EVALUATION OF HYDROXYPROPYL METHYLCELLULOE (HPMC) AS A TABLET COATING MATERIAL USING CONVENTIONAL PAN COATING

By

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BY THE NAME OF ALLAH

To

My parents, my wife, my brothers and sisters for their encouragement, support and unceasing prayers

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ABSTRAK

PENILAIAN HIDROKSI PROPIL METIL SELULOSA (HPMC) SEBAGAI BAHAN PENYALUT TABLET MENGGUNAKAN KUALI PENYALUT KONVENSIONAL

Berbanding salutan gula aneka jenis yang banyak digunakan sebagai salutan farmaseutikal suatu masa dahulu, salutan filem merupakan pilihan utama dalam industri farmaseutikal masa kini. Dalam kajian ini, kesesuaian hidroksipropil metilselulosa (HPMC) (Pharmacoat 606) sebagai sistem salutan filem tablet ditentukan dan dikenalpasti. Ujian penembusan kelembapan dan ciri-ciri mekanikal filem nyah akueus dikaji dengan menggunakan sel penembusan kelembapan dan teknik daya-tegangan. Sifat jelekitan larutan HPMC yang mengandungi polietilena glikol (PEG 400, PEG 1000), triasetin dan alkohol polivinil (PVA) dibandingkan dengan larutan HPMC tanpa sebarang bahan lain. Kesan bahan pemplastik ke atas suhu peralihan kaca bagi sistem–sistem ini dikenalpasti untuk mengesan keserasian antara polimer-bahan pemplastik dan keterlarutcampuran Pharmacoat 606 dan alkohol polivinil. Proses penyalutan dilakukan dengan menggunakan alat penyalut konvensional. Ujian pelarutan dijalankan untuk menentukan ciri-ciri pelepasan drug daripada suatu salutan HPMC yang mengandungi PEG 400, PEG 1000, triasetin dan alkohol polivinil dengan menggunakan parasetamol sebagai drug model. Keputusan menunjukkan bahawa kedua-dua gred PEG dan triasetin merupakan bahan pemplastik yang efisien untuk Pharmacoat 606. Hal ini dapat dilihat daripada kajian daya tegangan dan peratus pemanjangan sehingga filem putus. PEG 400 memberi keputusan yang bermakna. Penggunaan bahan pemplastik and PVA mengurangkan jelekitan larutan Pharmacoat 606. Keputusan juga menunjukkan bahawa Pharmacoat 606 sesuai digunakan untuk penyalutan filem akueus konvensional.

ABSTRACT

Even though pharmaceutical coatings were once predominantly of the sugar coating variety, film coating has become the process of choice in the pharmaceutical industry today. In this study the suitability of hydroxypropyl methylcellulose (HPMC) (Pharmacoat 606) as a tablet film-coating system was evaluated. The moisture permeability and mechanical properties of some aqueous free films were evaluated using permeability cell and stress-strain techniques respectively. The tackiness of HPMC solutions containing polyethylene glycols (PEG400, PEG1000), triacetin, and polyvinyl alcohol (PVA) were compared to that of HPMC alone. The effect of plasticizers on the glass transition of these systems were evaluated in order to elucidate the polymer-plasticizer compatibility as well as the HPMC-polyvinyl alcohol miscibility. The coating process was performed using a conventional pan coater. Dissolution tests were conducted on paracetamol tablet coated with HPMC films containing PEG400, PEG1000, triacetin and polyvinyl alcohol in order to study the effect of coating on the release properties of the model drug. The results showed that both grades of PEG as well as triacetin were efficient plasticizers for HPMC as demonstrated by the tensile strength and percentage elongation at break measurements, with the effect of PEG400 being the most pronounced. The addition of the plasticizer as well as PVA decreased the tackiness of HPMC solutions. Overall, the results of these studies indicate that Pharmacoat is a suitable material for aqueous conventional film coating.

CHAPTER 1

INTRODUCTION

INTRODUCTION

Utilization of some kind of a coating process to modify the characteristics of dosage forms especially tablet has long been practiced for over 150 years (Lieberman et al., 1990). Tablet coating is perhaps one of the oldest pharmaceutical processes still in existence. Methods and materials for coatings dated back over 1000 years. For example early Islam made references to pill coatings based on mucilage of psyllium seeds. Subsequently, Avicenna was reported to have used gold and silver for pill coating then White (1922) mentioned the use of finely divided talc as a coating material, while Kremers and Urdang (1940) described the introduction of the gelatin coating of pills.

The current pharmaceutical process of sugar coating originated in the middle of the nineteenth century (Lieberman et al., 1990) and has been used successfully to coat numerous products and is still popular in certain quarters. Suitable equipment for sugar coating is a coating pan, which was invented 150 years ago and underwent only minor changes until the late 1940s and early 1950s, with conventional pan being the mainstay of all coating operations up to that time (Porter, 1980). In response to a growing demand for a more efficient coating process, coating equipment manufacturers started to introduce equipment with high drying efficiency so in the last 20 or 30 years there have been some significant advances made in coating process technology. At the same time, pharmaceutical scientists identified new polymeric materials that are suitable for coating pharmaceutical dosage forms. They include the scientists at Abbott Laboratory who developed the first tablets coated with a film of polymer (Seitz et al., 1998). The coating was composed almost exclusively of cellulose derivatives, although acrylate derivatives were also used to some extent (Banker et al., 1981).

