

School of Pharmacy

**AQUEOUS FILM-COATING WITH THE ULTRA-COATER
(HYBRID COATER)**

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ABSTRACT

Hydroxypropylmethylcellulose (HPMC), which is available in different degrees of substitution and viscosity designations, is one of the most commonly used cellulosic polymers in aqueous film coating. It is relatively easy to process due to its non-tacky nature and has been known to produce smooth and clear films. For aqueous film coating, it is cost effective to use a coating formulation containing a high concentration of polymer without affecting the viscosity or spray rate and compromising on the quality of the film coat. Hence, it is ideal to use a polymer of low viscosity grade. The rheological properties of HPMC with various viscosity grades were determined. It was found that HPMC Methocel E3 had the lowest viscosity and was the least affected by the increase in polymer concentration.

Additives can modify the film properties, including the glass transition temperature of the coating polymer. Glass transition temperature influences the viscosity of the coating solution and the mechanical properties, adhesion and permeability of the film coat. Various concentrations of different additives were incorporated in HPMC formulations to study the effect on these properties. Some long-chain fatty acids were included in the study to investigate if their hydrophobic carbon chains could retard moisture permeation of HPMC films. It was observed that HPMC films containing water-soluble additives produce films with clarity similar to those without additives, whereas those with hydrophobic additives tend to be patchy or hazy in appearance.

A vinyl pyrrolidone / vinyl acetate copolymer (S630) was investigated for its influence on HPMC films, comparing the results with a commonly used plasticizer, polyethylene glycol (PEG) and another copolymer, polyvinyl alcohol (PVA).

Intrinsic properties of the solutions, such as viscosity and glass transition temperature, were evaluated. The effect of S630 on the film properties, such as physical appearance, surface roughness, moisture permeation and mechanical properties, as well as its ability to promote better adhesion of the film coat to the core surface, were compared. S630 was found to be effective both as a film-former and plasticizer, reducing the glass transition temperature and viscosity, but enhancing the tensile strength, elongation and work of failure of the cast film. The water vapour permeability was slightly increased but not to the same extent as with polyethylene glycol (PEG). A 10% concentration of this copolymer increased the adhesive strength and toughness of the HPMC film coat.

Aqueous film coating was carried out in the ultra-coater, using HPMC coating formulations containing 8% w/w of solids, without or with 10% concentration (based on dry weight of total solids) of the additives, PEG, polyvinyl alcohol (PVA) and S630, for coating the tablets. Capsule-shaped lactose tablet cores of specific surface area, hardness, weight, friability and disintegration time were used to study the process variables. Process variables, including air flow rate, temperature and humidity, coating application rate or pump flow rate, atomising air pressure and speed of the rotating disk, were investigated in order to obtain the optimum operating conditions for these solutions. It was found that the process parameters were similar for all the coating formulations containing 8% solid. The additives used in the coating formulations had little influence on the coating process. The ultra-coater was an effective unit for the aqueous film coating of tablets with a batch size of not less than 5 kg.

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INTRODUCTION

A. Film coating

Pharmaceutical film coatings have been applied to solid dosage forms such as tablets, granules, pellets, crystals or other particles. Film coating defines the formation of a thin membrane, usually between 20 to 100 μm , which follows the contours of the substrate, including scores and engravings on tablet surface. Such coatings have been employed to separate incompatible active components in the same dosage form. Currently, a large number of coating polymers are available for use in the manufacture of pharmaceutical dosage forms with controlled release of the active ingredient. The rate-controlling polymer membrane in film coating can modify the release characteristics for the controlled or sustained release of drug. Film coating of tablets is commonly used for protecting the integrity of the core material, especially those that contain an ingredient that is susceptible to moisture, light or atmospheric oxidation. In places where the relative humidity (Rh) is high, such as those in some tropical countries where the Rh ranges from 80% to 90%, protection against the permeation of water vapour is of utmost importance for moisture sensitive drugs.

Upon ingestion, an appropriate film coat can mask any unpleasant taste or odour, minimize gastric irritation and prevent destruction of the drug by gastric acid or enzymes. Tablets coated with a water-soluble cellulosic films are easier to swallow than uncoated tablets because there is less adhesion to the esophageal mucosa from the lubrication provided by the dissolving cellulose (Bauer, Lehmann, Osterwald, &

Rothgang, 1998, p. 127). Film coating also offers better protection and ease of handling, packaging and transport. Moreover, a glossy and smooth film coat enhances the aesthetic value of the product.

Due to environmental safety and health-related issues, aqueous film coating is currently employed to circumvent the restrictions imposed by the use of organic solvents. The high cost of using organic solvents, as well as the solvent recovery systems required for their use, made aqueous film coating the current method of choice in the pharmaceutical industry.

The advantage of aqueous film coating is that water is safe, non-toxic, inexpensive and readily available. However, consideration has to be given to two main concerns. Firstly, the high latent heat of vaporization leads to increase in drying times and the energy cost incurred. It is also difficult to carry out aqueous film coating on moisture sensitive drug cores as hydrolysis may lead to the degradation of the active ingredient.

A.1. Aqueous-based coating polymers

At present, aqueous-based coating polymers that are used for pharmaceutical solid dosage forms are predominantly cellulose derivatives, acrylic resin derivatives and copolymers (Radebaugh, 1992; Kumar & Banker, 1993; Hogan, 1995). The cellulose derivative polymers can be classified into four main groups based on their methods of preparation (Wallace, 1990; Kumar & Banker, 1993). Commonly used examples of each group are given below.

- (a) hydrocelluloses produced by hydrolysis, e.g. microcrystalline cellulose,
- (b) cellulose esters produced by esterification, comprising of enteric esters, e.g. hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate and hydroxypropylmethylcellulose acetate succinate; non-enteric esters, e.g. cellulose acetate, cellulose triacetate, cellulose sodium phosphate, cellulose acetate butyrate, and cellulose acetate propionate,
- (c) oxycelluloses produced by oxidation, e.g. oxidized cellulose, oxidized regenerated cellulose and
- (d) cellulose ethers produced by etherification, e.g. sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, croscarmellose sodium, ethylcellulose, methylcellulose and hydroxyethylcellulose.

One of the most commonly used aqueous-based polymers for film coating is hydroxypropylmethylcellulose (HPMC). HPMC is manufactured by heating the cellulose fibres in alkaline solution which in turn is treated with methyl chloride, yielding the methyl ether of cellulose. Propylene oxide is used in addition to methyl chloride to obtain the hydroxypropyl substitution. The product is purified and milled to a fine, uniform powder. Different grades of HPMC possess varying ratios of hydroxypropyl and methyl substitutions. The degree of substitution will affect the solubility and thermal gel point of the polymer, as well as the water vapour permeability and mechanical properties of such polymeric films.

The viscosity of HPMC in solution is determined by the chain length and the size and extent of its branching. Hence, HPMC coating polymers come in many different viscosity grades, assigned with a number of viscosity designations defined by the

nominal viscosity of a 2% w/w aqueous solution at 20°C (Hogan, 1995). Generally, to minimize coating time and maximize production efficiency, the lowest possible viscosity grade of the polymer is the ideal choice as the high solid content in the coating solution results in less water to be removed and minimizes the contact between the tablet core and water. The sprayable solution viscosity for aqueous film coating is in the range of 150 to 400 MPa.s (“A brief review of the coating process”, 1995). The apparent viscosity of aqueous HPMC solutions is proportional to the molecular weight and lowering the molecular weight reduces the physical properties of the film coat. The advantage of using a low viscosity grade polymer is limited if film quality, such as moisture permeability and mechanical properties, is compromised. For this reason, very low viscosity grade HPMC, is seldom used alone as the coating polymer.

A.2. Additives used in aqueous film coating

To enhance the properties of polymeric films, different additives, such as plasticizers and film formers or copolymers, have been incorporated in aqueous coating formulations. The function of a plasticizer is to soften films, reduce brittleness, increase flexibility and ductility. Incorporation of a plasticizer affects the glass transition temperature of the coating polymer. Glass transition temperatures reflect the physical properties, such as viscosity of the coating solution and the mechanical properties, adhesion and permeability of the film coat (Aulton, 1995). An over-plasticized film will lose toughness and the excess plasticizer may also result in a patchy or spotty appearance of the film when it exceeds the capacity of the coating polymer and is

separated out from the system. The selection of a suitable plasticizer depends on the structure of the plasticizer. In order to be effective, it must interpose itself between the polymer chains and interact with the forces that hold the chains together, thus extending and softening the polymer matrix. Such plasticizers were found to adhere more strongly to tablet compacts than additives with limited plasticizing effect (Felton & McGinity, 1997). The addition of a plasticizer in a coating formulation affects the coating process as the diameter of the spray droplets would increase because of increased mobility and spreading properties of droplets on the substrate surface (Honary, Orafi & Shojaei, 2000). Substantial attention has been given to the influence of plasticizers on HPMC films (Entwistle & Rowe, 1979; Okhamafe & York, 1983, 1984; Sakellariou, Rowe & White, 1986) and sodium carboxymethylcellulose films (Wan, Heng & Chia, 1994).

Copolymers have been used with primary aqueous polymers in some coating formulations. An additive that has been used in binary systems with HPMC is polyvinyl alcohol, a synthetic polymer which interacts with the coating polymer, resulting in decreased diffusivity. Okhamafe and York (1983) stated that the physiochemical changes that affect the diffusion coefficient of HPMC films would in turn determine the permeability of the films.

Film coating formulations often include auxiliary components, such as pigments, anti-adherents, antifoaming agents and surfactants. These additives may improve the appearance of the dosage form, facilitate the processing of material and influence the spreadability of the coating solution droplets on the substrate core (Felton & McGinity, 2002). Titanium dioxide has been used in film coating formulations as an opacifier to improve the stability of light-sensitive drugs (Felton & McGinity, 2002). Titanium

dioxide and talc have been investigated for their effect on moisture permeation by Okhamafe and York (1985a). The effect of citric acid and urea on glass transition, softening, melting, plasticization and crystallinity of HPMC and polyvinyl alcohol film coating formulations have also been reported by them (Okhamafe & York, 1987). Polydextrose and titanium dioxide have been used with HPMC films for a study on the effect on mechanical and adhesive properties (Lehtola, Hainamaki, Nikupaavo & Yliruusi, 1995a).

Acetic Acid ethenyl ester, polymer with 1-ethenyl-2-pyrrolidinone or vinyl pyrrolidone / vinyl acetate copolymer under the trade name of Plasdone S-630 has been used recently in HPMC formulations. This copolymer has shown promise in enhancing film formation, giving HPMC film coats a clear and smooth appearance, as well as good mechanical and adhesive properties, without adversely affecting the water vapour permeability.

B. Process and product parameters in aqueous film coating process

The film coating process is very complex, involving many variables that have a significant influence on one and other. Many problems can occur, some attributed to the process conditions and others include substrate core and the coating formulation. Optimum settings have to be established with the core size, core surface, coating formulation and desired coating technique in mind. Many review articles on process conditions, product variables and equipment considerations for aqueous coaters have

contributed new insights to researchers in aqueous coating formulations (Jones, 1988; Mathur, 1992).

B.1. Process parameters

Operational conditions and techniques produce critical effects for the coating process. Alteration of the parameters can have beneficial or detrimental results on the film coating. For example, by controlling the flow rate of the heated ventilator air, the large amount of energy can be effectively used for drying. Thus, the efficiency of the coating process can be optimized by accurately timing the spray application of the coating fluid. Generally the process variables can be divided into the following categories.

B.1.(i) Delivery systems

(a) Nozzles

Coating fluid can be atomized by hydraulic or pneumatic nozzles. Hydraulic nozzles are airless, one-fluid nozzles using high-pressure pumps. The coating liquid is sprayed through a small nozzle tip at relatively high pressure. This is a hydrodynamic process and the sprayed droplet size depends on the viscosity and surface tension of the coating fluid, as well as, the nozzle design, spray rate and uniformity and intensity of the applied pressure (Bauer et al., 1998, p. 158). Airless spray nozzles are not suitable for aqueous-based coating solutions because the liquid flow rate of water is much lower

than the common organic solvents. To lower the spray rate of an airless nozzle either the pressure or the nozzle size must be reduced. When the liquid pressure is reduced, the degree of atomization deteriorates and when the nozzle size is reduced, problems of frequent nozzle blocking may arise (Cole, 1995).

Pneumatic nozzles are usually two-fluid air nozzles that deliver the coating liquid at a low pressure and the liquid is sheared simultaneously into fine droplets by compressed air. This is a kinematic atomization process whereby the coating fluid is accelerated to high speed by the compressed air. The pressure is usually set between 0.5 and 3 bars (Bauer et al., 1998). These nozzles are commonly used in aqueous film coating systems because the spray droplet size is independent of the liquid flow rate and atomization, resulting in a narrower droplet size distribution. Air nozzles have two main advantages over the airless ones. Firstly, they have larger apertures, making them more versatile for spraying suspensions, dispersions or other high-viscosity fluids as the clogging tendency is considerably reduced. Secondly, the spray and fluid delivery rates are easier to control than the airless nozzles that are highly sensitive to pressure fluctuations. However, atomization by compressed air results in higher evaporation rates of the coating liquid. For aqueous film coating, the rapid evaporation of water may subsequently increase droplet viscosity that affects the spreadability on the core material. In view of this, this type of nozzle is best placed in a position near the substrate cores so as to minimize the droplet travel distance (Tan, 1996).

The three-channel or three-component nozzle described by Bauer et al. (1998, pp. 159) is the latest type of air nozzle with an additional channel. A second gas or component can be introduced through this channel to create a special microclimate

around the nozzle aperture. This is very useful for a film former with a relatively high minimum film-forming temperature that requires high temperature for the coating operation. Air at low temperature can be introduced through the additional channel to form a relatively cool microclimate around the nozzle. The spray fluid first passes this zone of moderate temperature and excessive spray drying or clogging of the nozzle is prevented. The actual drying process begins only when the droplets have reached the core bed in the hot zone.

Investigations into nozzle design and the importance of nozzle positions are well documented (Rankell, Scott, Lieberman, Chow & Battista., 1964; Davies & Gloor, 1973; Schaefer & Worts, 1977a, b; Aulton & Banks, 1978; Olsen, 1989).

(b) Pumps

The selection of pumps used for the coating process depends on the characteristics of the coating solution. There are three main types of pumps, namely piston, gear and peristaltic pumps. The piston pump uses adjustable stroke length or speed to control its flow rate. In the event of minor clogs in the nozzle, its inbuilt pressure is able to clear the system. The main disadvantages are difficulty in cleaning and pulsation in the flow as the piston changes direction.

The gear pump enables the smooth and precise delivery of liquid because of its design. It has a cavity of specific volume in which two gears mesh at very close tolerance. However, it is not suitable for pumping latex and pseudolatex coating materials due to pressure build-up between the gears.

With the peristaltic pump, liquid is delivered through a flexible plastic or silicon rubber hose by means of a multi-lobed, adjustable-speed pump head. Hence this type of pump is the simplest and easiest to clean. It is also ideal for latex and pseudolatex coating materials as there is no pressure built-up in the pump. Some of the disadvantages include low liquid pressure, inability to pump viscous liquids, fluctuations in the liquid delivery rate and pulsation as the lobes change (Mehta, 1989).

B.1.(ii) Coating pans

There is a large variety of designs for coating pans. Besides containers used for fluidized bed coating, film coating can also be performed in conventional coating pans of varying design and made of different types of material. For pan coating operation, improvements for a more effective drying process have been made in the pans themselves, e.g. by means of perforations in order to enable automation and optimization (Bauer et al., 1998, pp. 71). Perforated pans can be effectively used for aqueous film coating.

B.1.(iii) Air volume, temperature and humidity

The rate of drying of the coating liquid is controlled by the rate of heat transfer from the air to the solvent and the rate of mass transfer of the solvent to the coating surface. The drying rate is determined by several factors, such as latent heat of vaporization, the surface area of the material being dried, the relative humidity of the

incoming drying air, the velocity and direction of the airstream and the geometry of the drying chamber (Mehta, 1989).

The design of the coating equipment has a major influence on the distribution of the spray droplets on the core surface and the quality of drying. The inlet air quantity and its temperature determine the drying efficiency, the spray rate and thus the product temperature. This has a direct effect on the quality and uniformity of the film coat. In film coating, the coating fluid must dry quickly without forming a fluid layer on the cores, otherwise sticking may lead to surface roughness or picking. Orange-peel appearance is one of excessive roughness, a result of poor spreading of the coating droplets on the core surface. Picking occurs when the droplets on the core surface are not sufficiently dry when it re-enters the bulk of cores. The two main coating defects, namely picking and the orange peel effect are mostly related to process conditions, such as atomization and drying process (Aulton & Twitchell, 1995a).

