theophylline from the coated granules could be adjusted by varying the amount of hydroxypropyl methylcellulose added to the ethylcellulose/dibutyl sebacate dispersion. The presence of the water-soluble polymer in the coating probably led to the formation of pores during dissolution, which enhanced the access of the dissolution medium to the core. The release rate increased with an increase in the amount of hydroxypropyl methylcellulose added (Gebre-Sellassie et al, 1988 ; Rekhi et al, 1989).

As was expected, Gebre-Sellassie et al (1988) and Ozturk et al (1990) reported that the dissolution data for coated pellets with different levels of coating showed the drug release related to the weight of coating material deposited on the pellets ; that is, higher coating levels yielded slower rate of release.

Gebre-Sellassie et al (1988) also further reported that the coating levels apparently affected the duration of lag time, the higher the coating level, the longer the lag time. The lag time disappeared when the coating levels were very low or when higher

concentrations of a water-soluble additive like hydroxypropyl methylcellulose were added to the coating formulation.

The drug release from latex coated dosage forms is strongly affected by variables influencing the coalescence of the polymer particles and hence the film formation process. Not only those mentioned formulation variables, but also the further described process variables such as coating temperature and curing conditions that have to be investigated in order to obtain reproducible drug release profiles.

When polymeric coating systems composed of a latex or pseudolatex are used to coat pellets or tablets, film deposition on the substrate must be followed by a curing stage in which the spherical submicron polymeric particles coalesce to form a continuous film. The cured pellets appeared to have numerous spherical polymeric particles fused to each other to form a continuous films coating. In contrast, the uncured pellets had distinct polymeric spheres that had not coalesced. Harris, Ghebre-Sellassie and Nesbitt (1986) found that the uncured film not only led initially to a very fast drug release but also that the rate of release changed as a function of time, leading to inaccurate and irreproducible dissolution profiles.

Goodhart et al (1984) studied the conditions that promote complete coalescence for an Aquacoat<sup>®</sup> / triethyl citrate film formulation by comparison its "steady-state" release profile with that of an ethylcellulose/triethyl citrate film formed from an alcohol solution. The steady-state release from pellets coated with the alcohol solution was considered to be the end point, because film formation from a polymer solution was dependent only upon the



polymer chains' entanglement with solvent evaporation, rather than upon the plasticizer/particle softening/surface tension/temperature mechanism of latex (that is, Aquacoat<sup>®</sup>) film formation.

Gebre-Sellassie et al (1988) revealed that there were no significant differences among the dissolution profile of pellets coated at bed temperature of 28, 34 and 40°C. Although these temperatures were high enough to bring about satisfactory heat and mass-transfer during coating, they had little effect on the basic molecular disposition of the deposited film.

The curing process may be accelerated simply by fluidizing the coated pellets at elevated temperatures for a short period of time as demonstrated with Aquacoat<sup>®</sup>-coated pellets (Harris, Gebre-Sellassie and Nesbitt, 1986). In contrast to oven drying, fluid-bed drying causes maximum contact between the fluidizing air and the surfaces of pellets, and it brings about more efficient drying conditions. Dissolution profiles studied by Gebre-Sellassie et al (1988) indicated that the release profiles of the samples which were fluidized at elevated temperature for a period of time, and the release rate were much faster than those of the pellets cured at 60°C in an oven. This observation implied that the curing phase was not complete.

Although the release profiles of diphenhydramine HCl pellets after storage at room temperature remained unchanged, Gebre-Sellassie et al (1988) also discovered that storage of pellets at 60°C led to a significant reduction in the rate of release. This film coat was somewhat unstable at temperature above 45°C. The phenomenon was not substrate-dependent because pseudoephedrine HCl

pellets also showed a reduction in their rate of release when storage at elevated temperature. Arwidsson et al (1991) concluded that increasing in storage temperature and/or plasticizer content gave a more complete coalescence and thus a lower release rate.

Because curing process was the time-dependent process, Ghebre-Sellassie et al (1988) revealed that storage of pellets at 60 °C for more than one day did not lead to any significant change in the rate of release, which suggested that complete coalescence had occurred. Bodmeier and Paeratakul (1991 b) found that only one hour of exposure at 60 °C was adequate to affect the curing process. Others, Lippold, Sutter and Lippold (1989) subjected the coated pellets to thermal posttreatment for one hour at 68 °C.

Bodmeier and Paeratakul (1991 b) who investigated the effect of process variables, both coating condition (coating temperature) and curing conditions (curing temperature and curing time), on the drug release also supported that the drug release was strongly affected by the curing conditions and to a lesser extent by the coating temperature.

During the curing or storage stage, the coated pellets may adhere to one another because of the softening and tackiness of the film. Although the tackiness eventually subsides after the temperature is lowered, the possibility of the film rupturing is always present, this could have a detrimental effect on the dissolution properties of the film.