Recognizing the deficiencies of the sugar-coating process, advocates of film coating achieved greater success by using coating systems that use highly volatile organic

solvents to form coating solutions. However, the high cost of organic solvents coupled with pollution and safety hazards associated with the use of organic solvents have limited the use of solvent based film coating in pharmaceutical dosage forms. As a result, water-based coating systems were reintroduced in the early 1970s and gradually replaced organic-solvent-based solutions in many applications. The advances in equipment design began with the development of Wurster process, continued with the evolution of side-vented pans, and as a result, the drying efficiency was maximized. Improved drying capabilities have permitted the increased use of aqueous film-coating techniques, which has led to it being process of choice for tablet coating (Porter, 1990).

1.1 WHY COAT?

There are benefits that can be obtained when a dosage form is coated, and they include: Masking undesirable taste, odours and colours, improving aesthetic qualities of the product, facilitating the swallowing of the dosage form, protecting the drug from the storage environment (air, moisture and light), modifying drug release characteristics, reducing ingredient interactions, improving the mechanical integrity of the finished product and facilitating handling especially during packaging.

1.2 ISSUES RELATING TO FILM FORMATION

During a film coating process, we must convert a liquid into an essentially dry solid. Dry films are those that resist blocking when two coated surfaces (e.g. two coated tablets) are brought into contact for two seconds under a pressure of 20psi. Such block resistance occurs when the viscosity of the coating exceeds 107 Pa.s (Burrell, 1962). A viscosity conducive to such blocking occurs when a coating is exposed to temperatures that exceed its glass transition temperature (T_g) by approximately 20 °C (William et al., 1955). If the temperature of a product (during the coating process or storage of the coated product)

exceeds the glass transition temperature of the modified polymer by more than 20°C, tackiness becomes a problem. The presence of plasticizer and retained solvent may reduce the glass transition temperature of the polymer well below the normal value for the polymer.

When forming coatings from polymeric solutions, we are essentially converting a viscous liquid into a viscoelastic solid passing through various stages, comprising of:

(1) Initial rapid evaporation of solvent from the atomized droplets of coating liquid cause an increase in polymer concentration and a contraction in volume of the droplets.

(2) Further loss of solvent from the film at a slower rate which is now controlled by the rate of diffusion of solvent through the polymer matrix.

(3) Immobilization of the polymer molecules at the solidification point, further solvent loss from the film at a very much-reduced rate and concurrent formation of shrinkage stresses within the film as a result of constraint imposed by the immobility of polymer molecules and the adhesion of coating to substrate.

According to Banker (1966) there are two sets of forces in film forming process; one operates between the film forming polymer molecules (cohesion force) and the other between the film and substrate (adhesion force). The degree of cohesion in film structure is fundamental to film properties. In order to obtain high levels of cohesion, two phenomena are necessary that are: the cohesive (autoadhesive) strength of the material must be relatively high and the continuous surfaces of the film material must coalesce on contact. Diffusion theory explains coalescence of polymer molecular layers or surfaces. According to this theory: the movement of individual macromolecules or segment of macromolecules between and within film may occur under a variety of conditions, including during gelation, when polymers are deposited in solution over a previous

polymer layer, or at elevated temperature corresponding to semisolid state (Banker, 1966).

The factors which may affect film cohesion (polymer surface to polymer surface) include: surface contact time, contact temperature, contact pressure, coat thickness, coat solution or dispersion concentration, degree of polymer salvation and viscosity (Banker, et al 1981). Temperature is directly related to cohesion. It is well known that a more cohesive film obtained when a warm coating solution is applied to warm substrate. In addition, total solvent removal requires heating the film to a temperature significantly above the glass transition temperature of the solvent-free polymer (Wicks, 1986). However excessive heating beyond the limits may cause premature drying of the sprayed coat, slipping and peeling of the coat or development of pinholes in the coat caused by solvent vaporization under high localized vapour pressure through a case-hardened film surface. Temperature affects not only cohesion but also adhesion. The adhesion between polymer film and substrate is generally promoted by increased temperature.

The cohesive strength (or peeling strength) is referring to as work of erges/cm^2, required to separate bonded layers of film (Banker, 1966). The cohesive strength of the film has found to increase in zero order function of film thickness up to a fixed value after the cohesive strength is constant even with further increase in thickness.

Contact time refers to the duration during which a newly deposited polymer film layer is "setting up" and the polymer molecules are capable of diffusion and orientation either as a whole or in part (Banker, 1966). Rapid solvent evaporation in film coating process facilitates rapid coating. However solvent, which flashes prematurely, may produce noncohesive films due to a premature immobilization of the polymer molecules in the film structure prior to molecular orientation, as well as due to poor diffusion of the polymer molecules in the film.

Viscosity, and hence solution concentration and polymer solvation affect the cohesion of high polymer. At low viscosity or a high polymer salvation levels self-diffusion would be promoted. In addition, at low viscosity, the coating solution will be runny, hence coating time increased and some deposited film may separate from the bulk of previously homogenous film substrate. Intermediate viscosity usually results in the highest cohesive strength of the polymer.