High absolute humidity, i.e. the actual humidity within the coater, affects the drying capacity in aqueous film coating systems. Since high absolute humidity may reduce the drying capacity, the coating rate must be decreased so as to avoid the problem of over-wetting. Most coaters have psychometric charts to provide a convenient means of determining the capacity of the outlet air to carry the evaporated moisture. Both temperature and humidity should be carefully monitored and controlled in order to ensure reproducible coating conditions. The outlet temperature also indicates overall drying conditions, whereas the bed temperature indicates the drying temperature of the core surfaces. Generally, temperature monitoring of the inlet air, outlet air and surface bed is beneficial. Results of many experiments have shown that the optimum inlet air

temperature for most tablets lies in the range of 50°C to 80°C that maintains a bed temperature of approximately 40°C to 45°C (Cole, 1995). A lower temperature is generally employed when heat-sensitive polymers and organic solvents are used.

B.1.(iv) Spray techniques

For film coating, the droplets of spray fluids must be able to spread on the surface of the core material and coalesce to a liquid film, yet dry quickly enough to prevent the formation of a fluid layer. After a very short time the tablet is covered with a thin polymer membrane. Subsequently, the film surface is properly wetted and the droplets coalesce well on it. Once the droplets have spread, the remainder of the solvent in which the polymer is dissolved evaporates, the film becomes stronger and shrinks at the same time. If spraying occurs too fast, the film dries too slowly and sticking of the cores may occur due to over-wetting. If spraying is too slow, the coating bed of core material gets too hot and core sticking may occur owing to softening of the films.

There are basically two types of spraying techniques, intermittent and continuous spraying (Bauer et al., 1998, pp. 70-71). In intermittent spraying, the coating fluid is applied in small portions at alternate intervals with a non-spray cycle to allow uniform drying of each portion. If drying and spraying are carried out intermittently, there is a higher risk of premature drying of spray droplets with resultant material loss. Continuous spraying is faster as the drying air is introduced simultaneously together with the coating fluid. If drying and spraying are concurrent, the coating fluid usually spreads and dries more evenly, and less of it is required. However, this technique

requires careful adjustment of spray rate, temperature and air flow. Preference is always given to a greater air quantity at lower temperatures.

B.1.(v) Atomizing pressure

Atomizing pressure influences the size distribution of the coating fluid droplets as well as the volume and velocity of the atomizing air. When the air pressure is increased, the droplets become finer. Changes in atomizing pressure will lead to changes in droplet size (Khan et al., 2001). Increase in atomizing air pressure may result in a decrease in surface roughness (Aulton & Twitchell, 1995a; Harrison et al., 1991).

B.2. Product variables

Besides the process conditions under which a film coat is applied, the constituents and properties of the core substrate and the coating formulation also influence the properties of film coats. Film coating must be carried out under optimized conditions according to core size, core surface and coating formulation. Some researchers (Aulton, 1995b; Fukumori, 1994; Lehmann, 1994) have documented the importance of product variables in developing aqueous-based coating systems for solid dosage forms.

B.2.(i) Characteristics of the coating liquid

Coating application is very dependent on the concentration of the coating liquid and the spray rate. Water has a higher latent heat of evaporation and hence takes a longer time to evaporate than organic solvent. To reduce the coating time, it would be ideal to use a high concentration of solids. However, high concentrations result in high viscosity and the droplet size and spreadability of the liquid droplets are affected. Droplet spreadability is one of the factors that will influence the roughness and appearance of a coated product (Honary et al., 2000). These may have a detrimental result on the quality of the film coat. The spray rate is affected by the capacity of air for the solvent being used, tackiness of the coating being applied and the speed of particles traveling through the coating zone.

When the droplets of coating fluids impinge on a tablet surface, their physical properties, such as viscosity, surface tension and tackiness may influence the contact angle, degree of spreading and degree of penetration into the substrate surface. These factors affect the coating process. In order to reduce process time as well as the amount of liquid to be removed, it would be beneficial to have a coating formulation with high concentrations of solid. The concentrations of some polymers, such as HPMC, have a profound effect on viscosity, with the viscosity increasing with concentration. For example, a doubling in concentration from 6 to 12% causes a greater than ten-fold increase in viscosity (Aulton & Twitchell, 1995b). Lower viscosity will result in larger number of smaller droplets and higher viscosity results in larger droplets. Hence, it is

important to investigate the rheological properties of a coating formulation to assess how it would behave during the film coating process.

B.2.(ii) Characteristics of substrate cores

Weight, surface area, shape, porosity, hardness and friability of the substrate core are important parameters in film coating. If tablets are used as cores, they must be biconvex or have curved surfaces to prevent sticking or stacking during film coating.

The substrate cores being coated should have adequate hardness and strength to withstand the abrasive and mechanical forces while tumbling in the coating pan or fluidized bed. During film coating, the impact and stress may result in fragments being dislodged. These detached particles may subsequently re-attach to the cores or are incorporated into the coating solution. Friable cores may also undergo erosion during coating. Therefore, cores for coating must be sufficiently robust to withstand the associated abrasive forces during coating in order that the product is satisfactory with respect to appearance and performance.

Film coating requires the core surfaces to be smooth and dust free. When the surface of the core is porous, the formation of the film coat will be affected as some of the coating material will fill the pores, making the film coat thinner. When the substrate core is a tablet, the pores may be too large to be covered up by the coating material, resulting in a poor film coat.

The active ingredient of the substrate cores may contribute to the appearance of the film coated product. Substances migrating from the cores into the coating may

impair the appearance. Substrates that contain large proportions of poor wetting active ingredient are difficult to coat due to their hydrophobic core surface (Porter, 1997).

C. Aqueous film coating of tablets

The coating process is divided into several steps. First, the inlet air is turned on to preheat the tablets to the desired temperature and dust is simultaneously extracted. Next the film coat is applied. The processing conditions must be such that the water phase evaporates within a minimum of time. A small portion of coating solution can be applied very slowly at this stage, to impart mechanical stability to the tablet cores. This will prevent further dust formation that may impair the quality of the film during the coating process. Subsequently, the heated air supply is increased and the coating solution or suspension sprayed as continuously as possible onto the swiftly moving core bed. The inlet air temperature is adjusted in such a way that the bed temperature is maintained about 10°C to 20°C above room temperature. The inlet air temperatures required for this purpose are between 50°C to 90°C, depending on spray rate, water content of the formulation and drying efficiency of the equipment (Bauer et al., 1998, pp. 80). Besides inlet air temperature and quantity, air flow and core bed movement have to be carefully controlled. Upon completion of the coating process, it is necessary to run a post-drying phase. The movement of the core bed during post-drying must be drastically reduced in order to minimize attrition.

Pan coating is preferred for the film coating of tablets as fluid bed coaters are more suitable for small particles. In fluidized bed coaters the process time can be just

about halved, but tablets of high crushing strength are required to withstand the high mechanical stress generated in this type of equipment (Bauer et al., 1998, pp. 80).

D. Evaluation methods for film coating

Many methods have been used to evaluate the effectiveness of a film coating process and / or its formulation. Investigations have included the effect on the glass transition temperature, moisture permeation and surface morphology. Free films have been used frequently to evaluate the mechanical properties and moisture permeability. Currently there is much interest in the evaluation of film adhesion, i.e., the adhesion between tablet substrate and its film coat.

D.1. Glass transition temperature

At the glass transition temperature (T_g), an amorphous polymer softens and undergoes a transition from a glassy state to a rubbery state because of increased segmental mobility (Nyamweya & Hoag, 2000). T_g influences the mechanical properties and permeability (Nair, Nyamweya, Gonen, Martinez-Miranda & Hoag, 2001), as well as adhesiveness of polymeric films. Common methods for this thermal analysis of polymeric systems include differential scanning calorimetry (DSC) and thermomechanical analysis. Many researchers have carried out T_g determination using the DSC to study the effect of additives on polymeric films (Okhamafe & York, 1985, 1988; Pourkavoos & Peck, 1993; Acarturk & Sencan, 1996; Felton, Austin-Forbes &

Moore, 2000; Wu & McGinity, 2000, Nyamweya & Hoag, 2000; Nair et al., 2001). It had been reported that the plasticizer, polyethylene glycol (PEG), lowered the Tg of HPMC, whereas polyvinyl alcohol increased the Tg of HPMC due to the presence of a crystalline phase in the blend (Okhamafe & York, 1985b). Felton and McGinity (1996) also found a relationship between polymer adhesion and the Tg of acrylic resin copolymer film, with stronger adhesion occurring when the Tg of the film was lowered. Changes in the Tg of a polymer would directly affect the internal stress within the film and consequentially, the incidence of crack formation in the coating (Felton & McGinity, 2002).

D.2. Moisture permeation

Film coating offers a protective barrier against the transmission of gases, atmospheric oxygen and most importantly, water vapour, into the dosage form. The evaluation of the moisture permeability of polymeric films has been carried out extensively to investigate the effect of some additives in polymeric film coating formulations.

In addition to the “moisture, air and temperature perm cup” reported in the ASTM method used by some researchers (Joshi, Kral & Topp, 1989; Johnson, Hathaway, Leung & Franz, 1991), other types of permeability cups or set-ups have been used. A commonly used apparatus comprises of a glass vial containing a drying agent, such as calcium chloride, silica gel or anhydrous potassium acetate, to provide a gradient for water vapour permeation (Heinamaki et al, 1994; Remunan-Lopez & Bodmeier,

1996; Acarturk & Sencan, 1996). However, it is imperative that the test apparatus has a good seal between the test film sample and the holder.

Many researchers had carried out studies on the effect of additives on moisture permeability of polymeric films. Plasticizers have proven to alter the moisture permeability characteristics of polymeric films. Heinamaki, Lehtola, Nikupaavo and Yliruusi (1994) reported that moisture permeability of HPMC films decreased with increasing molecular weight of PEG. Okhamafe and York (1983) reported that while PEG increased moisture permeability, polyvinyl alcohol decreased it. It has been reported by Acarturk & Sencan (1996) that an increase in water vapour transmission resulted in an increase in the in vitro release rate of drug.

D.3. Surface roughness of films

For aesthetic reasons, a smooth and glossy film is desirable for a film coated pharmaceutical dosage form. Surface roughness of the film contributes to the appearance of the film coat as those with a smooth surface tend to have a glossy appearance. On the contrary, those with a rough surface will appear dull. The measurement of surface roughness not only quantifies the surface characteristics of the film but also helps to provide information on the behaviour of the atomized film droplets on the core surface and facilitates the optimization of the coating process (Aulton & Twitchell, 1995a).

The scanning probe microscope is suitable for evaluating surface roughness of films quantitatively. Values are given for the arithmetic mean of roughness, the maximum height roughness and the 10-point mean roughness. The arithmetic mean of

roughness is most commonly used for the analysis of the film surface (Aulton & Twitchell, 1995a).

D.4. Mechanical properties of films

Stress-strain tests using free films have been used to evaluate mechanical properties, such as tensile strength or maximum tensile stress, elastic modulus and tensile percentage strain at break to gauge the performance of the film coat. Maximum strength at break is an indication of the film strength, i.e. a larger value corresponds with a stronger film. Elastic modulus is a measure of the stiffness of the film. The interaction of a plasticizer with the polymer generally decreases the elastic modulus (O'Donnell & McGinity, 1997). Generally, the evaluation of the tensile strength and the elastic modulus are the standard approach to the characterization of the mechanical properties (Lafferty, Newton & Podczeck, 2002). The tensile strain at break is the percentage strain or elongation at the tensile stress at break if the sample breaks without yielding (Aulton, 1995). It is a measure of the capacity of a film to deform prior to failure. Thus, high elongation indicates a ductile or extensible film and lowered elongation indicates a reduction in the deformation capacity of the film, i.e., a more brittle film. The area under the force-displacement curve is the work of failure, i.e. the work in straining the sample to failure, measured in joules. It is related to the film toughness and this property is important in film coating as it relates to the ability of the coating to withstand shock loads without damaging the integrity of the film (Aulton, 1995). An ideal film coat should be hard and tough with high tensile strength and elastic modulus (Heinamaki et

al., 1994) as well as, a large area under the curve and moderate extension before breaking.

Generally, plasticizers not only reduce the modulus of elasticity, but also the tensile strength of the polymeric films. Hence their compatibility and concentration are very important. Incorporation of PEG, a plasticizer often used in HPMC formulations to enhance film flexibility, reduces hardness and tensile strength, thus lowering the resistance to high-speed packaging and handling (Heinamaki et al., 1994). It also disturbs the continuity of the polymer chains, decreases the molecular order and increases chain mobility of the polymer matrix, leading to increase diffusivity. These effects are not desirable, especially when the film coat is necessary to protect moisture-sensitive cores in an environment of high humidity and water itself has a plasticizing effect. Other investigations on the effect of plasticizers on the mechanical properties of polymeric films included the effect of triacetin and polyethylene glycol (Johnson, Hathaway, Leung, & Franz, 1991) and that of glycerol and PEG of different molecular weight (Aulton & Abdul-Razzak, 1981).

Another additive used in binary systems with HPMC is polyvinyl alcohol. Okhamafe and York (1983) reported that polyvinyl alcohol decreased the film hardness and elastic modulus but not to the same extent as HPMC-PEG films. Reduction in film properties may give rise to problems like cracking, resulting in lost of integrity of the film coat. For these reasons, investigations on film coating formulations often examine both the water vapour permeability and mechanical properties of the film.

D.5. Film adhesion

Film-forming polymers must show a certain tendency to adhere to the material to be coated. The adhesion depends on the chemical and physical interactions between polymer, solvent, plasticizer and the core surface.

D.5.(i) Adhesive properties of films coated on tablets

The adhesion process between the tablet core and the film coat starts at the application of the film coating fluid when the sprayed droplets impinge on the surface of the tablet cores. If the contact lasts, the coating fluid is adsorbed and diffused into the core. The duration of this contact depends on the viscosity and spreadability of the coating fluid, the surface characteristics of the core and the contact angle between the fluid and the tablet.

Strong film-tablet adhesion is also essential for pharmaceutical film coating as poor adhesion not only has visible film-coating defects but also affects the stability of moisture sensitive drugs and compromises the mechanical protection that the film coat provides to the substrate cores (Felton & McGinity, 1999). The adhesion of the film is influenced by many factors, including the solubility difference between the polymer and solvent and the surface characteristics of the tablet surface, such as surface tension, surface roughness and hydrophobicity. In addition, the compression force used for the tablet compact also plays a role as tablets compressed under high compression forces tend to be smooth, resulting in poorer adhesion and those compressed under low force

may have higher porosity, resulting in a rough surface for better adhesion of the film (Bauer et al., 1998, p. 200). A study on the influence of tablet hardness on the adhesive properties of polymeric films has reported that there was a decrease in adhesive properties with the harder tablets (Felton & McGinity, 1996) and that the rougher surfaces in softer tablets resulted in stronger polymer adhesion (Felton & McGinity, 1999).

Adhesive properties have been shown to decrease with ageing (Felton & McGinity, 1997). However, it had been reported by other researchers that adhesion of tablets coated with aqueous film coatings was less affected by ageing when pigments, either talc or titanium dioxide, were included in the film coating formulation (Okhamafe & York, 1985c).

The effect of plasticizers on the adhesive properties of polymeric films has also been investigated. Felton and McGinity (1997) have reported that hydrophilic plasticizers in polymeric coating formulations have significant influence on the film adhesion to hydrophobic tablet surfaces whereas formulations with water insoluble plasticizers had no effect on the film adhesion of such tablets. Inclusion of the additives, namely microcrystalline cellulose, lactose and Tween 20, has been shown to influence the adhesion of HPMC films (Khan, Fell & Macleod, 2001).

D.5.(ii) Methods of evaluating adhesion

Evaluation methods to determine film adhesion involve measuring the force required to peel or detach a standardized strip of film from the surface of the coated

tablet. During the adhesion test, two types of failure may occur, adhesive and / or cohesive failure (Felton & McGinity, 1999). For the study of film-tablet adhesion, the data obtained should be from adhesive failure. Adhesive failure occurs when the film coating is completely removed from the tablet surface with a minimal amount of core particles attached. Cohesive failure is due to different forces that cause the lamination of the tablet core during the test, resulting in particles of the tablet being found on the surface of the film coating.