Once the pellets were coated to desired coating level with the sustaining coat, Harris, Ghebre-Sellassie and Nesbitt (1986) immediately applied an overcoating, that was water-soluble. The

overcoating eliminated the tackiness usually observed at elevated temperatures and facilitated curing. Because of its water solubility, the overcoat had a negligible effect on the release characteristics of the pellets when it was applied in a separate step.

Some authors reported other factors, in addition to those aforementioned formulation variables and process variable, that could also influence the drug release characteristics. Ghebre-Sellassie et al (1988) noted that the rate of drug release was predominantly a function of the solubilities of the drugs, both in the dissolution medium and in the vehicle used to prepare the coating formulation. Lippold, Sutter and Lippold (1989) found the reduction of permeability by increasing ionic strength and decreasing the temperature of the dissolution medium. If it appeared that osmotically driven release was an important mechanism, increasing the osmotic pressure of the medium could cause a decrease in the rate of release (Ozturk et al, 1990).

Although the partition theory may explain drug transport through truly hydrophobic membranes, Iyer et al (1990) revealed that the same mechanism did not hold true for coatings based on cellulose derivatives. The drug release from pellets coated with dispersion-based polymers was mediated by a dialysis (diffusion) mechanism whether a molecule was acidic, basic or neutral. As a result, the release rates were highly dependent on the pore diameter and tortuosity in the membrane, and these characteristics were, in turn, governed by the coating formulation, the processing conditions and the coating thickness. If the drug applied to the core material is of low molecular weight and is water-soluble (osmo-active agents), the drug release from the coated pellets was mainly driven by osmotic pressure,

with a minor contribution by diffusion through aqueous pores and perhaps solution/diffusion (partition) through the polymer membrane (Ozturk et al, 1990).

Miller and Vadas (1984) suggested a substrate related physical instability in the disintegration behaviour of various tablets coated with aqueous dispersion of ethylcellulose mixed with hydroxypropyl methylcellulose. Upon storage at elevated temperature and relative humidity, they observed no changes in disintegration times with the sodium bicarbonate tablets or with tablets containing microcrystalline cellulose. However, they observed marked increases in disintegration times with the acetylsalicylic tablets; these increments depended on both temperature and relative humidity.

### III. Methods of Film Preparation and Evaluation.

Kanig and Goodman (1962) pointed out the benefits of testing unsupported films, particularly with reference to reducing the number of variables involved in the system. Such variables as the substrate and the technique of application would complicate the picture.

There still remains a choice in the method of preparing the film itself, either to cast it onto a flat surface or to spray the polymer solution from an atomizer.

Radebaugh et al (1988) and Patel, Gohei and Desai (1992) used clean glass plates with boundaries on the edges, to prepare free unsupported films. Gibson, Rowe and White (1988) and Ononokpono and Spring (1988) also pretreated the glass plates with dichlorodimethyl silane before casting the polymer solutions. Uniform thickness was ensured by leveling the plates and pouring solutions of polymers in

such a way that the weight of dried polymer per unit area of glass plate was constant.

Lachman and Drubulis (1964) and Munden, Dekay and Banker (1964) produced cast films on glass plates with a casting knife. Their apparatus consisted of a brass knife edge supported by a frame mounted on two runners. A precise gap could be set between the knife edge and the casting surface by using screw adjustments. The knife, sliding on the support runners, was drawn over a pool of polymer solution, leaving a wet film of fairly uniform thickness. Mortada et al (1990) and Munden, Dekay and Banker (1964) also used Petri dishes and film casting on a mercury substrate. The method produced films of controlled uniform thickness, but the hazards of mercury make it undesirable (Radebaugh, 1992).

Other suitable substrates such as Teflon<sup>®</sup> molds (Gutierrez-Rocca and McGinity, 1993) and aluminum foil (Dittgen, 1985), have also been found to be successful.

A thin-layer chromatography applicator has been reported as effective in spreading polymer solutions (Aulton, Abdul-Razzak and Hogan, 1981 ; Ononokpono and Spring, 1988). The thickness of solution applied can be controlled to give the desired final film thickness. This technique gives a more perfect specimen, i.e. one which can easily be prepared with a very uniform thickness and free from bubbles or any defects (Aulton, 1982).

Another casting technique employs a rotating cylinder (Okhamafe and York, 1983). The films were cast on the inner surface of a lipped Perspex cylinder rotating at 10 rpm and maintained at 40-42°C for 6 hr. The rotating cylinder appeared to have no advantage over

flat leveled plates, but exhibited disadvantages. The geometry of the cylinder impaired the removal of some films. In additions, ridges and striations could develop during the drying process, which could lead to variations in thickness and nonreproducible results (Radebaugh, 1992).

Evaluating aqueous-based colloidal films by the traditional casting technique is difficult, as the suspended components will often settle during the drying process. This results in a film with two entirely different surfaces that are not representative of the type of coating that will be achieved on the dosage form. The pseudolatex compositions do not yield satisfactory cast film, but by means of spraying is the only appropriate method available to evaluate these preparations (Seitz, 1988).