Good adhesion between a polymer and the surface of a substrate is a major prerequisite for the film coating of the pharmaceutical dosage forms (Rowe, 1977; Okhamafe and York, 1985a; Nadkarni et al., 1975). The loss of adhesion may lead to an accumulation of moisture at the film-tablet interface and will significantly affect the stability of the moisture sensitive drugs. Loss of adhesion may also compromise the mechanical protection that the film coating provides to the solid substrate (Stanley et al., 1981). The two major forces that have been found to affect polymer-substrate adhesion are the strength of the interfacial bond and internal stresses within the film coating (Felton and McGinity, 1999). The total stresses within a film is the total of all stresses acting on the polymer, including stress due to shrinkage of the film on evaporation of the solvent, thermal stress due to the difference in thermal expansion of the film and the substrate, and volumetric stress due to the change in volume when a substrate swells during storage. The addition of plasticizing agents to coating formulations generally decreases the internal stress in the film by decreasing both the elastic modulus and the glass transition temperature (T_g) of the film coating (Rowe, 1981; Gutierrez and McGinity 1994; Johnson et al., 1991). A relationship was found between polymer adhesion and the T_g of the film, with stronger adhesion occurring when the T_g of the film was lower (Entwisted and Rowe, 1979).

1.3 AQUEOUS FILM COATINGS

Film coatings are an internal part of the dosage form development process. The process of film coating involves the application of a thin polymeric film onto the surface of a solid substrate.

1.3.1 Why using aqueous film coatings

Development of aqueous-based coating materials has eliminated the safety hazards and emission problems to flammable organic solvents. The transition to aqueous processes was due to the hazards associated with using flammable and potentially toxic solvents, dealing with the environmental issues that are associated with using organic solvents and high costs of organic solvent and the need for expensive solvent recovery system.

Although the use of water allows us to avoid many of the shortcomings described in the previous paragraph, water is not however, a panacea to the problems. The use of water may bring about its own set of problems that are associated with the use of aqueous system, such as: the possibility that processing time will be increased, the potentially negative impact on drug stability if water is not effectively removed during processing, the increased likelihood that the harsher process conditions used may affect characteristics of drug dissolution and high latent heat of vaporization of water compared to organic solvents.

When organic solvents were used exclusively, all coating formulations were applied as polymer solutions, since it was possible to find some solvent that would be suitable for each polymer that we might wish to use. Now that aqueous film coating is so popular, we are faced with a dilemma, namely how to apply non-water-soluble polymers (i.e. those used for modified-release applications) as aqueous systems and still retain the functional effects of the resultant coatings. For film coatings that are not intended to modify drug release characteristics (e.g. those that use water-soluble polymers), polymer solutions can

still be used. For the non-water-soluble polymers, aqueous dispersions or latexes must be used. Although aqueous polymer solutions and aqueous polymer dispersions appear to behave in a similar fashion, they have distinctly differing requirements in terms of the process conditions required to achieve optimal performance.

The popularity of aqueous coating formulations means that we now have to deal with two types of coating systems, namely: solutions of polymers in water and dispersions (latexes) of polymers in water.

The applications for film coatings are quite diverse. Since some applications require some functionality of the coating formulation, it is not uncommon to see film coating described as either (1) functional film coatings which are used when drug release characteristics need to be modified, and are represented by delayed-release (enteric) coatings, extended-release (sustained) coatings or (2) non-functional (conventional) film coatings which are typically reserved for situation in which it is necessary to improve product appearance, ease of swallowing, product stability, and for taste masking.

Conventional film coating is also the area where aqueous technology has gained the highest acceptance (Lieberman et al., 1990), where the coating is mainly designed to improve product appearance, stability and ease of ingestion of the dosage form, but not alter drug-release characteristics from that dosage form. This fact reveals that aesthetics are of paramount importance in pharmaceutical industry and consequently influence the selection of materials to be used in the formulation. This selection is often based on the factors that affect the mechanical and physical properties of the coating, such as permeability, elastic modulus, tensile strength and elongation of the polymer film.

1.4 BASIC INGREDIENTS USED IN CONVENTIONAL FILM-COATING FORMULATIONS

1.4.1 Polymers

Polymers are a class of natural or synthetic chemicals that are characterized by having repetitive structural units. They are formed by polymerization or depolymerization process and have a large molecular size (Lieberman et al., 1998). In the film coating formulations the polymer is the major ingredient and consequently this material will have the greatest impact on the final properties of the coating. Ideal properties for the polymer include the ability to produce coatings that have suitable mechanical properties and the appropriate solubility in gastrointestinal fluid.

A multiplicity of differing chemical types is available, each in turn often having various grades (as determined by viscosity or molecular weight). Common polymers used in conventional film coating formulations are classified as: (1) Cellulosics: (hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose, methylcellulose, ethylcellulose, sodium carboxymethycellulose. (2) Vinyls: polyvinyl pyrrolidone. (3) Glycols: polyethylene glycols. (4) Acrylics: dimethylaminoethyl methacrylate-methylacrylate acid ester copolymer, ethylacrylate-methylmethacrylate copolymer.

Hydroxypropyl methylcellulose (HPMC) has an advantage in that it is soluble in both organic solvents and water over the entire biological pH range. In this study, HPMC low-viscosity type (6 cP type) was used as the coating polymer, and blends of this polymer and partially hydrolyzed polyvinyl alcohol were also used, physical and mechanical properties of the coat were studied accordingly.