Many methods have been developed to assess the adhesion between the coated film and the tablet core. Earlier methods, such as the “Scotch tape test” and “Scratch test”, had many limitations due to the small size, shape and the non-uniform surface roughness of the tablet (Felton & McGinity, 1999). Accurate quantitative measurements were challenging as there were many inherent difficulties, such as the lack of uniformity of adhesion for the film coat and the inconsistent rates for detaching the film. The predominant method for determining film adhesion to tablet core is the butt adhesion test (Felton & McGinity, 1996, 1997, 1999; Felton et al., 2000). In recent years, many variations of the butt adhesion technique have been reported. Adaptations of this technique have made it possible to detach the film from the surface of the tablet under a constant rate of deformation.

In this study, a modified butt adhesion technique is employed using a tensile tester attached with a custom-made tablet holder. The tablet holder replaced the grips of the tensile tester in securing the tablet sample. It was able to hold a truncated tablet sample, yet allow free rotation to facilitate the peeling of the coated film from the tablet.

As the entire film surface of the truncated tablet was detached during the test, the difficulty of obtaining a uniform surface area of the test film sample was overcome.

Tablets for film coating are usually biconvex or have curved surfaces to prevent sticking or stacking during film coating. However, most adhesion studies have involved the use of flat-faced tablets (Fisher & Rowe, 1976; Rowe, 1977; Lehtola et al., 1995b; Felton & McGinity, 1996) in order to obtain a uniform contact surface with the adhesive tape used in the test. It is difficult to coat tablets with flat surfaces due to their sharp edges and the tendency for agglomeration. Beveled edges have been used to reduce the sharp angle of the flat tablets. Recent studies have involved flat-faced tablets with beveled edges (Felton & McGinity, 1996, 1997, 1999; Felton et al., 2000) to overcome the difficulties created by the sharp edges of the flat-faced tablets during the coating process and to lower the internal stresses within the film. In this study, the tablet core is capsule-shaped (caplet), a long and curved shape commonly used for film coating. The truncated caplet was securely held by the pins on both sides of the tablet holder to facilitate the peeling of the entire film coat.

The force of adhesion or the adhesive strength and area under the stress-strain curve or adhesive toughness can provide a more accurate quantitative measure of the film-tablet adhesion. Stronger adhesion is evidenced by the increase in adhesive force. Increase adhesive toughness is reflected by the increase in area under the curve, i.e. the work done to detach the film from the surface of the solid core. The adhesive properties of polymeric film coat are well represented by the adhesive strength and adhesive toughness (Felton & McGinity, 1996, 1997).

OBJECTIVES

The objectives of the study involve evaluating the application of a coating onto unit dosage forms which is a useful and important process in the pharmaceutical industry. The coating system provides greater flexibility for the formulator in designing high quality dosage form for this purpose.

Currently, aqueous film coating is the method of choice for the pharmaceutical industry. The objective of this project is to formulate an aqueous HPMC coating solution to include an additive that can promote the ideal physical properties of a film coat. Various film formers (copolymers) and plasticizers were selected to determine their influence on the intrinsic properties of the solutions, such as viscosity, and glass transition temperature of the polymeric films. The effect of these additives on the film properties, such as appearance, surface roughness, moisture permeation and mechanical properties, as well as their ability to promote better adhesion of the film coat, is to be evaluated. A new copolymer, vinyl pyrrolidone / vinyl acetate copolymer, was to be studied to evaluate its influence on HPMC films and to make comparisons with a commonly used plasticizer, polyethylene glycol and another copolymer, polyvinyl alcohol.

Aqueous film coating processes were to be carried out in an ultra-coater which is a hybrid coater. The coater combines both fluidised bed technology with the conventional perforated pan coating. The process variables and product variables were to be evaluated to determine the optimum operating conditions for tablets of

standardized specifications. The efficiency of the coating system was to be evaluated by the physical appearance, film coat thickness and coated film – substrate core adhesion.

EXPERIMENTAL

A Materials

A.1. Polymers

Polymers used in this study were different grades of hydroxypropyl methylcellulose (Methocel[®], Dow Chemical, U.S.A). Hydroxypropyl methylcellulose (HPMC) consists of a polymeric backbone containing a repeating structure of anhydroglucose units. It was prepared by treatment with methyl chloride yielding a methyl ether of cellulose and propylene oxide to obtain hydroxypropyl substitution on the anhydroglucose units. Hence different grades of HPMC possess varying ratios of hydroxypropyl and methyl substitution. Methocel E, F, J and K series are the different types of HPMC products used for pharmaceutical applications. For Methocel E, F and K, the major constituent is the methoxyl substitution as indicated in the degree of substitution in Table 1. Cast films prepared from a sample each from Methocel E, F and K series, namely E50, F50 and K100, were investigated for their moisture permeability. Concentrations used were 2, 3, 4 and 6% w/w.

Table 1. Degree of Substitution for HPMC used in the study (“Chemistry of Methocel”, 1997).

HPMC (Methocel series)	Methoxyl degree of substitution	Methoxyl (%)	Hydroxypropyl molar substitution	Hydroxypropyl (%)
Methocel E	1.9	29	0.23	8.5
Methocel F	1.8	28	0.13	5.0
Methocel K	1.4	22	0.21	8.1

Films from HPMC Methocel "E" series, the grades recommended for film coating, were further evaluated for their moisture permeability as well as mechanical properties. The six grades investigated were E3 Prem LV[®], E5 Prem LV[®], E6 Prem LV[®], E15 Prem LV[®], E50 Prem LV[®] and E4M Prem[®]. The number in the different grades identifies the viscosity in mPa s determined in water at 20°C at a concentration of 2%. The letter "M" is used to represent 1000. E4M is the only high viscosity grade in the HPMC E series used in the study. "LV" indicates the low viscosity grade. The polymers of lower viscosity grades are usually used as film-formers in film coating while those of higher viscosity grades are useful as release rate retardant polymers for water-soluble drugs. The concentrations used in these investigations performed on cast films were 2, 3, 4 and 6% w/w. (Table 2)

The grade selected as the polymer for film coating and further investigations was the one with the lowest viscosity grade in the E series, namely, Methocel E3 LV.[®] The supplier's specification for the HPMC E3 LV when measured with an Ubbelonde viscometer at 20°C at a 2% concentration in water was 2.4-3.6 mPa s. The concentration used for tablet coating was 8% w/w solid content. (Table 2)

Table 2. Formulae of HPMC solutions for cast films and coated films.

Formulations	Cast Film	Coated Film
Additive (%) ^a	<i>As indicated in Table 3</i>	10 & 20*
HPMC E3 (%)	qs ^b	qs ^b
Total solid content (% w/w)	3	8
Quantity per preparation	300 g	3 kg

^a based on dry weight of total solid content;

^b quantity sufficient to make up to 100% of solid content

* *HPMC film coats containing 20% additive were not used for further testing because of poor film quality.*

HPMC is soluble in water with no sharp solubility limit and the maximum concentration depends on solution viscosity. It is soluble in cold water but must first be thoroughly dispersed in the water to prevent lumping. It is insoluble in hot water and undergoes a reversible transformation from solution to gel upon heating. The technique for complete solubilization and hydration of HPMC solution is to disperse the HPMC powder in 1/5 to 1/3 its total volume of water heated to above 90°C, followed by adding the remaining water as cold water or ice. Once the temperature at which the HPMC becomes water soluble is reached, hydration occurs and viscosity increases. The rheology of HPMC solutions is affected by its molecular weight, concentration, temperature and presence of other solutes. HPMC solution is stable over a wide pH range from 3 to 11 (Wade & Weller, 1994).

A.2. Additives

The additives used for studying the effect on moisture permeability of HPMC films included copolymers, a plasticizer, fatty acids and the salt of a long-chain fatty acid. Polymeric additives included two grades of polyvinylpyrrolidone (Plasdone K90[®] and Plasdone C15[®], ISP Technologies, USA), two grades of sodium carboxymethylcellulose (Cekol 30[®] and Cekol 300[®], Nijmegen, Metsa-Serla, Holland), polyvinyl alcohol, 98-99% hydrolyzed (Aldrich Chemical, USA), ethenyl ester polymer with 1-ethenyl-2-pyrrolidinone or vinyl pyrrolidone/vinyl acetate copolymer (Plasdone S-630[®], ISP Technologies, USA). A plasticizer, polyethylene glycol 1500 (Merck-Schuchardt, Germany), a fatty acid, citric acid 1-hydrate GR (Merck, Germany) and the

sodium salt of a long-chain fatty acid, sodium oleate (BDH Chemicals Ltd, England) were also studied. The additives were investigated for their influence on the mechanical properties of HPMC cast films. Hydrolyzed polyvinyl alcohol (PVA), vinyl pyrrolidone/vinyl acetate copolymer (S630) and polyethylene glycol 1500 (PEG 1500) were additives that were further investigated for their effect on film coating solutions and film coats of HPMC E3 LV. (Abbreviated name and composition of additives are shown in Appendix I.)

Three long-chain fatty acids were included in the study. They were lauric acid, $C_{12}H_{24}O_2$ (Merck-Schuchardt, Germany), palmitic acid, $C_{16}H_{32}O_2$ (Merck-Schuchardt, Germany) and oleic acid, $C_{18}H_{34}O_2$ (BDH Chemicals Ltd, England). As the long-chain fatty acids were not soluble in water, they were first dissolved in absolute ethanol B.P. before incorporating into the HPMC solutions. Their concentrations were $\leq 1\%$ in view of the difficulty in incorporating the ethanolic fatty acids. The additives and their concentrations are listed in Table 3.

Table 3. Concentrations of additives employed in film coatings.

HPMC E3 Films	Additive	*Concentration (%)
Cast film for moisture permeation test only (3 % w/w solid)	Plasdone K90	1, 5, 10
	Plasdone C15	1, 5, 10, 20
	Cekol 30	10
	Cekol 300	10
Cast film for moisture permeation & mechanical tests (3 % w/w solid)	Polyvinyl alcohol	5, 7.5, 10, 15, 20, 30
	Plasdone S-630	5, 7.5, 10, 15, 20, 30
	PEG 1500	5, 7.5, 10, 15, 20, 30
	Citric acid	5, 10, 20, 30
	Sodium oleate	5, 10
Cast film for moisture permeation & mechanical tests incorporated with long-chain fatty acids (3 % w/w solid)	Lauric acid	0.05, 0.1, 0.2, 0.3, 0.5, 1.0
	Oleic acid	<i>(Concentrations were the same for all fatty acids.)</i>
	Palmitic acid	
(i) Film coat for film thickness & butt adhesion tests	Polyvinyl alcohol,	10
(ii) Cast film for glass transition and surface roughness tests (8 % w/w solid)	Plasdone S-630	10
	PEG 1500	10

* based on dry weight of total solid content

A.3. Desiccants

Desiccants used for forming a dry gradient for the moisture permeation tests were anhydrous calcium oxide (Merck, Germany) and silica gel, blue with indicator, 2-5 mm (Sino Chemicals, Singapore). The water vapour permeability of HPMC films were mostly evaluated using modified screw-capped narrow neck bottles containing calcium oxide. HPMC films incorporated with fatty acids as additives were tested using a permeation cup to facilitate a larger test surface area. This was because the quantity of such additives was small, ranging from 0.05 to 1% based on the total solid dry weight and the effect would be more observable with a larger test surface area. The permeation cups were similar in design to the one described in the ASTM Method but were smaller and made of stainless steel instead of aluminium.

A.4. Tablet core

Capsule-shaped lactose tablets or caplets were prepared as cores for coating. These caplets were made with the following specifications.

Weight (mg):	650
Thickness (mm):	6.6-6.7
Surface area (mm ²):	300
Hardness (Kp):	12.1-17.8
Disintegration time (min):	5 minutes
Friability (%):	0.35

B Methodology

B.1. Preparation of HPMC Solutions

As powders of cellulose ethers tend to swell strongly in water and form clumps but are less soluble in hot water because of reduced hydration, HPMC had to be first suspended in hot water and then cooled down by stirring with cold water. HPMC was dispersed in about 50% of the water heated to above 80°C. The additive, previously dissolved in water, was incorporated gradually with vigorous stirring. The dispersion was then transferred to an ice bath for rapid hydration. Water was added to make up to weight, followed by further agitation (i) by stirring with a magnetic stirrer at 500 rotations min⁻¹ for 30 min for solutions to be used for casting films or (ii) by using a turbine homogenizer (L4R, Silverson Machines, England) at high speed for 20 min for the film coating solutions. When the additive was a long-chain fatty acid, i.e. lauric, oleic or palmitic acid, the fatty acid was first dissolved in 30 ml of absolute ethanol. The ethanolic fatty acid solution was incorporated into the HPMC solution by using the homogenizer at high speed for 10 minutes. The emulsifier head was rinsed with some water and wiped dry. The solution was made up to weight, followed by further agitation as described in method (ii). This was because homogenization was more effective than incorporating the fatty acid by stirring into the HPMC solution. All the solutions were then allowed to hydrate overnight at 5°C and equilibrated to room temperature before use.

B.2. Preparation of Cast Films

Films were cast using 19.999 to 20.005 g of film casting solution using even and flat glass plates of 97 mm diameter. These were placed on glass slabs previously leveled with a spirit level in a hot air oven set at 45°C for 24 h. The oven was validated for uniformity of drying. This was determined by the rate of water evaporation in different parts of the oven. (Figure 1). Casting plates containing HPMC solutions were placed in positions where the rate of evaporation was from 0.7 to 0.9 g h⁻¹.

Dried films were harvested, sealed in a polyethylene bag and kept in an environment-controlled room set at 25°C ± 1°C and relative humidity of 55 ± 5%. Sample preparation for both moisture permeation and mechanical tests were carried out in this room where the films had been conditioned for not less than 5 days.

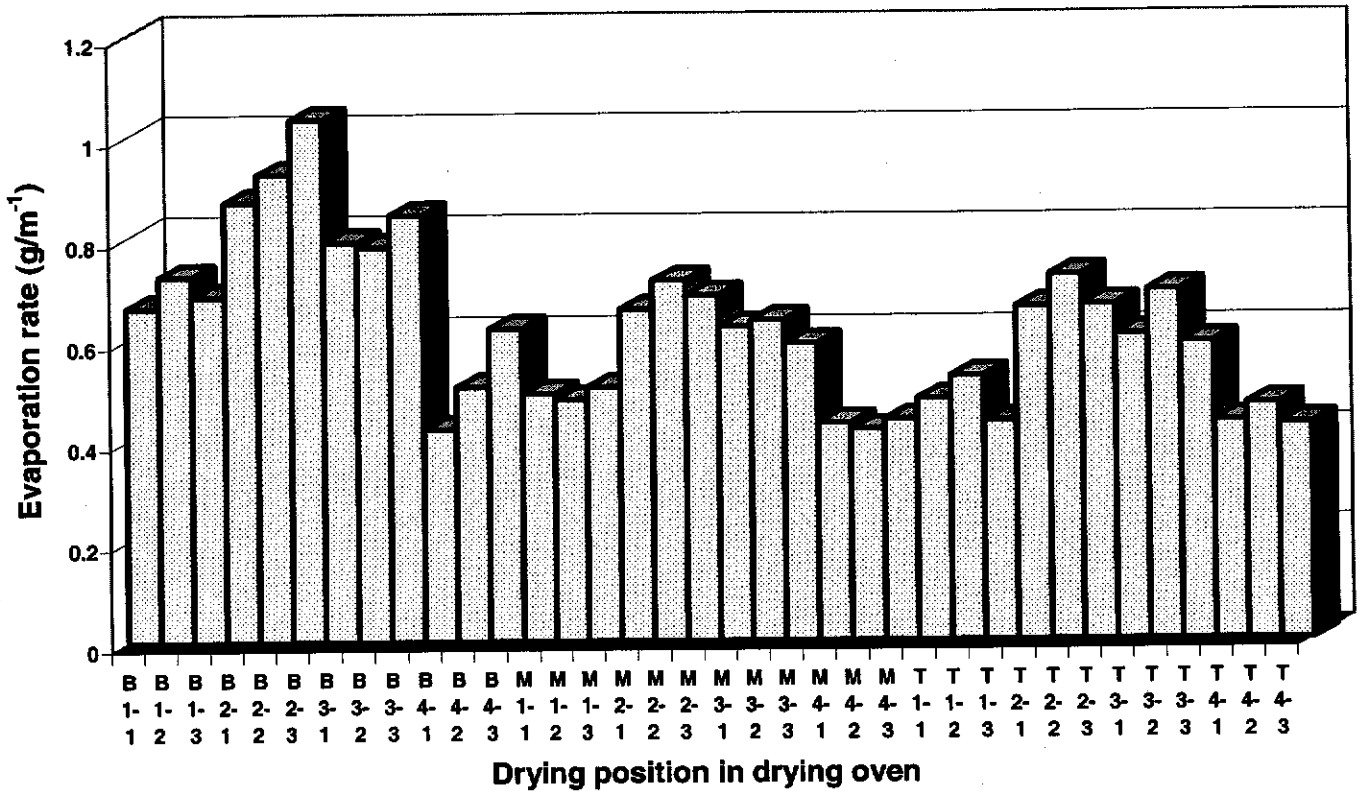


Figure 1. Heat distribution in drying oven as shown by the rate of evaporation: shelf positions at B (bottom), M (middle) and T (top); top digit represents the row position from left (no.1) to right (no.4) and bottom digit represents the position of the jar from the front (no.1) to back (no.3).