Chainey and Wilkinson (1985) also employed a "flash casting" method which involved the spraying of latexes of various polymers onto a hotplate and found this method to be superior for free film preparation of latexes, compared with casting onto other substrates.

Sprayed films are thought by many to be a more realistic representation of the film in its end-use state, even though they are more difficult to reproduce because of processing subtleties. To obtain uniform representative films, very much care must be used in the spraying process.

Zaro and Smith (1972) suggested an apparatus and technique that would allow the preparation of both cast and sprayed free films from the same coating solution and permit application to simulated dosage forms during a single experiment. The apparatus consisted of a Teflon<sup>®</sup>-coated metal plate with carefully machined holes

to accurately accommodate tablets so that only the tablet surfaces were exposed to the coating formulation. A comparison of both spray and casting techniques on the mechanical properties of films was also presented.

Allen, DeMarco and Kwan (1972) have designed a standard apparatus for preparing free films, which consisted of two major elements ; the spray nozzle and revolving cylinder. The purpose of their design was to control and accurate condition in order to obtain reproducible results since it was indicated from their studies that processing conditions could have dramatic effects on the properties of sprayed films.

A particularly useful apparatus to evaluate film composition is a spray box (Reiland and Eber, 1986) in figure 5. This permits the spraying of a film on an appropriate sheet or dosage form under closely controlled conditions. The rate of application, the drying rate, and the distance of the sprayer from the dosage form can be controlled, and they will be representative of the actual coating process.

Li and peck (1989 a) applied the coating dispersion onto the Parafilm<sup>®</sup>, taped onto a glass plate, as a fine spray using a chromatograph spray bottle and compressed air. Hutchings, Clarson and Sakr (1994) and Ghebre-Sellassie et al (1986) also used a Teflon<sup>®</sup> coated rotating glass as the sprayed coating substrate.

In applications, sprayed films are more realistic for studies and investigations ; cast films must serve as models for sprayed applications. Cast films have the advantage of far fewer variables in the system. It is up to the investigator to decide

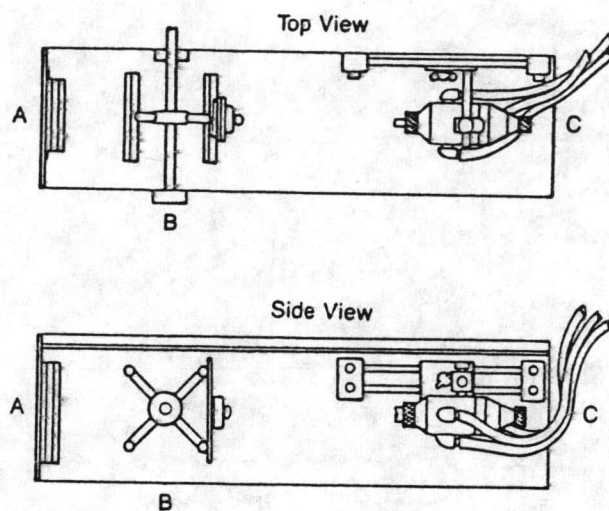


Figure 5 Spray box drawing: exhaust filter (A); rotating sample holder (B); spray gun assembly (C)



whether spraying or casting will provide the information necessary to solve the problem or characterize the system at hand (Radebaugh, 1992).

The physicomechanical properties of films are a function of the composition of the film and the nature in which the constituents of the film interact under specified environmental conditions. The most important constituent is the polymer. Its physicomechanical properties dominate those of the coating. Therefore, the most useful methods of evaluation include the characterization of the rheological, mechanical, and thermal properties of the polymers. A variety of test procedure are available, each providing different information to guide in formulation and quality control.

Stress-strain tests are the most commonly used mechanical tests, and are most commonly used by pharmaceutical scientists to evaluate polymeric films (Aulton, Abdul-Razzak and Hogan, 1981 ; Gibson, Rowe and White, 1988 ; Gutierrez-Rocca and McGinity, 1983 ; Kim et al, 1992 ; Okhamafe and York, 1983 ; Qurashi, Blair and Allen, 1992). In such a test, a sample is deformed (strained) at a constant rate and the build-up of stress is measured over time (Redebaugh, 1992).

The film is cast or sprayed onto a suitable substrate. After drying the test pieces should be cut out using a standard template. A number of test pieces should be cut from the same sheet so that the test can be repeated to ascertain reproducibility. Care must be taken during cutting to avoid jagged edges which will produce stress concentrations during loading. Before testing, it is advisable to check for bubbles and other obvious defects ; any such strips should be discarded. The thickness of the test piece should be

measured prior to testing, in a number of places to find the mean and to check for non-uniformity caused by, for example, and unlevel glass plate during drying. The film is then fixed into the flat faced grips of a machine that can apply an accurately known tensile load at a constant rate of grip separation. Instron testers have been used successfully for the measurement (Aulton, 1982).

Indentation testing, measurement of the adhesion, and other test procedures were described elsewhere (Aulton, 1982 ; Radebaugh, 1992).