1.4.1.1 Types of HPMC used for film coating

HPMC is classified according to its constituent groups, composition, and viscosity. USP XXI prescribes for substitution types corresponding to commercially available products that are 1828, 2208, 2906, and 2910, by appending a four digit number to the nonproprietary name; the first two refer to the approximate percentage content of the methoxy group (OCH3) and the last two define that of hydroxypropoxyl groups (OCH2CHOHCH3).

An application of hydroxypropyl methylcellulose (HPMC) for film coating first appeared in a patent by Singister, R. E. of Abbot Laboratories in 1960. The lowest-viscosity HPMC available then was 50 cP, and the coating cost was rather high. In 1965, Shin-Etsu Chemical Co., Ltd (Japan) developed low-viscosity type of HPMC (Pharmacoat 3, 6, 15 cP type) and commercialized under the trade name Pharmacoat. The solvent systems most commonly used in film coating with HPMC were mixtures of organic solvents. The main reason for using organic solvents originally in film coating was the problem of higher latent heat of vaporization of water compared to that of organic solvent. This problem was largely overcome by later development of high efficiency coating equipment that is side vented pan (McGinity, 1989).

The chemical name of HPMC is cellulose, 2-hydroxypropyl methyl ether. It is available in several grades, which vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2%w/w aqueous solution at 20 °C. HPMC is manufactured by taking a purified form of cellulose, obtained from cotton linters or wood pulp, and reacted with sodium hydroxide solution to produce swollen alkali cellulose, which is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methylhydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules. HPMC of lower viscosity (less than 15 cPs) is produced by depolymerization of higher viscosity HPMC

(McGinity, 1989). Structural formula of HPMC is shown in Figure 1.

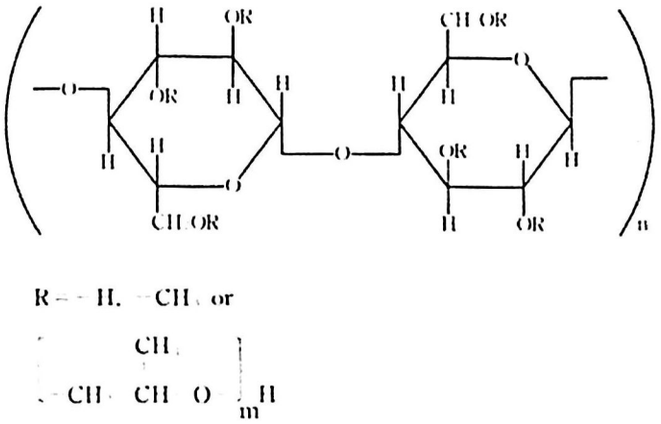

Fig. 1 Chemical structure of HPMC. R = H, CH3, or CH3CH (OH) CH2.

1.4.1.2 Viscosity of HPMC aqueous solutions

Rheology of an aqueous solution of HPMC is affected by its molecular weight, concentration, temperature, and the presence of other solutes. Viscosity is usually measured, in water, at 25°C using a solution containing 2% w/w polymer (Williams et al., 1955). The relationship between solution viscosity and polymer concentration is expressed by the following equation:

$\eta^{1/8} = (C.\ \alpha) + 1$ (1)

Where ŋ is the solution viscosity in millipascal-second, C is the polymer concentration in solution expressed in percent and (α) is a constant specific to molecular weight. The value of (α) can be used to calculate the viscosity at the desired concentration. Most formulations of HPMC require predetermined viscosity and regardless of the delivery system, the coating solution must be formulated to have a viscosity of sprayable solution. Viscosity required for aqueous film coating is commonly less than 100 cP. The maximum

concentrations available depend upon the viscosity type of HPMC used, though there are other factors that should be taken into consideration (McGinity, 1989).

Aqueous solutions of HPMC gel on heating. The temperature-viscosity relationship of 6% solution of HPMC 3-cP, and that of 6-cP showed a drastic increase in viscosity near 60°C (McGinity, 1989). Therefore, a problem might be encountered at temperatures higher than this. In the preparation of formulations, the resultant viscosities may be considerably higher than expected. This can be caused by the interaction of HPMC with one or more of the formula ingredient. The extent of this effect depends on the concentration of interacting materials.

1.4.1.3 Polymer blends

With the gradual discovery of new film formers, greater attention is likely to be paid in the near future to blending of existing materials with a view to achieve better film characteristics (Okhamafe and york, 1983). Mixed polymer systems were introduced to increase formulation flexibility, often with respect to film mechanical properties and with a view to increasing sprayable solution (has a viscosity less than 100 cP) for aqueous coating systems. Mixed polymer systems can be in a form of mixtures of different molecular weight grades of the same polymer (for example, HPMC 3 cP and HPMC 6cP), or mixtures of different polymer chemistries, such as (HPMC + HPC, HPMC + maltodextrins, or HPMC + polyvinyl alcohol (Okhamafe and york, 1985a). In this study, moisture permeability, glass transition temperature and mechanical properties of free hydroxypropyl methylcellulose/polyvinyl alcohol film blends plasticized with triacetin, polyethylene glycol 400 and polyethylene glycol 1000, were evaluated.

1.4.2 Plasticizers

Plasticizers are one of the most important additives that are used in coating formulations to modify film properties. Plasticization are of two types; the first is internal plasticization, and refer to a situation in which chemical change are made within the structure of the polymer itself. The second, termed external plasticization occurs when external additives (plasticizers) are added to the polymer.