B.3. Determination of Apparent Viscosity

Viscosity of the 3% w/w HPMC solutions with and without additives was measured using a rotational viscometer (LV1, Brookfield Engineering Lab, USA) with spindle no. 1 attached, rotating at shear rates of 12, 30 and 60 rotations min^{-1} at 25°C. The spindle was immersed in the solution contained in a 400 ml tall-form beaker. Three readings were taken at each shear rate. The apparent viscosity was obtained as a quotient by multiplying the dial reading with the multiplying factor for shear stress with the shear rate from the spindle velocity.

For the HPMC solutions with fatty acids, the flow time was measured using a U-tube viscometer of size C. The flow time was used to indicate the viscosity of solutions. U-tube, size C, has a nominal viscometer constant of $0.03 \text{ mm}^2 \text{ s}^{-1}$ and a kinematic viscosity range of between 6 to $30 \text{ mm}^2 \text{ s}^{-1}$. The viscometer was clamped in a constant temperature bath (TCV 40, Tamson, England) set at 32°C. The determinations were carried out in triplicate and the results averaged. The viscosity of the test solution was calculated from the following equation:

$$\nu = K (t_1 / t_2)$$

where ν is the viscosity of the test solution, K is the constant, t_1 and t_2 are the flow times of test solution and water respectively.

Viscosity of 8% w/w solid content solution used for film coating was obtained using a rheometer installed with analytical software (RheoStress 1 with RheoWin QC, HAAKE Instruments, USA). Measurement was made using the Z10 DIN sensor at shear rates of 50 to 500 rad. s^{-1} and the temperature was controlled by a thermocontroller

(DC30, ThermoHaake, HAAKE Instruments, USA) for various temperatures from 30°, 40°, 45°, 50°, 55°, 60°, 65°, 70° to 80°C. Three replicates from each formulation were determined and viscosity values obtained at 300 and 450 rad s⁻¹ were used for comparison.

B.4. Moisture Permeation Tests

B.4. (i) Modified screw-capped bottles containing calcium oxide

Disks of 20 mm diameter were cut from cast films, using only films with thickness of 0.08 ± 0.01 mm. The test disk was clamped between two sets of polyethylene (PFTE) and stainless steel gaskets. The diameter of the gaskets was 19 mm and each had a central bore of 12 mm diameter to facilitate an exposed area of 1.13 cm². The washers with the film disk were secured using an aluminium screw cap with a central opening over a 28 ml glass bottle. Each bottle contained 20 ± 0.001 g of calcium oxide, to produce a gradient for moisture permeation across the film. The bottles were placed in a controlled environment chamber (KBF 115, WTC Binder, Germany) set at 25°C and 75% relative humidity. Two controls, one without a barrier film and the other with a 0.08 mm thick polyethylene film in place of a sample, were also included. The samples were weighed periodically using an electronic precision balance (A200S, Sartorius, Japan) over a period of 30 ± 1 days. The experiment was performed with five replicates. The result for moisture permeation was obtained by plotting the gradient of the slope formed by weight gained from moisture transmitted across the film over the

test period in days against the concentrations of additive. Only films with 0, 5, 10, 20 and 30% additive were used for moisture permeation tests.

B.4.(ii) Moisture permeation cell containing silica gel

HPMC film samples incorporating long-chain fatty acids were tested using a “Moisture, Air & Temperature Perm Cup”, similar in design to the one designated in ASTM Method D1653. However, the permeability cup for measuring vapour transmission of materials was of different dimensions from the ASTM standard and was constructed with stainless steel instead of aluminium. Both diameter and depth of the cup cavity were 25 mm, resulting in a face opening of 4.91 cm² and a volume of 12.28 cm³. Each contained 10g of silica gel. The test sample was clamped between two gaskets, one made of teflon and the other of rubber. The gaskets had the same dimensions as the clamp ring with a central bore of 25.0 mm diameter and the outer diameter of 37.5 mm. Test samples of the cast films were cut to the outside dimensions of the clamp ring, resulting in circular disks with a thickness of 0.08 ± 0.01 mm. The sample was mounted on top of the moisture permeation cup and secured with the clamp ring engaged to two stainless steel pins on the top surface of the cup, leaving an exposed film area of 4.91 cm². The set-up was sealed against the cup surface by tightening the cap that had a central opening exposing the test area. Two samples from the same film, i.e., one from the outer surface exposed to the environment and the other from the inner surface against the surface of the plate, were tested. The permeation cups were placed in the same controlled environment chamber with similar temperature and humidity

settings as described in moisture permeation test (i). The samples were accompanied by two controls, one without silica gel and the other with silica gel but had a 0.08mm thick polyethylene film in place of a film sample. The samples were weighed every 2 h for the first 6 h, followed by measurements taken at 24-h intervals for the next 4 days using an electronic precision balance (PG 1003-S, Mettler Toledo, Japan). After every weighing, the cup was gently shaken to redistribute the silica gel. Unlike the narrow-neck screw capped bottles used in method (i), the larger surface area of the permeation cells limited the test period to a few days instead of 30 days. The experiment was performed with three cast films for any film formulation. The results for moisture permeation were obtained by plotting the gradient from the slope formed by weight gained from moisture transmitted across the film over test period in days against the concentrations of additive.

B.5. Surface Roughness Analysis

Surface roughness of the cast films made from the 8% solid solution was determined using a scanning probe microscope (SPM-9500J, Shimadzu, Japan). The films were dried in the same oven under similar conditions as those with 3% solid. The plates of dried films were stored in a desiccator for 2 to 3 days. Each sample was measured at 3 sites on both surfaces of the film, one side exposed to the environment and the other, against the surface of the plate. Maximum scanning height for each test was set at 1 nm and 2 nm simultaneously. Measurements were in triplicate and results averaged.

B.6. Determination of Glass Transition Temperature

The films with 8% solid content were left to equilibrate in a desiccator for not less than 2 days before determining the glass transition temperature using a differential scanning calorimeter (DSC-50, Shimadzu, Japan). The sample was first heated at 20°C min⁻¹ to 160°C. This step was to remove moderately bound moisture so that its endotherm would not obscure the desired thermal transitions (Okhamafe & York, 1987). It was then rapidly cooled to 25 ± 1°C and reheated at 20°C min⁻¹ to 200°C. Accurately weighed samples between 5 to 6.4 mg were placed in crimped aluminium sample pans and the T_g determined from the thermograms of reheated samples. Triplicate measurements of HPMC films with each type of additive were performed and the T_g determined from the thermograms of reheated samples. Triplicate measurements were carried out and the mean indices taken to determine the T_g.

B.7. Film Coating

Coating of caplets was carried out using a hybrid vertical fluidized tablet coater (Ultra-coater MP1, Aeromatic-Fielder, UK). This is a unique coater that utilizes a perforated peripheral coating chamber. The spray nozzles are in fixed positions very close to the tablet bed to minimize the distance of travel for the solution droplets to the coating zone. Air volume was kept constant and the temperature and humidity during the process were closely monitored and controlled.

A 5-kg load of caplets was coated with 3 kg of coating solution. The coater was connected to a peristaltic pump (504U, Watson Marlow, England) for delivering coating solution at a controlled rate. The tubing of the pump was dipped in the solution contained in a 5-L beaker standing on a magnetic stirrer. The solution was stirred very gently throughout the coating process. Both beaker and magnetic stirrer were placed on a heavy-duty electronic balance (EB 3200H, Libror, Shimadzu, Japan). The other end of the tubing was connected to the two spray nozzles of the coater by means of a Y-connector. Coating solution was sprayed tangentially using a pair of diagonally arranged two-fluid spray nozzles set at 40° from the normal in the direction of the tablet flow. Different coating parameters, such as pump flow rate, atomizing pressure, air flow rate and rotating speed of the rotating disk in the coating chamber, were used to determine the optimum operating conditions as listed in Table 4.

Table 4. Experimental and optimal parameters used for coating the caplets.

Process conditions	Settings	
	Experimental	Optimal
Batch size of caplets (kg)	3, 4 & 5	5
Pump flow rate (%)*	12, 13, 14 & 15	12 & 13
Atomizing pressure (bars)	2.5 & 3.0	3.0
Air flow rate (m ³ h ⁻¹)	60 & 70	70
Inlet air temperature (°C)	80	80
Disk rotating speed (rotations min ⁻¹) - during coating process - during post-drying phase	20, 22, 25 & 30 12 - 15	22 15

*Pump flow rate at 12 and 13% was equivalent to 13 and 16 ml min⁻¹, respectively.

B,8. Determination of Film Thickness

B,8.(i) Cast film from solution with 3% solids

Thickness of the cast films was measured using a thickness gauge (7305, Mitutoyo, Japan). The film disk for the moisture permeation test was measured at 4 points in different directions whereas the mechanical test sample was measured at 5 equidistant points along the entire film of 50 mm x 10 mm. Only samples that met the specifications of $80 \pm 10 \mu\text{m}$ and $85 \pm 10 \mu\text{m}$ for the moisture permeation and the mechanical tests respectively, were used. Samples not within the desired thickness and uniformity were rejected.

B,8.(ii) Film coat from solution with 8% solids

A thin and uniform cross-section of a coated caplet was cut with a sharp cutter. The film coat thickness was measured by placing the cut sample (Figure 2) under a stereomicroscope (SZH, Olympus, Japan), equipped with a video camera (CCD-IRIS, Sony, Japan) and displayed on a monitor (PVM145E, Sony, Japan). The image was analyzed using a computer program (Foster Findlay Synoptics System, PC-Image.) The microscope was calibrated with a 10 mm stage micrometer, giving a resolution of $3.7879 \mu\text{m}$ per pixel. Thickness of the film coat was measured using digital vernier calipers (500-216, Mitutoyo, Japan) connected to a digimatic mini-processor (DP-1AT, Mitutoyo Japan). Ten cut samples were used to determine film thickness from each

batch of coated caplets. For every sample, thickness was measured at 10 points along the section of film coat and the mean of all thickness values of each batch calculated.

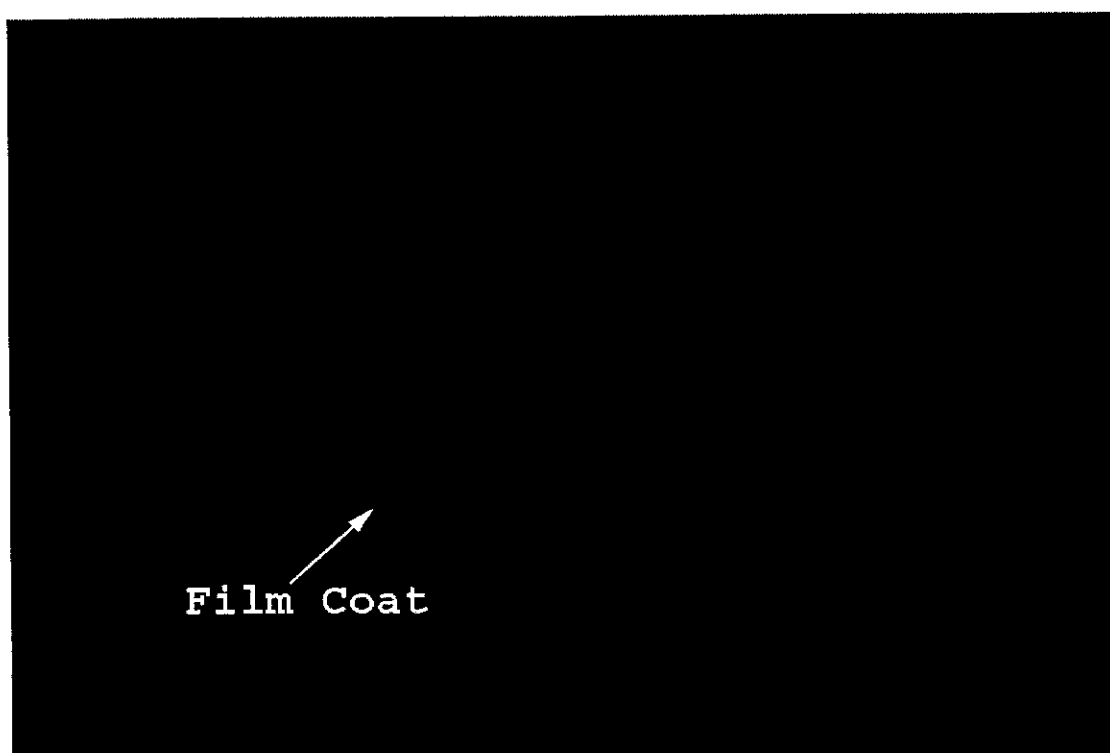


Figure 2. Cut caplet sample for the film coat thickness measurement.

B.9. Evaluation of Mechanical Properties of Cast Films

The mechanical properties of both the free and coated films were determined using a tensile tester (E-Z Tester, Shimadzu, Japan) with a 100 N load cell and crosshead speed of 10 mm min⁻¹. Tensile tests were performed on 50 mm x 10 mm samples of free film strips. Stress-strain curves giving maximum stress, elastic modulus, strain at break (% elongation) and work of failure (area under the curve) were obtained. Measurements were taken under environmental conditions of 25°C ± 1°C and 55 ± 5% relative humidity.

Sample strips were cut from the cast films. Each strip was mounted on a thin rectangular cardboard frame, 80 mm x 30 mm, with a central opening of 50 mm x 20 mm. The sample was mounted centrally on the frame, allowing a test strip of 50 mm x 10 mm. The two sides of the sample frame were cut after the film was clamped in position with the upper and lower grips of the E-Z tester. The tensile test for the cast film was carried out with the initial gauge length of 50 mm and a crosshead speed of 10 mm min⁻¹. Sample preparation was carried out in the same environment as the test. Ten samples, each with a thickness of 85 ± 10 µm, were tested for each formulation. Films with large variations in thickness or noticeable deformities were rejected. Special care was taken to avoid jagged edges that would produce stress concentration. Films with concentrations of S630 above 15% w/w of the solid content dry weight could not be used for tensile testing as they adhered strongly to the casting plate and were difficult to peel.

B.10. Evaluation of Adhesive Properties of Film Coats

A modified butt adhesion test was employed to test the film coat – substrate surface adhesion. The adhesion tests were performed on coated caplets with truncated ends, using the tensile tester at initial gauge length of 24 mm and crosshead speed of 200 nm min⁻¹. A 6.25 mm wide adhesive tape was attached centrally around the circumference of the test caplet, leaving a short length of folded tape to be clamped to the upper grip of the tester. The ends of the caplet were cut off, resulting in a sample width of approximately 8.5 mm. The film on the coated caplet surface nearest to the folded part of the tape was carefully detached and lifted up together with the attached tape for clamping to the upper grip to facilitate the peel test. A custom-designed tablet holder (Figure 3) was fitted to the tester in place of the lower grip. The truncated caplet was held in place by a pin one each side of the holder. The pins secured the sample yet allowed free rotation for peeling the film supported by the adhesive tape attached to the film coat. Adhesive strength and toughness were determined from stress-strain curves similar to those from the tensile test of cast films. Twenty samples from each batch of coated caplets were evaluated. For control, a piece of non-stick tape wrapped tightly twice around the circumference of an uncoated caplet was unrolled. As the length of tape to be detached from the caplet was twice that of the test sample, the area under the curve would be affected. Maximum adhesive force of the film coat was corrected by subtracting the measured value with the value obtained from the control. A total of at least five replicates were carried out and the results averaged.