Plasticizers are typically nonvolatile, high-boiling substances (Bodmeier and Paeratakul, 1994). When added in adequate amount to a polymer, they alter certain physical and mechanical properties of the polymer films (Bodmeier and Paeratakul, 1994; Fukumori et al., 1993, 1987; Gutierrez-Rocca and McGinity, 1994; Lachman and Drubulis, 1964; Martin et al., 1993; Repka and McGinity, 2000b; Rowe, 1981, 1978; Wang et al., 1997; Wu and McGinity, 1999). For example, the addition of an effective amount of a plasticizer reduces the intermolecular forces along the polymer chain, and consequently, lowers the glass transition temperature and modulus of elasticity. As a result, films exhibit more flexibility (Bodmeier and paeratakul, 1994; Entwistle and Rowe, 1979; Johnson et al., 1991; Okhamafe and York, 1983; Rowe, 1983; Sears and Touchhette,1982), easier thermal processing (Repka and McGinity, 2000a), improved adhesiveness (Al-Dujaili et al., 1986; Lin et al., 1991; Porter, 1980), reduced friction and controlled water vapor permeability (Heinämäki et al., 1994; Porter, 1980; Saettone et al., 1995). The types and amount of plasticizer that can be used depend upon the nature and concentration of the polymer to be plasticized (Bodmeier and Paeratakul, 1994).

The basic requirements of any plasticizer in a polymer system are, efficiency (the ability of the additive to achieve the desired result for the least amount added), compatibility (consideration of how effectively the plasticizer interacts with the polymer, the level up to which that interaction occurs, and the relative "permanence" of that interaction), and permanence (which is often attributed to lack of compatibility, such that

the plasticizer will separate from the polymer, diffuse to the surface of the coating, and appear as "oily droplets" that may eventually evaporate). Common plasticizers used in conventional film coatings are classified as; polyhydric alcohols, acetate esters, phthalate esters, glycerides and oils.

1.4.3Colorants

Colorants are included in film coating formulations to improve the appearance and visual identification of the coated product. Certain types of colors can provide other physical benefits. Colorants are classified as water-soluble dyes, aluminum lakes, other lakes, inorganic pigments and natural colorants. Although it is preferable to use water-soluble additives in aqueous coating, the use of pigments has persisted because they increase solids content of coating solution without dramatically affecting viscosity (Alton et al., 1986), and improve the moisture barrier properties of the film coatings (Porter, 1980). Pigment addition to film coating affects the mechanical properties of the film in that it decreases tensile strength and increases elastic modulus (Rowe, 1983a; Rowe and Forse 1983).

1.4.4 Anti-tack agents

The recognition of the problem of tackiness (Alam and Parrott, 1972; Lindberg and Johnson, 1972; McGinity, 1989) has led to the use of a variety of pharmaceutical additives as anti tack agents (Wan and Lai, 1992a, 1992b). Tack is a concept that is widely used to describe the forces or energies involved in the separation of two parallel surfaces initially in contact through intervening thin liquid film (Chopra and Tawashi, 1982).The tackiness may cause the tablets to stick to each other or to the walls of the coating apparatus. Coating formulations consisting of soluble polymeric film-formers, particularly the water-soluble cellulose ethers (Al-dujaili et al., 1986; Lindberg and

Johnson, 1972) are known to be tacky in nature. Anti tack additives employed in sufficient quantities can reduce the tackiness of the film former, whilst also exerting a significant influence on the drug release behavior of sprayed films formed from water-soluble polymers (Lucy and lai, 1993). Examples of anti-tack additives used in film coating formulations include talc (Fukumori, et al., 1987), silicon dioxide and kaolin (Ghebre-Sellassie et al., 1986). Incorporation of plasticizers such as polyethylene glycol, triacetin, triethyl citrate and film formers polyvinyl alcohol in HPMC solution have all reduced tack force (Heng et al., 1996).

1.5 EVALUATION METHODS OF COATING SYSTEMS

Until the late 1970s, the typical approach to formulating new coating was to evaluate only its end-use properties on the substrate. Parameters such as moisture/air permeability, drug release profile, abrasion resistance, and stability were tested. It is also important to evaluate the film or film forming materials prior to their end-use. A fundamental understanding of the physical and mechanical properties of the components of film-coating formulation and their interaction is essential to enable the formulators to predict end-use properties, thereby saving time and money. The most useful methods of evaluation include the characterization of the moisture permeability, mechanical, and thermal properties of the film coatings. A variety of test procedures are available each providing different information to guide in formulation. In this study, free films were evaluated for their mechanical, permeability, and thermal properties and the coating solutions were evaluated for tackiness.

1.5.1 Mechanical properties

Mechanical properties of free films are measured to assess the strength or toughness of the films and their deformation characteristics. Parameters such as tensile strength,

toughness and elongations can be measured to evaluate the film properties. These properties are an important characteristics which help to predict the stability and release property of film-coated dosage forms and also provide information concerning possible interaction between the components (such as polymer, plasticizer, pigment) in the coating films (Baie and Sarwar, 1995; Guo et al., 1993; Johnson et al., 1991; Obara and McGinity, 1994; Okhamafi and York, 1983, 1985a; Parikh et al., 1993; Sakellariou et al., 1985).

1.5.2 Permeability studies

Another parameter used to characterize free films is water vapour transmission. Studies that measure the transmission can be used to evaluate film integrity and the permeability of the film to water vapor which in turn provides useful information about the effect of the film on the stability of the coated product (Gurny, 1976; Wang, 1994). Water vapor permeability as defined by the American Society for Testing and Material (ASTM) is "the rate of water vapor transmission through unit area of flat material of unit thickness induced by unit vapor pressure differences between two specific surfaces, under specific temperature and humidity (ASTM, 1993). Two methods that are used to measure the water vapor transmission are the desiccant method and the water method (Lieberman et al., 1998).

Other parameters of interest to the pharmaceutical scientist, which are involved in the permeability of polymeric film, are the rate of diffusion of solute through a free film (which can provide a good measure of the inherent properties of the film) and oxygen permeation (Okamafe & York, 1983). Several workers did extensive reviews of the techniques and mathematical derivations and theories for calculating rates of moisture permeation (Banker, 1966; Patel et al., 1964; Woodruff et al., 1972). In this study, the

water vapor transmissions of the formulations studied were evaluated as a function of plasticizer concentrations and types.

1.5.3 Thermal analysis

Thermal analysis includes all methods in which a physical property is measured as a function of temperature while the substance is subjected to a temperature program (Giron, 1997). There have been many techniques derived for thermal analysis.

Thermal analysis is widely used for polymers and copolymers (Hatekeyama and liu, 1998; Turi, 1995) to analyze their glass transition temperature, melting and oxidation. The glass transition temperature (T_g) is defined as the onset motion of chain segments in the amorphous region of a polymer (Bacon and Charles, 1971). Different techniques used to study these properties include: differential scanning calorimetry (DSC) (Enwistle and Rowe, 1979; Okhamafe and York 1985a), differential thermal analysis (DTA), thermal mechanical analysis (TMA) and tensional braid pendulum (Sakellariou et al., 1985; Zhu et al., 2002).

Glass transition temperature is a value that reflects a fundamental property of amorphous polymers (Lieberman et al., 1998) that determines their end-use properties such as mechanical properties and permeability. Polymer-polymer compatibility or miscibility (Fried et al., 1978; Min and Pearce, 1981; Okhamafe and York, 1985a; Sakellariou et al., 1993b) and crystallinity (Okhamafe and York, 1985a) may be evaluated from T_g data. The plasticization efficiency and compatibility may also be evaluated by measuring the glass transition temperature of the polymeric material as a function of plasticizer concentration (Sakellariou et al., 1993a, 1994; Wu and McGinity, 1999). Plasticizer and water depress the glass transition temperature of a polymer.

The compatibility of polymers in blends can be studied by DSC (miscible blends give only one phase). Immiscible blends of two polymers exhibit the two glass points at the

same temperatures as each respective polymer. In miscible blends, a new glass point with values between the glass transitions of the polymers is observed. Partially miscible blends have two glass points which are between the glass points of the polymers. Differential scanning calorimetry (DSC) is typically used to measure the polymer glass transition temperature (Zhu et al., 2002), however this technique is not sensitive enough to identify T_g of certain polymers. Modulated temperature Differential scanning calorimetry (MTDSC) has been shown to be more effective and provide greater resolution and sensitivity (Ferrero et al., 1999; Hill et al., 1998; McPhillips et al., 1999; Reading et al., 1993).

1.5.4 Tack measurements

The film-forming tablet coating solutions are known to be tacky in nature (Chopra and Tawashi, 1984), particularly those consisting of water-soluble cellulose ethers (Al-Dujaili et al., 1986; Lindberg and Johnson, 1972). Tack should not be confused with viscous nature of the system; tack is not necessarily connected with the viscosity. However there is a close connection between the rheological properties of the polymer solution and its adhesive properties (Wan & Lai, 1992a, 1992b).

Most film-forming polymers become tacky during their drying phase, which is the major cause of undesirable particle agglomeration during the coating process (Chopra and Tawashi, 1982; Wan and Lai 1992a, 1992b). The problem caused by the tackiness of coating solution during film coating process is the sticking of tablets to each other and to the wall of the coating apparatus (Wan and Lai, 1992a). Only a limited extent of the studies to evaluate the tack properties of coating formulation has been reported (Chopra and Tawashi, 1982, 1984, 1985; Kovacs and Merenyi, 1990). Methods for quantitative assessment were also reported (Chopra and Tawashi, 1982, 1984, 1985; Wan and Lai,

1992a, 1992b). In this study tack measurements were carried out according to the technique reported by Wan and Lai (1992a,1992b).

1.6 COATING PROCESS AND EQUIPMENTS

The pharmaceutical coating process has evolved from an aqueous one (sugar coating) into a non-aqueous one (solvent film coating), and finally back to an aqueous once again (aqueous film coating). Processing technology has made the transition from the complex (sugar coating), into the relatively simple (aqueous film coating). Coating technology, once an art, now has a more scientific basis where the skills of individual operators have become less critical to the overall success of the operation (Berger, 1988; Thomas, 1981). The selection of the appropriate coating equipment and optimum processing conditions are essential factors that significantly influence the formation of continuous and reliable coatings.

1.6.1 Effect of processing variables in coating pans

Processing parameters need to be optimized to achieve the complete coalescence of polymer particles during or subsequent to the coating operation.