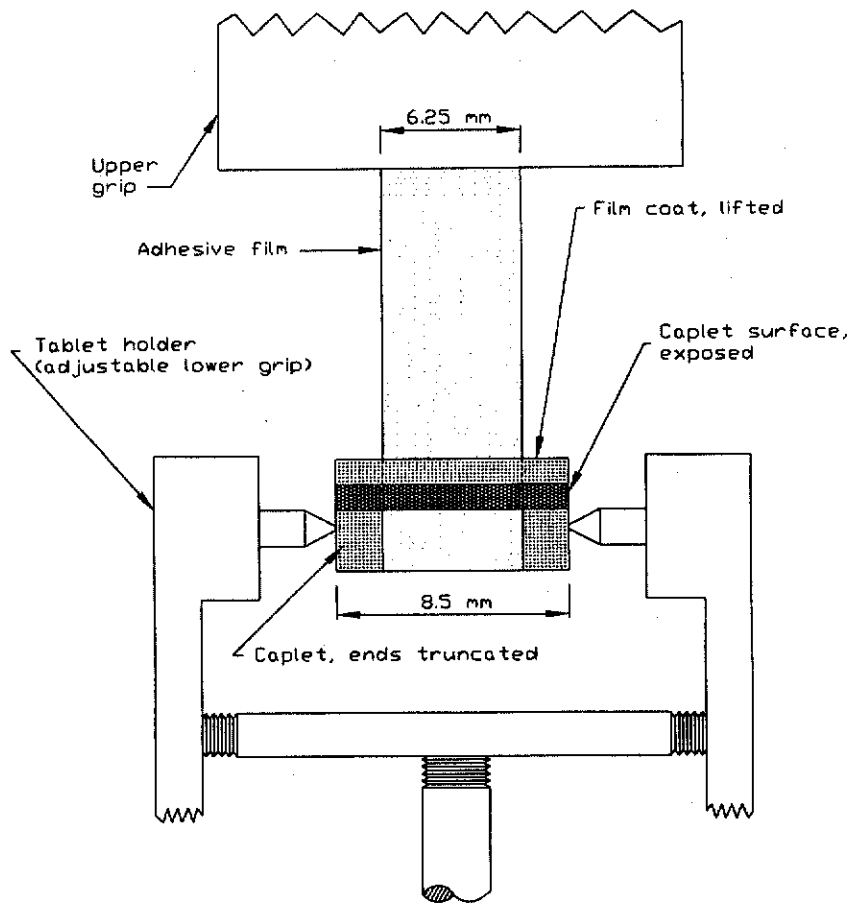


Figure 3. Custom-designed tablet holder for the modified butt adhesion test.

RESULTS AND DISCUSSION

A. Appearance of cast films

HPMC films, E50, F50 and K100 were smooth, clear and colourless. However they were hard and stiff owing to their high viscosity grade. Films from the HPMC E series had similar good physical appearances. Their thickness varied with the viscosity grades, with the more viscous solutions producing thicker and stiffer films. For film coating, it would be ideal to use a low viscosity grade HPMC. Hence, HPMC E3 LV was the polymer used for the coating processes in this study.

Unplasticized HPMC E3 LV films were clear, transparent and colourless. When cast, they were not strongly adhering and could be easily detached from the surface of the casting plate. Some portions, particularly at the edges were self-detached from the glass surface. The inclusion of additives resulted in changes to the appearance of the films with regard to their clarity varying from clear to hazy and the appearance of spots and patches resulting from their incompatibility and separation.

HPMC generally produce an excellent film coat but there were instances where there were difficulties relating to the ability of the film coat to adhere satisfactorily to the tablet surface (Lehtola et al., 1995). Adhesiveness, as observed by the extent of the film sticking to the glass plate surface, was also altered by the inclusion of some additives. An additive may cause HPMC film to become more easily detached or adhered more strongly to the casting plate to the extent of being impossible to remove from the glass

surface. The appearances of HPMC E3 films incorporated with various concentrations of different types of additives are shown in the following table (Table 5).

Table 5. Physical appearance of HPMC films containing various concentrations of different additives.

Additive	Conc. (%) based on polymer dry wt	Appearance		
		Clarity	Adhesive	Spots / Patches / PS* & any other comment
Without additive (HPMC E3 only)		+++	++	
Plasdone K90	1, 5, 10, 20, 30, 40	+++ +	+ ++++	Patches, spots & PS
Plasdone C15	1, 5, 10, 20, 30, 40	+++ +++ +++	++ ++++	<i>Brittle</i>
Cekol 30	10	+++	+++	Spots
Cekol 300	10	+++	+++	
Polyvinyl alcohol	5, 7.5, 10, 15, 20, 30	+ +	>5% +++ 30% ++++	Spots Spots++
Plasdone S-630	5, 7.5, 10, 15, 20, 30	+++ +++	++ ++++	
PEG 1500	5, 7.5, 10, 15, 20, 30	(+++)* (+)* (+)*	+ ++++ ++++	Spots+ Patches & spots+ <i>Corrugated & soft</i> Patches & spots ++ <i>Corrugated & soft</i>
Citric acid	5, 10, 20, 30	+++	++	
Sodium oleate	5, 10	+	+	Spots++ <i>Brittle</i>
Lauric acid C ₁₂ H ₂₄ O ₂	0.05, 0.1 0.2, 0.3 1.0	+++ ++ +	++ ++ ++	PS
Palmitic acid C ₁₆ H ₃₂ O ₂	0.05, 0.1 0.2, 0.3 1.0	+ + +	+++ ++ 	<i>Brittle</i>
Oleic acid C ₁₈ H ₃₄ O ₂	0.05, 0.1 0.2, 0.3 1.0	++ ++ +++	++ + +	Spots* Patches++

Ratings for Table 5:

<i>Clarity</i>	<i>+</i>	<i>=</i>	<i>hazy, not clear at all</i>
	<i>++</i>	<i>=</i>	<i>not very clear, slightly hazy throughout or in some sections</i>
	<i>+++</i>	<i>=</i>	<i>clear & transparent</i>
	<i>()*</i>	<i>=</i>	<i>became hazy (+) upon exposure</i>
<i>Adhesive</i>	<i>+</i>	<i>=</i>	<i>easy to peel , with films "popped away" from surface</i>
	<i>++</i>	<i>=</i>	<i>not very adhesive, with edges "lifted up" or surface undulating</i>
	<i>+++</i>	<i>=</i>	<i>adhesive, some parts stick to plate/with slight "crumpled" edges</i>
	<i>++++</i>	<i>=</i>	<i>very adhesive, stick strongly to glass surface, not peelable</i>
<i>Spots/patches</i>	<i>+</i>	<i>=</i>	<i>few and scattered</i>
	<i>++</i>	<i>=</i>	<i>many or large areas</i>
<i>PS</i>		<i>=</i>	<i>signs of phase separation</i>

Generally water soluble additives, such as sodium carboxymethylcellulose, polyethylene glycol, polyvinylpyrrolidone and citric acid, are miscible with aqueous HPMC solutions. Hence, films with these additives had good clarity and appearance, similar to those without any additive. HPMC-S630 films had equally good physical appearance but were considerably more adhesive. Films with more than 10% S630 had portions adhering very strongly to the glass surfaces. Nonetheless, such films were also evaluated for their moisture permeability and mechanical properties unless it was not possible to obtain suitable size test sample. HPMC films with polyvinylpyrrolidone, Plasdone K90 and Plasdone C15, had physical appearances and adhesion levels similar to those of S630. At 10% concentration, sodium carboxymethylcellulose, Cekol 30 and Cekol 300, produced clear and more adhesive HPMC films. However, some spots were seen in the HPMC-Cekol 30 films. Phase separation was observed in HPMC solution containing Plasdone K90 at concentrations of 20% and above.

PEG 1500 is very soluble and HPMC films plasticized with less than 20% PEG appeared satisfactory immediately after harvest but hazy patches developed during storage. Similar films with concentrations of 20% or higher were not clear but hazy in appearance with signs of blooming. The reason for this observation was the co-additive's solubility and compatibility, causing the excess plasticizer to be separated and reassembled as tiny spots on the surface of the film. This phenomenon has been reported by Aulton et al. (1981). Upon exposure to more humid environments of a relative humidity of 60% or higher, HPMC-PEG films also turned hazy and had an oily feel. Moisture enhanced this effect shown by PEG as it facilitated the uptake of water vapour, making the films soft, flexible and moist.

Additives that were difficult to dissolve in water, such as sodium oleate and PVA, resulted in the appearance of hazy patches or hazy films. This effect was due to the incompatibility of the additive with HPMC or when the concentration of additive exceeded the limit where it could remain in solution. HPMC films, in which PVA was incorporated, were not transparent but translucent in appearance with “honeycomb-patterned” patches and raised spots, more evident with increased PVA concentration. This was attributed by Okhamafe and York (1983) to PVA being separated from the system after it had exceeded the level at which it was compatible or soluble in HPMC. Films with 30% PVA were covered with white spots that adhered to the glass plate surface, resulting in most films being punctuated with little holes upon harvesting. Nonetheless, such films were also evaluated for their moisture permeability and mechanical properties. Care was taken to select films without any holes for the moisture permeation test so that the integrity of the test sample was not compromised. This was carried out by putting harvested films against a light source and visually picked out films that have no detectable puncture holes. Additives, such as Plasdone K90, also affected HPMC film appearance only when used above a 10% concentration level.

The long-chain fatty acids were insoluble and there were difficulties incorporating the ethanolic fatty acids in the aqueous HPMC solutions. In spite of the low concentrations used, the fatty acids had a significant influence on the appearance and adhesiveness of HPMC films. Both oleic and palmitic acids with longer carbon chains of 18 and 16 carbon atoms respectively, affected the appearance of HPMC films even at concentrations as low as 0.05%. HPMC-palmitic acid films were hazy in appearance. Lauric acid, however, did not affect the appearance when incorporated at

concentrations of 0.1% and below. Above 0.1%, the deterioration in appearance was very prominent in HPMC films with lauric acid. When 1% lauric acid was incorporated, phase separation of the HPMC solution was observed. Both palmitic and oleic acid had reduced adhesiveness when used above a 0.1% concentration. HPMC films with 1% palmitic acid were brittle.

B. Apparent Viscosity of HPMC solutions

Viscosity measurement is one of the simplest means of investigating the molecular interaction of components in a polymeric solution. Except for the solutions that included fatty acids, the apparent viscosity of HPMC solutions was measured using rotational viscometers with variable rates of shear. This is useful for evaluating the effects of concentration on the viscosity of a polymeric solution that may exhibit pseudoplastic behaviour where there is a progressive fall in viscosity as the shear rate increases.

The capillary U-tube viscometer was used for fatty acids because low concentrations of 1% and below were incorporated.

B.1. The apparent viscosity of (i) low viscosity grade HPMC E series and (ii) 3% w/w HPMC E3 solutions containing various concentrations of different additives, measured with the Brookfield rotational viscometer.

The six grades investigated were E3 Prem LV[®], E5 Prem LV[®], E6 Prem LV[®], E15 Prem LV[®], E50 Prem LV[®] and E4M Prem[®]. The number in the different grades identifies the viscosity in mPa s determined in water at 20°C at a concentration of 2%. E4M was the only high viscosity grade studied and the viscosity at 2% concentration in water was approximately 4,300 mPa s at 25°C. As the viscosity was high, it was not included in Figure 4 which provides data on the shear stress of solutions with various concentrations of different low viscosity grades in the HPMC E series. Viscosity was obtained by multiplying the dial reading with the multiplying factor for the test spindle and the shear stress was obtained by multiplying the viscosity by the shear rate in rotations per s, i.e. 0.2 and 0.5 rotations per s for 12 rpm and 30 rpm respectively.

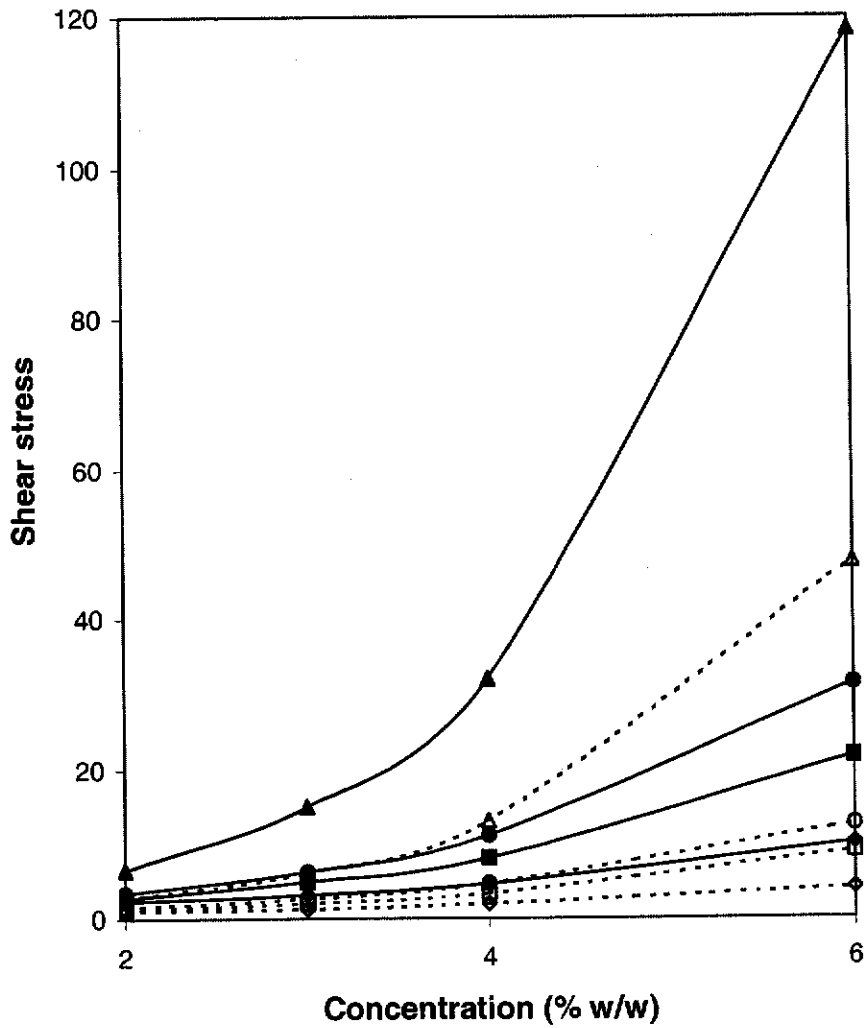


Figure 4. Shear stress of different viscosity grades of HPMC E series measured at shear rates of 12 rpm (opened symbols) and 30 (closed symbols) rpm. E3 (\diamond), E5 (\square), E6 (\circ) and E15 (\triangle). (Bars are +1 s; n = 3).

Viscosity measurement for 2, 3, 4 and 6% solutions from the HPMC E series showed that these solutions had non-Newtonian flow properties. The shear stress increased with increasing shear rates of 12 and 30 rpm or 0.2 and 0.5 rotations per s at 25°C. It was noted that at 2% w/w concentration, there was little difference in the shear stress for HPMC E3, E5 and E6. At the 6% concentration however, there was an approximately a 4-fold increase in shear stress for E3 and 17-fold increase for E15. E3 is the lowest viscosity grade in the series and had the lowest increase in shear stress with increasing concentration. In view of the advantage of using low viscosity grade HPMC for film coating, E3 was selected for further investigations.

Figures 5a and b show the shear stress of HPMC solutions with various concentrations of different additives determined under the same test conditions using the rotational viscometer. Similar trends were observed. Shear stress increased with increasing shear rate. Generally, additives that function as copolymers increase the apparent viscosity of HPMC solutions. The incorporation of 10% sodium carboxymethylcellulose, Cekol 30 and Cekol 300, resulted in a sharp increase in the viscosity of HPMC solutions, with Cekol 300 showing a more prominent influence. Plasdone K90 increased the apparent viscosity of HPMC solution proportionately with increasing concentration whereas the lower viscosity Plasdone C15 had less influence. PVA, a commonly used copolymer, increased the viscosity of HPMC to approximately the same extent as Plasdone C15. For the coating process, it is not recommended to use an additive that increases the viscosity of the film coating solution as this will lead to the formation of larger droplets and an increased likelihood of spray nozzle blockage (Aulton & Twitchell, 1995).