1.6.1.1 Spray rate

The spray rate has an influence on tablet bed temperature and the droplet size of atomized fluid. The bed temperature falls as spray rate is increased, and the relationship between them will be linear up to a point. Once that point is reached, overwetting and saturation of the bed will occur. The droplet size of the atomized liquid will increase as the spray rate increases which will cause the product being coated to be overwetted. Spray rate depends on three factors: (1) capacity of air to accommodate the solvent being used (atomizing

air); (2) the tackiness of the coating being applied; (3) the speed with which the particles travel through the coating zone (Mathur, 1992).

1.6.1.2 Atomizing air volume and pressure

Atomizing air volume and pressure determine the size of droplet, the higher the values the smaller the droplets (Davies and Gloor, 1971). High atomizing air volume and pressure are not necessary for coating tablet. But for small particles (250 μm or smaller) high pressure and volume may be necessary to attain droplets small enough to avoid the formation of liquid bridges between particles at contact point and thus avoid agglomeration.

Poor atomization can influence uniformity of distribution of the coating material. Since atomization is so closely tied to drying rate, then there will also be a direct link to process time. Finally, process efficiency can be negatively influenced in several ways. These include excessively atomized droplets that dry too rapidly leading to a possible loss of coating material. Conversely, ineffective atomization may lead to overwetting, which may also decrease process efficiency because of the potential for the coating material to be transferred from the tablets to the walls of the coating vessel.

1.6.1.3 Drying air temperature

Drying temperature is a critical process variable that dictates the physical nature of the films. In general, product temperature is kept above the glass transition temperature of the film to promote mobility of the polymer chains. If the product temperature is kept below the glass transition temperature, it slows down or retards the polymer coalescence and leads to prolonged drying time and/or formation of incomplete films. Temperature significantly above glass transition temperature may cause tackiness and agglomeration of the coated particles. Too high product temperature leads to premature water

evaporation, thereby resulting in the formation of porous films (Liberman et al., 1998). The drying temperature may affect the structural make up of the coatings, and thereby affect the release of the drugs from the coated products.

Drying capacity of aqueous coating systems is affected by the drying air temperature and specific humidity. Specific humidity must be controlled to allow reproducible coating liquid application rates. Controlling the inlet air humidity can be achieved, either by dehumidification of coating area or by increasing the inlet temperature. Dehumidification is recommended since high temperatures can exert a detrimental effect on the characteristics of the finished products.

1.6.1.4 Pan speed

Pan speed directly influences the mixing, tablet abrasion, spray rate, coating distribution and process time. Pan speed is generally one of the major factors in achieving good uniformity. It is, however, a parameter that has to be tempered with the need to minimize tablet breakage. Running the coating pan as fast as possible will cause the tablets to dwell in the spray zone for a shorter period. This enables the spray rate to be increased and the tablets thus become less wet. Consequently, coating process time can also be reduced due to this improved uniformity and elevated spray rate.

1.6.2 Coating equipments

Coating equipment has evolved from the simple, but crude, into the complex and sophisticated. These days, an extensive array of equipment is used in modern pharmaceutical operations. Equipment used in film coating can be classified into three general categories: conventional pans figure (2.8), perforated pans and fluid-bed processors (McGinity, 1989).

1.6.2.1 Conventional coating pans

The term conventional coating pan was used to describe spherical, hexagonal, or pear-shaped pans. Based on varying shapes, traditional coating pans exist as pans mounted on an angled axis, with air blown onto and the resultant exhaust drawn from the surface of the moving bed of tablets (More up-to-date conventional coating pans are exemplified by the Pellegrini-style pans. These are more angular pans mounted on a horizontal axis, and with openings in both the back and front to permit access for the plenums which are responsible for supplying the drying air and effecting exhaust (Berger, 1988). Although ladling of coating liquids during the film coating process has been practiced, the more common method of applying the coating liquid in conventional pan coating is by using spray technique. The use of spray techniques permits the delivery of finely nebulized droplets of coating solution to the moving tablet mass in such a manner as to ensure uniform coverage while preventing adjacent tablets from adhering together, as the coating solution rapidly dries (Porter, 1982).

1.6.2.2 Perforated pans (side-vented coating pans).

The perforated pans are a modified version of conventional pans and were developed to improve drying efficiency, by drawing the air through the bed as opposed to supplying air to the bed surface only. Drying air is supplied to the bed in several ways however; the basis for all of them is one which enables the air to be introduced into the interior of the pan, drawn through the product being coated, and ultimately vented. Such equipment consists of a somewhat angular pan (with mixing baffles) that rotates on a horizontal axis. The earliest "side-vented" coating pan, the Accela-cota, was introduced in the 1960s. This concept has undergone many improvements since that time. Although most coating pans of this type work in the direct airflow mode (figure 1.2 a), some utilize the reverse airflow concept (figure 1.2 b), and some have the capability of doing both (figure 1.2 c).

Side-vented coating pans exist as fully-perforated drums (such as Thomas Accela-Cota, Manesty Accela-Cota, O'Hara Fastcoat, Glatt Coater, Glatt Procoater, Dumoulin IDX. Rama Coater, Cronimo Pan , etc), some machine designs utilize only perforated segments in the periphery of the cylindrical part of the pan wall (Vector Hi-Coater, Driam Driacoater, Hüttlin "Butterfly" Pan), while others use slotted openings rather than perforated areas. The drying process is more efficient with perforated pans as compared to conventional pans.