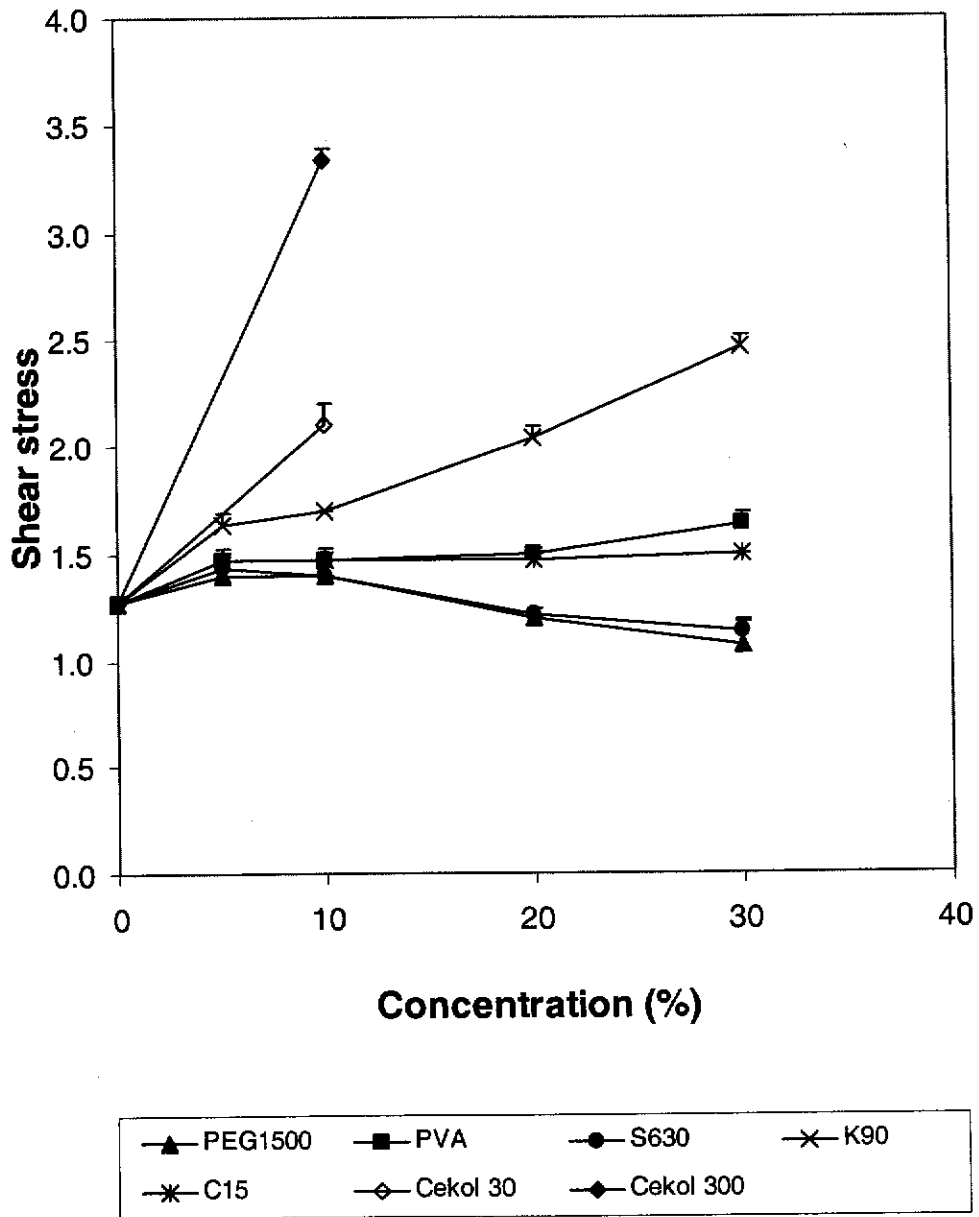


Figure 5a. Shear stress vs. concentration of different additives in HPMC solutions, measured at 12 rpm (0.2 rotation per s). (Bars are +1 s; n = 3) (Commercial name and composition are show in Appendix I)

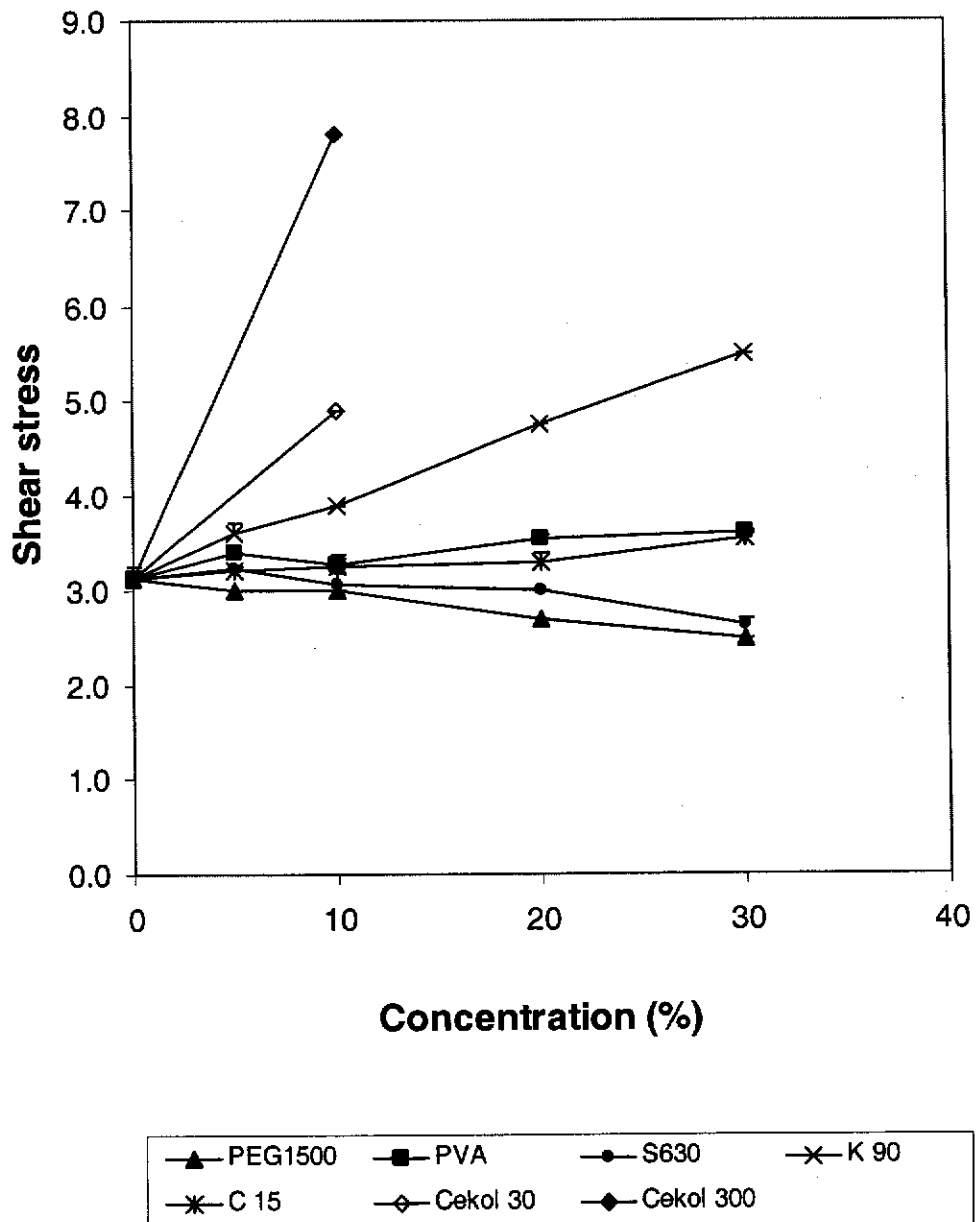


Figure 5b. Shear stress vs. concentration of different additives in HPMC solutions, measured at 30 rpm (0.5 rotation per s). (Bars are +1 s; n = 3) (Commercial name and composition are show in Appendix I)

From the viscosity results obtained, Cekol 30, Cekol 300 and Plasdone K90, were unsuitable as additives in HPMC coating solutions. Plasdone C15 had relatively little influence in the viscosity of HPMC solutions but the HPMC films containing above 10% C15 were brittle. Hence only PEG, PVA and S630 showed potential for use as an additive in HPMC film coating formulations.

The apparent viscosity of HPMC solutions containing the three selected additives, namely PEG, PVA and S630, was re-plotted in Figure 6. It shows distinctly that although S630 is a copolymer, its effect on viscosity appeared to be very similar to that of PEG 1500, a plasticizer. Except for a slight increase in viscosity at low concentration of $\leq 10\%$, increasing concentrations of both S630 and PEG 1500 lowered the viscosity of HPMC E3 solutions. The trend was reversed with PVA, another copolymer used in the study. PVA increased the viscosity of HPMC E3 solutions proportional to its concentration.

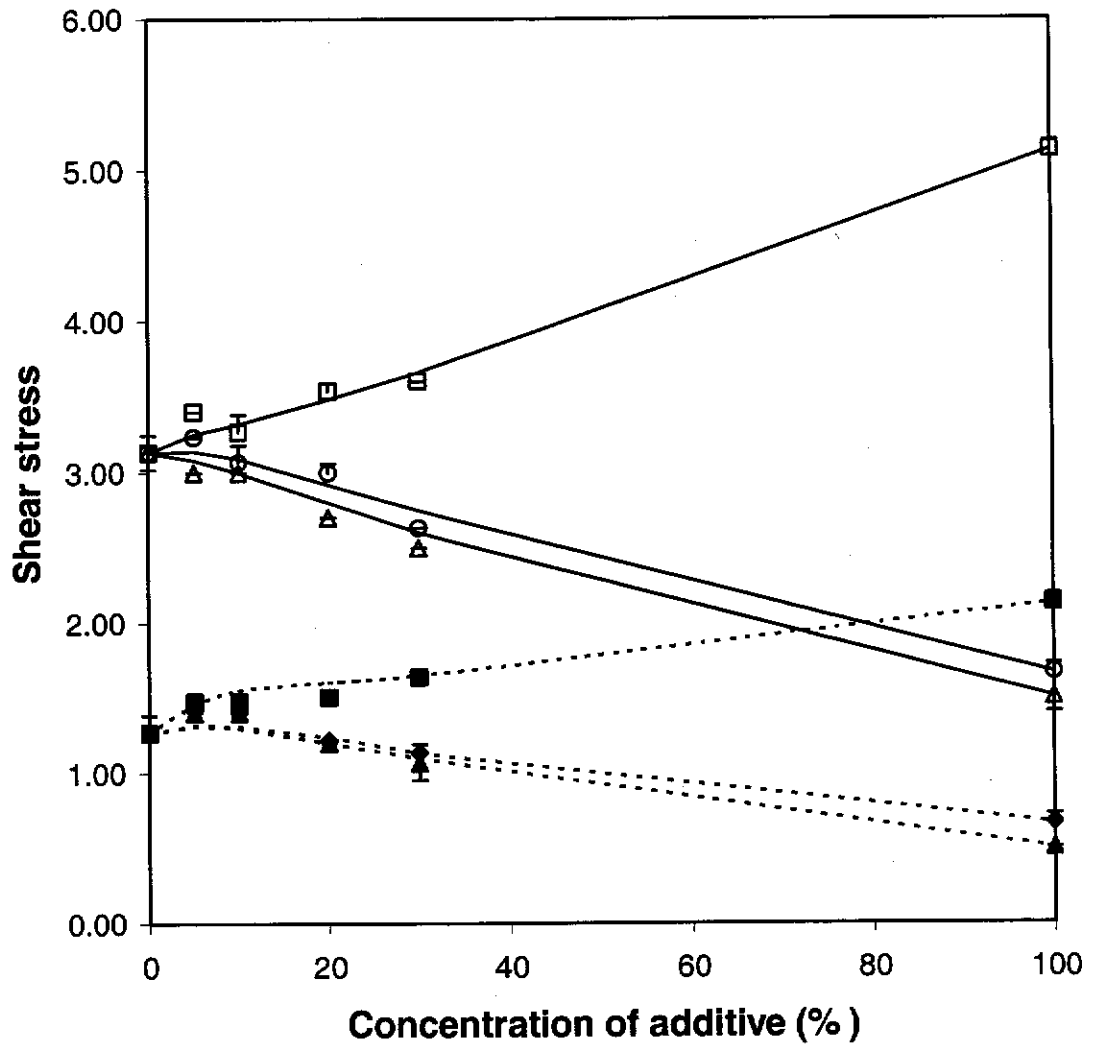


Figure 6. Shear stress of 3% HPMC solutions containing various concentrations of additives, PEG (▲ , △), PVA (■ , □) and S630 (● , ○), measured at shear rates of 12 rpm (closed symbols) and 30 (open symbols) rpm. (Bars are +1s; n = 3).

B.2. The apparent viscosity of HPMC E3 solutions containing various concentrations of different fatty acids, measured with the capillary U-tube viscometer.

The capillary U-tube viscometer is ideally used for measuring the viscosity of Newtonian liquids. However, in view of the low concentrations of fatty acids, 0.05 to 1.00%, incorporated in the HPMC solutions, the capillary U-tube viscometer was used to obtain the apparent viscosity of HPMC solutions containing fatty acids. Purified water was used as the reference. Viscosity in mPa s was calculated from the equation as given in the methodology. As shown in Figure 7, the viscosity of 3% HPMC E3 solution measured at 30°C was 4.15 mPa s. There was a sharp increase in viscosity when palmitic acid was incorporated. A concentration of 0.5% palmitic acid increased the viscosity of HPMC solution by 80%. Both lauric and oleic acids resulted in a slight increase at 0.4% concentration and above. From the results, palmitic acid was an unsuitable additive in HPMC solutions. Not only did it affect the physical appearance of HPMC films adversely, its effect of increasing the viscosity rendered it unsuitable as an additive for HPMC coating formulations.

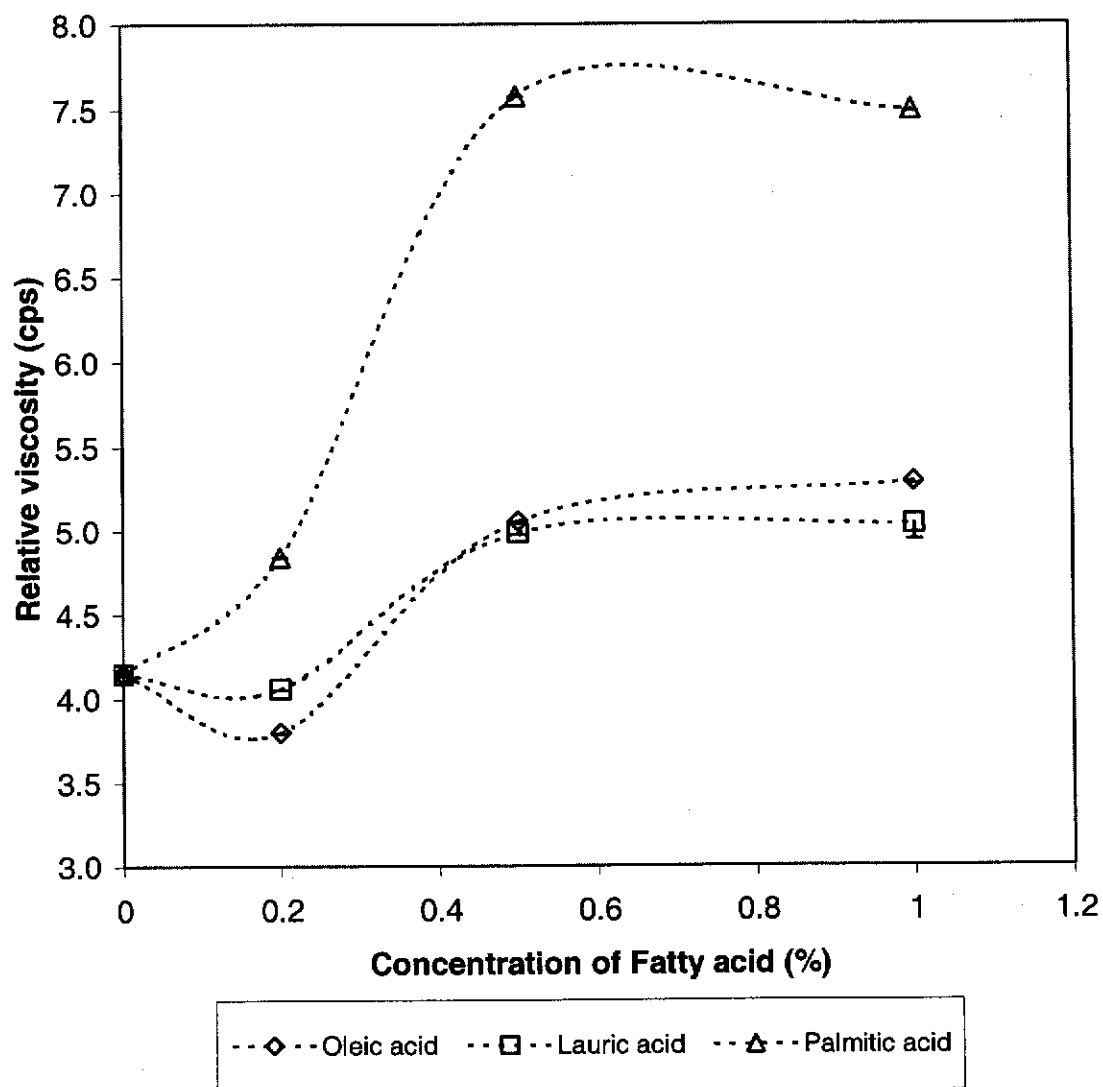


Figure 7. Relative viscosity of HPMC with varying concentrations of fatty acids.