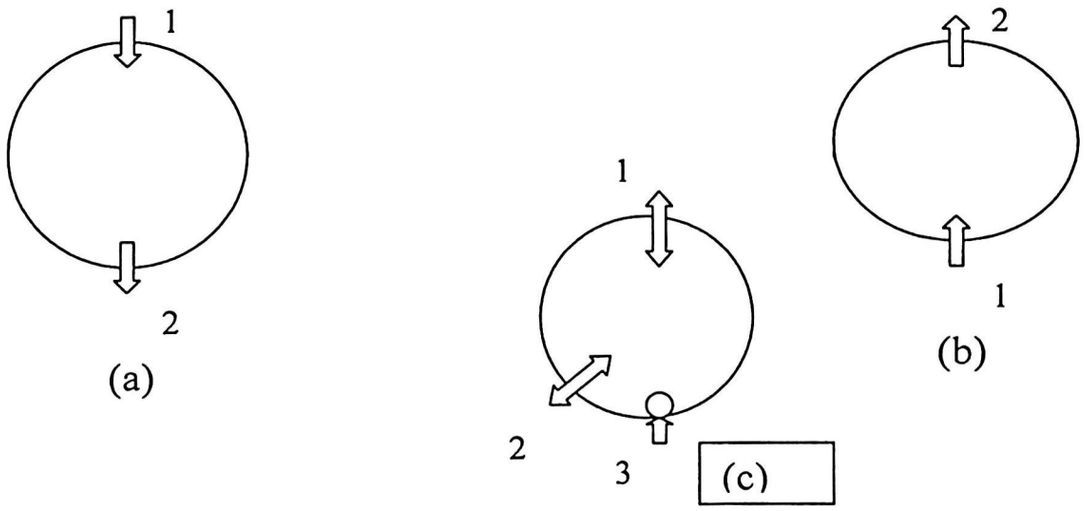

Figure 1.2: Schematic air flow diagrams for various types of perforated coating pans. 1 = inlet, 2 = outlet and 3 = inlet or outlet

1.6.2.3 Fluid-bed coating equipments

As a pharmaceutical process, fluid-bed equipment was first introduced as a means of drying granulations. The next step involved addition of spray equipment to allow the process to be used for spray granulation and drying. Then its use for coating was formalized in the 1950s with the invention, by Dale Wurster at the University of Wisconsin, of the Wurster coating process. The use of fluid-bed equipment in aqueous

coating system has increased greatly primarily due to (1) improved drying efficiency, (2) improved design considerations, and (3) increased experience.

Aqueous film coating can be applied to the fluidized material by a variety of techniques, including spray from the top (granulation or conventional mode), from the bottom (Wurster), or tangentially (rotary granulator). Top spray mode is not applicable for tablets, but small particles can be successfully coated in top spray granulator. The bottom spray (Wurster) coating system has had some success in tablet coating due to its high drying efficiency and good uniformity of distribution of the coating material, however, its use as a coating process for coating tablets has declined since the introduction of the aqueous process. The tangential spray or rotor process has also become adapted for the film coating of multiparticulates. The existence of these three processing concepts has resulted in the major suppliers of fluid-bed equipment offering all three as standard inserts (Bottom-spraying unit, Top-spraying unit, and Tangential-spraying unit) for a basic fluid-bed processing unit.

1.6.3 Ancillary equipments used in the coating process

In the coating process, along with the coating vessel there are other pieces of equipment, which are critical to the successful operation of the process. This is especially true of the applications and drying equipment. These ancillary equipments are: air-handling equipment (blowers and heat exchangers), liquid metering equipment (pumps), dosing systems (e.g. spray guns, sparges), coating liquid holding tanks, process monitoring systems, process control systems and effluent treatment systems (e.g. dust collectors, solvent recovery equipment).

1.6.3.1 Application equipment (spray equipment)

In terms of types of spray guns available for use in the pharmaceutical film-coating process, there are three types, namely: (1) Air spray application equipment: It is capable of delivering coating liquids at low to relatively high application rates. Atomizing air pressure and volume typically control droplet size and size distribution. Air-spray equipment is suited to small scale coating operation and those which involved aqueous formulation (where the atomizing air augments the drying capabilities of the air handling system). (2) Airless equipment: the equipment of choice for production-scale processes using organic solvents. This equipment is not suitable for the aqueous process, because there is no independent control over fluid-delivery rate as well as the atomization process, and the pressures required for adequate atomization usually result in spray application rates that are much too high for the aqueous process (Stern, 1974). (3) Ultrasonic spray nozzles, which have found utility in many applications, have not yet been found to function reliably in the aqueous film-coating process (Stern, 1974).

1.6.3.2 Metering/Delivery Equipment

Metering/Delivery equipment refers to equipment which enables coating liquids to be delivered from a bulk holding tank to the application equipment described in the previous section. The major issues to be concerned with are, the ability to supply the liquid at a controlled rate throughout the whole course of the coating run, the ability of the delivery device to supply the liquid evenly to all guns in a multiple gun set-up, the ability of the device to run without creating pulsations at the nozzle, the influence of the device on the physical stability of specialized coating fluids (such as aqueous polymer dispersions) and the ability of fluid delivery to remain linear over a wide range of operating speeds to facilitate pump calibration.