(Bars are $\pm 1s$; $n = 3$).

B.3. Using a Haake viscometer for 8% w/w HPMC solutions

For solutions with 8% solids, viscosity measurements taken at shear rates of 300 and 450 rad min^{-1} from 30°C to 80°C were selected for evaluation. It was also noted that HPMC solutions, with or without an additive, had discontinuities in viscosity at temperatures between 50°C to 70°C, reaching a peak at 60°C (Figure 8). The discontinuity at 60°C may relate to a change in hydrogen bonding structure of HPMC at that temperature. Similar results to those with 3% solids were found. PVA increased the viscosity whereas S630 behaved like PEG 1500 in causing a slight reduction in the viscosity of HPMC solutions.

Generally, HPMC solutions exhibit pseudoplastic flow behaviour and pseudoplasticity increases with increasing molecular weight or concentration. Overall, the changes in viscosity with the incorporation of additives were small as the major factors controlling the formulations were the viscosity of the polymer grade being used and the concentration of polymer in the solution.

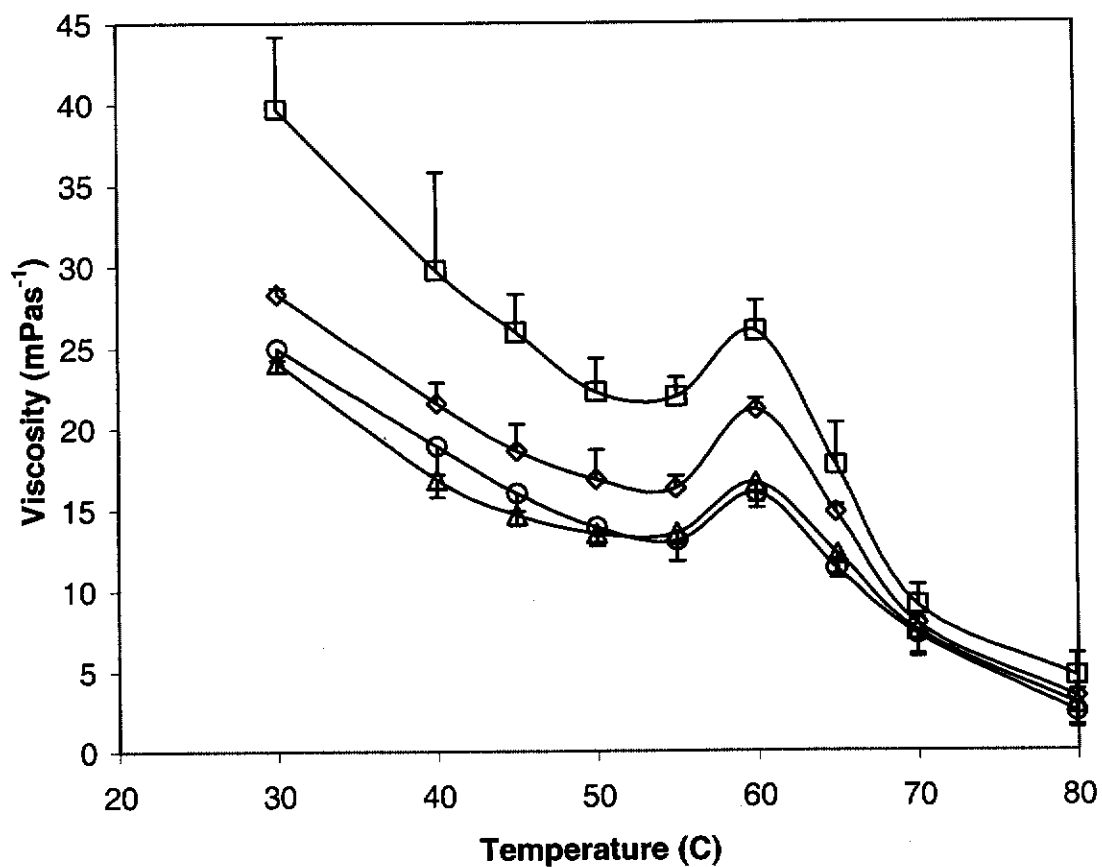


Figure 8. Apparent viscosity of 8% HPMC solutions at varying temperatures, measured at shear rate of 450 rad s^{-1} : without additive (◇) and with PEG(△); PVA (□); and S630 (○). (Bars are $+1\text{s}$; $n = 3$).

C. Moisture Permeation Tests

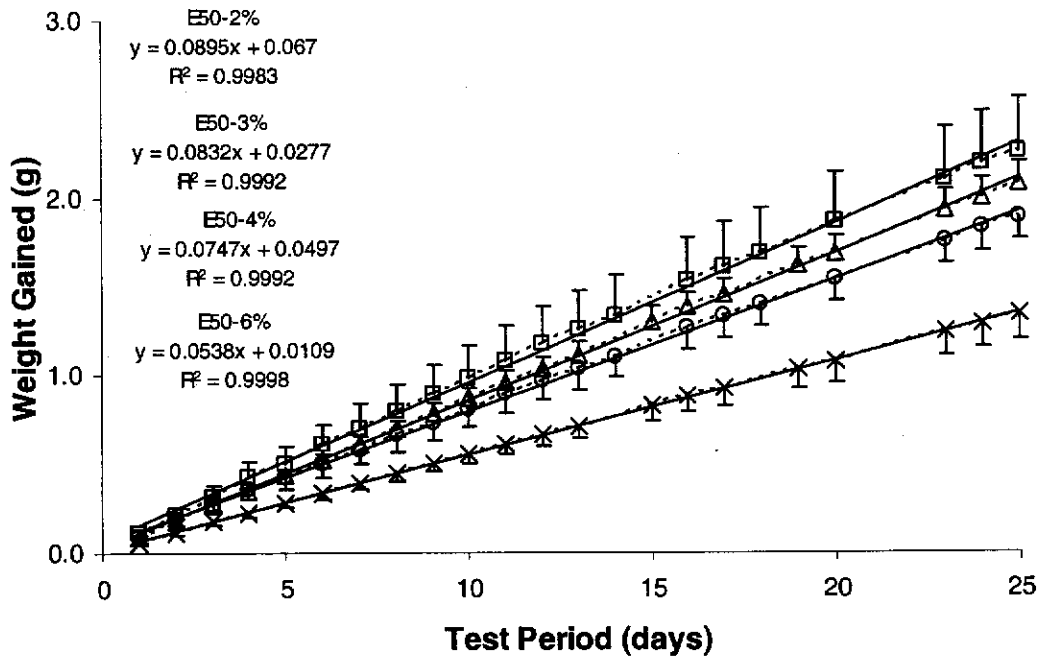
C.1. *Using modified screw-capped bottles containing calcium oxide*

The moisture permeation test using bottles containing calcium oxide provided a test area of 1.13 cm² film surface. The tests were carried out for (i) HPMC of different methoxyl substitution, (ii) different viscosity grades of HPMC E series and (iii) HPMC E3 containing different additives. The weight gained by water vapour permeating across the HPMC film from an environment of 75% relative humidity to that of low humidity provided by calcium oxide was noted. The weight gained was plotted against a test period of not more than 25 days as constant diffusion was observed in some test samples after this period. The rate of moisture permeation obtained from weight gained over days (gradient) was obtained from the trendline equation of the linear plot. This rate (g/day) was then plotted against the concentrations of additives. Examples of these plots are seen in Figures 9 and 10 respectively.

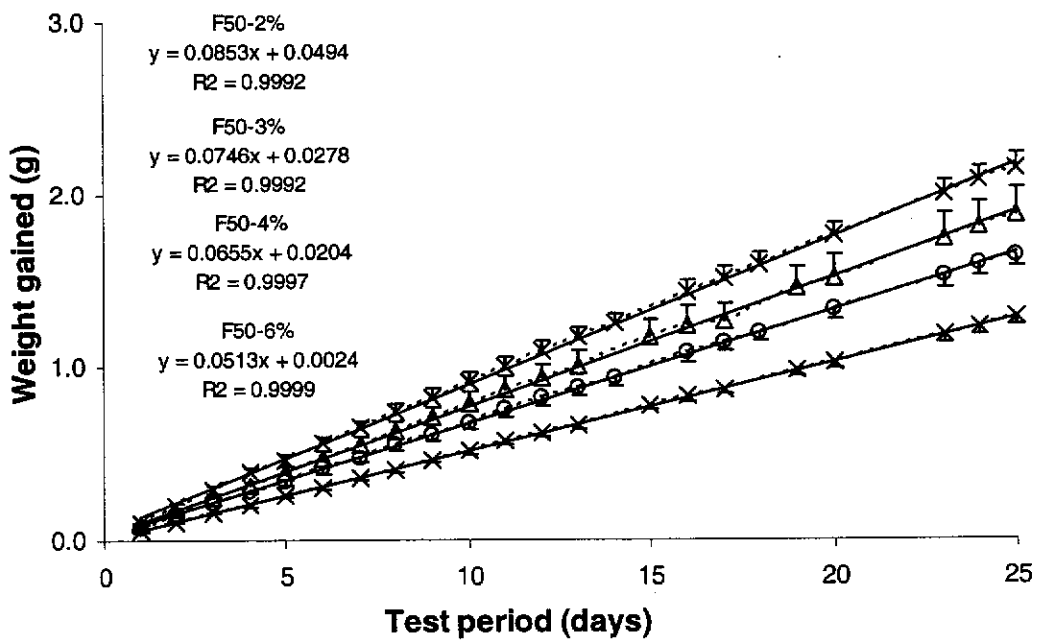
C.1.(i) HPMC of different methoxyl substitution

Figures 9 and 10 were plotted from results obtained from the moisture permeation test on different types of HPMC, namely E50, F50 and K100. Plots in Figure 9 show the amount of weight gained over the test period of 25 days from the moisture permeation tests. Figure 10 compares the moisture permeation rate (weight gained / day) obtained from the gradients in Figure 9 with the various concentrations of

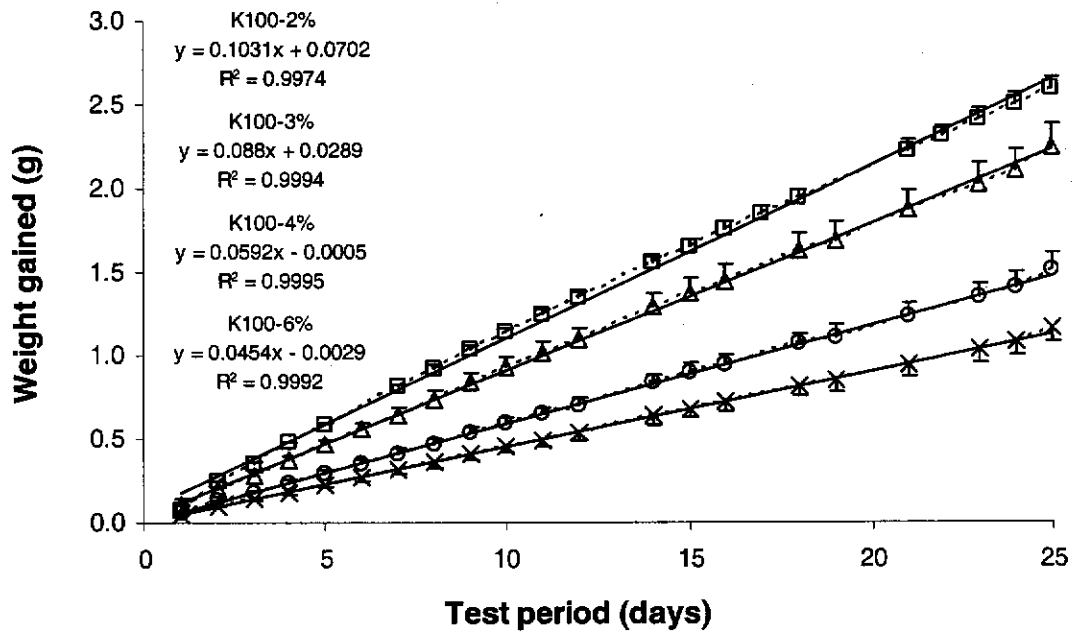
HPMC E50, F50 and K100 films. At concentrations of 4% and above, K100 had the lowest rate of moisture permeation, followed by F50 and E50 respectively. However, the result was reversed for K100 at concentrations below 4%. The disparity in results for 3% K100 could be due to the thick and uneven films as K100 solutions were very viscous. The results were reassessed by calculating the rate of water vapour permeation across the film in g/cm^2 in 25 days, based on the film sample area of 1.13 cm^2 . As shown in Table 6, the rates were from 1.35 to 2.25 g/cm^2 for E50, 1.28 to 2.15 g/cm^2 for F50 and 1.17 to 2.59 g/cm^2 for K100 at concentrations of 6, 4, 3 and 2% w/w respectively. This would probably be due to the larger quantity of polymer used and the thicker films obtained from higher concentrations. Water vapour permeation was lowest in K100 films. As the solutions from E50, F50 and K100 were viscous and their films, thick and uneven, they were deemed unsuitable for film coating and hence further investigation was not carried out.



E50



F50



K100

Figure 9. Weight gained over 25 days by different concentrations of HPMC (a) E50, (b)

F50 and (c) K100 films: (□) 2%, (Δ) 3%, (○) 4% and (×) 6%.

Trendline equations for linear plots are included.

(Bars are +1 s; n = 5)

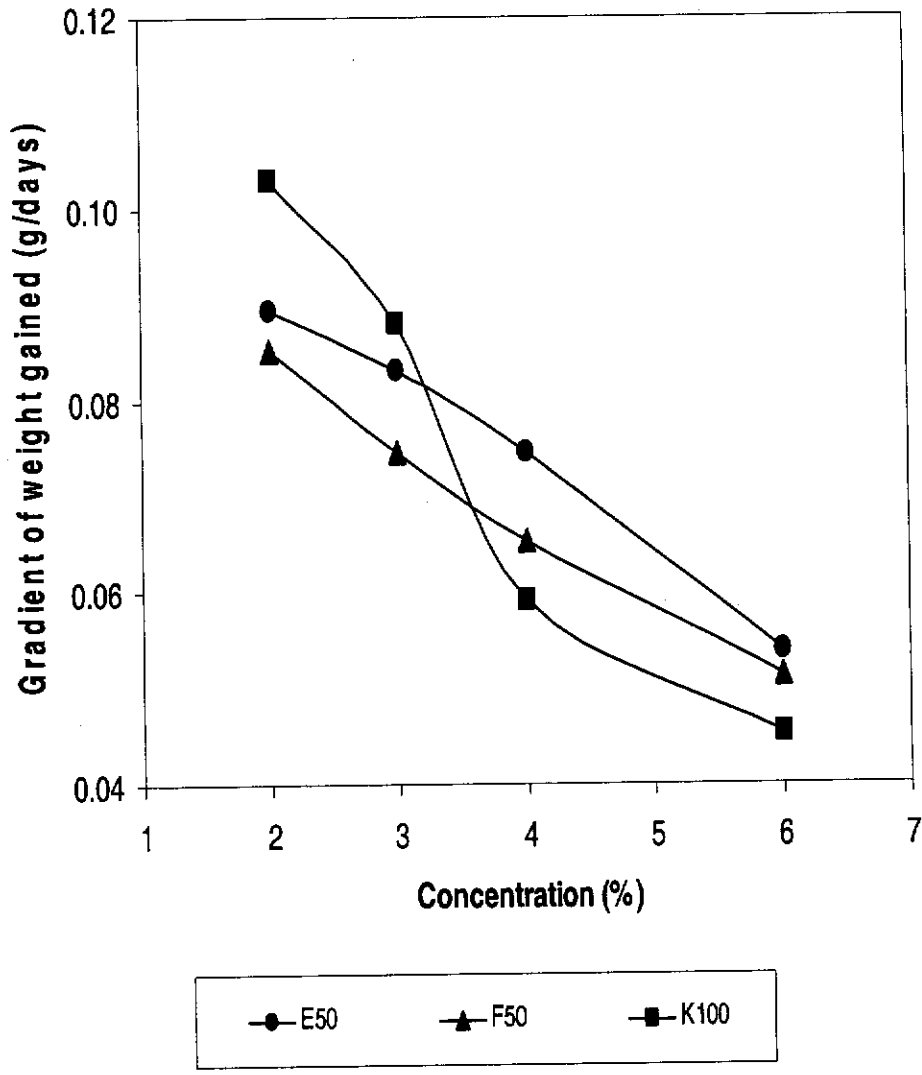


Figure 10. Rate of moisture permeation (g/days) for various concentrations of HPMC E50, F50 and K100 films. (Bars are +1 s; n = 5)

Table 6. Rates of moisture permeation in 25 days for various concentrations of HPMC E50, F50 and K100 films.

Concentration (%)	Weight gained (g)		Water vapour permeation rate ($\text{g cm}^{-2} \text{25days}^{-1}$)	
	Mean	Stdev	Mean	Stdev
E50				
6	1.3499	0.1454	1.1936	0.1286
4	1.8864	0.1259	1.6679	0.1113
3	2.0763	0.1212	1.8358	0.1072
2	2.2509	0.3063	1.9902	0.2708
F50				
6	1.2824	0.0411	1.1339	0.0363
4	1.6402	0.0632	1.4502	0.0559
3	1.8759	0.1537	1.6587	0.1359
2	2.1455	0.0828	1.8970	0.0732
K100				
6	1.1680	0.0853	1.0327	0.0754
4	1.5172	0.0934	1.3415	0.0826
3	2.2499	0.1352	1.9893	0.1195
2	2.5905	0.0728	2.2904	0.0643

C.1.(ii) Different low viscosity grades in HPMC E series

Moisture permeation tests were carried out on films from all the viscosity grades in the HPMC E series. While the films were dried from 2, 3, 4 and 6% w/w solutions, the highest concentration for E4M was 3%w/w due to its viscosity. Hence, it was not included in the comparison shown in Figure 11. From the figure, it appeared that there was no apparent relationship between the rate of moisture permeation of dried films and the viscosity of the solutions from HPMC of the same series. At 6% w/w, E3 had the lowest rate of moisture permeation, followed by E5. The rate was about the same for the remainder of the HPMC in the E series, namely E6, E15 and E50. At 4% w/w, the rate of moisture permeation, in decreasing order, was E50, E5, E15, E6 and E3. At 3% w/w, the lowest rate of moisture permeation was from both E3 and E15 films. Hence, E3 had consistently the lowest rate of moisture permeation in films from the E series. To determine if moisture permeation was affected by film thickness, the mean thickness of E3, E5, E6 and E15 test samples was compared in decreasing order of moisture permeability. Table 7 shows that both E3 and E15 films, which had the lowest moisture permeation rate, were also low in thickness. Hence, moisture permeation rate did not correspond with film thickness and the difference of 0.01 mm in thickness did not affect the permeation rate of water vapour. The tests also showed that moisture permeation rate in HPMC films from the E series was not related to their viscosity grade. As E3 had the lowest viscosity as well as moisture permeation rate, it was the polymer of choice for film coating in this study.

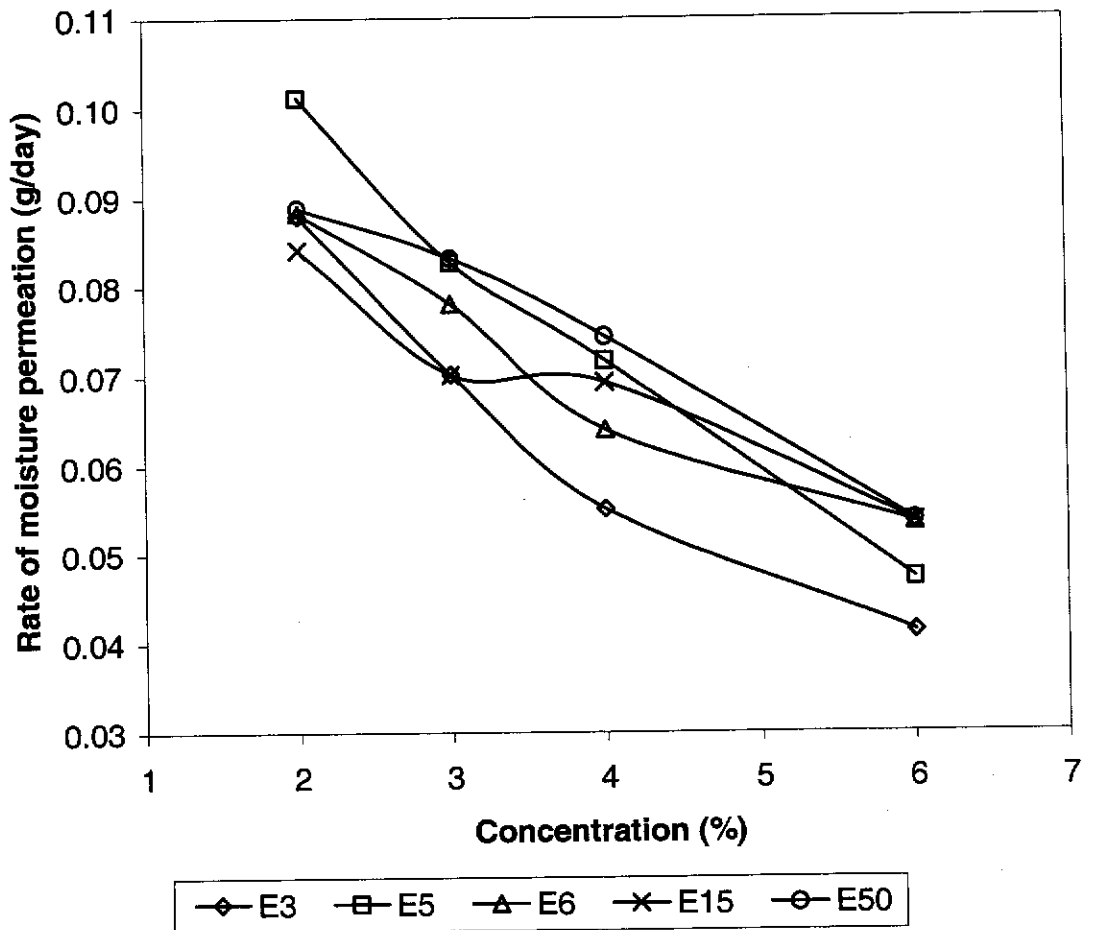


Figure 11. Moisture permeation rate of different low viscosity grades of HPMC films in the E series. (Gradients were obtained from plots in Appendix II).
 (Bars are +1 s; n = 5)

Table 7. Film thickness of 3% HPMC film samples for the moisture permeation test.

Moisture permeation (in decreasing order)	HPMC E series	Mean film thickness (mm)
1	E5	0.08 ± 0.01
2	E6	0.08 ± 0.01
3	E3	0.07 ± 0.01
(almost similar results)	E15	0.07 ± 0.01

C.1.(iii) HPMC E series with different additives

The additives incorporated in 3% w/w HPMC E3 solutions included citric acid, polyvinyl alcohol (PVA), S630, polyvinylpyrrolidone (K90 and C15) and sodium carboxymethylcellulose (Cekol 30 and Cekol 300). Except for sodium carboxymethylcellulose in which 10% was used, the concentrations for the remainder of the additives were 5%, 10%, 20% and 30%. Concentration of additives was based on the dry weight of the total solid content. However, due to the difficulty of obtaining suitable film samples, moisture permeation tests were not carried out for films containing more than 10% K90 and 20% C15. The rate of moisture permeation (g / day) for the additives was also plotted against their concentrations as shown in Figure 12. Polyvinylpyrrolidone and sodium carboxymethylcellulose increased moisture permeation in HPMC films. There was also increase rate of moisture permeation for HPMC-S630 films, but the increase was at a lower rate and peaked at the 20% concentration. Both PVA and citric acid reduced moisture permeation and showed potential as an additive in reducing the moisture permeability of the HPMC film.

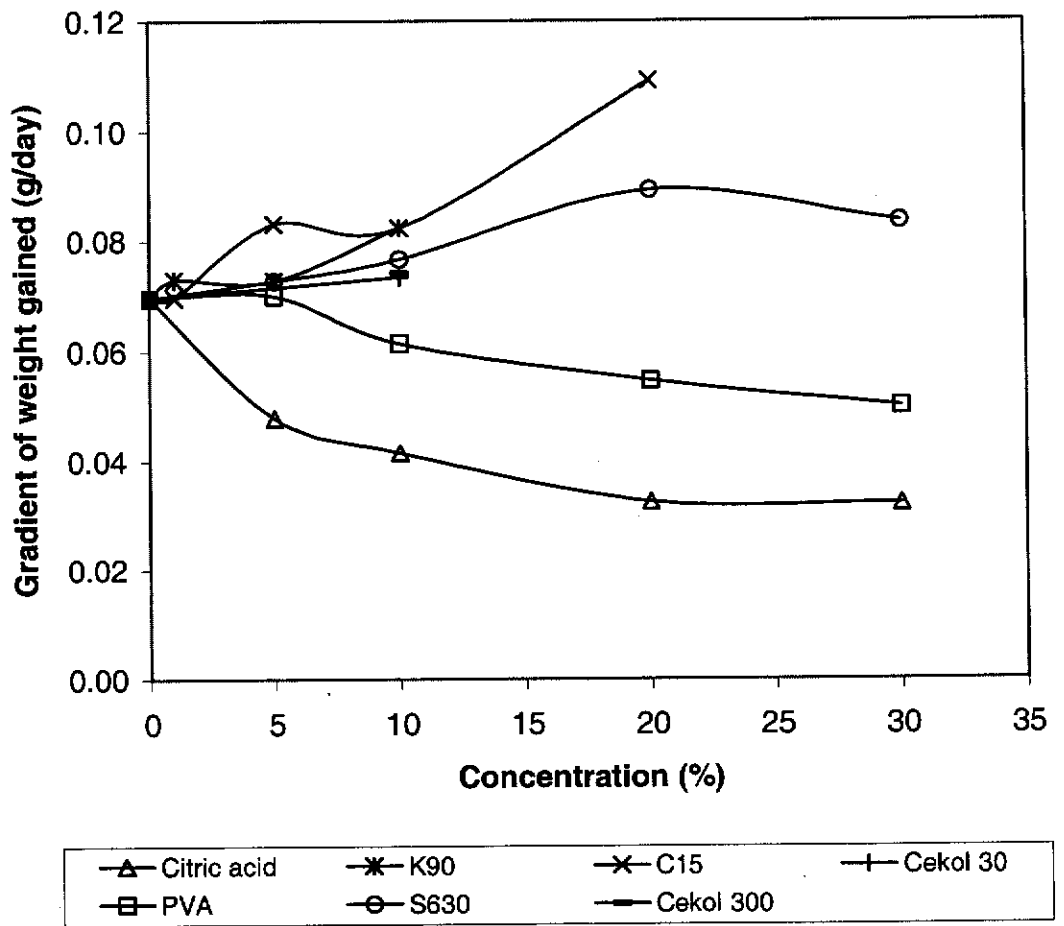


Figure 12. Moisture permeation rate of HPMC E3 with various concentrations of different additives. (Gradients were obtained from plots in Appendix III).
(Bars are +1 s; n = 5)

S630 and PVA were further investigated with PEG, a commonly used plasticizer for film coating formulations. Results from the moisture permeation test (Figure 13) showed that PEG produced a slight increase and decrease in the moisture permeation of HPMC films at the 5% and 10% plasticizer levels respectively, followed by a significant increase in moisture permeation with increasing concentrations. The reason for the initial influence as attributed by Johnson et al. (1991) could be due to the densification of the HPMC polymer films when smaller plasticizer molecules were added. PEG increases the diffusion coefficient of HPMC when the diffusion pathways become enlarged and passage of water vapour molecules is facilitated (Okhamafe & York, 1983). In order to maintain the integrity in moisture permeability, the concentration of PEG in HPMC films should not exceed 10% of the total solid weight. In fact, PEG is so highly hygroscopic that it cannot be used as the sole film former but serves as a plasticizer, pigment-stabilizing and gloss-enhancing additive. S630 showed a gradual increase in moisture permeability up to concentrations of 20%. After peaking at the 20% concentration, there was a reverse trend of decrease in moisture permeability for HPMC-S630 films. Overall, the increase in moisture permeability in HPMC-S630 films was quite close to that of PEG, except for 30% additive. PVA was found to reduce the moisture permeability of HPMC films, the reduction increasing with concentration. The decrease in moisture permeability in HPMC-PVA films was due to decreased moisture diffusivity. This could be attributed to the crystallinity of PVA enhancing the crystalline phase in the HPMC-PVA films, thereby reducing the diffusion pathways. (Okhamafe & York, 1983).

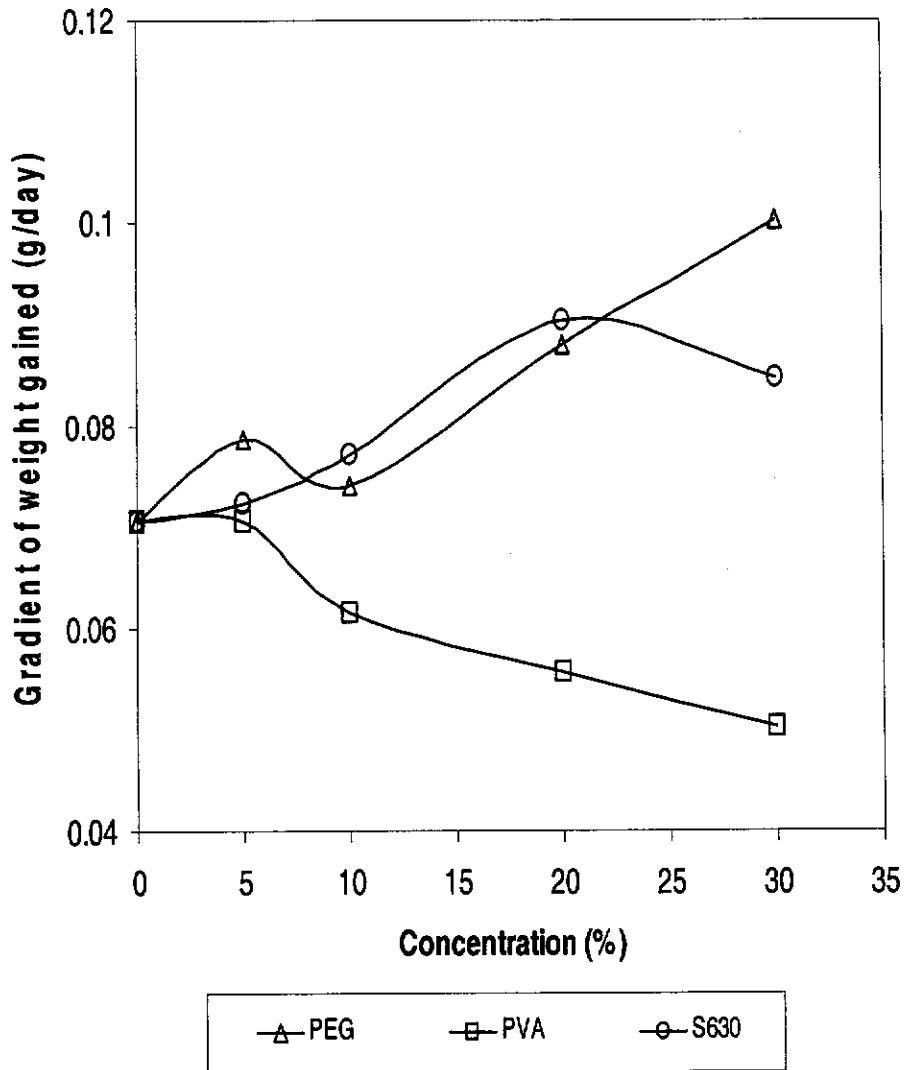


Figure 13. Moisture permeation of HPMC films in weight gained over days with various concentrations of PVA, S630 and PEG. (Gradients were obtained from plots in Appendix IV). (Bars are +1 s; n = 5)

C.2. *Using “Moisture, Air & Temperature Perm Cup” containing silica gel*

Long-chain fatty acids, namely lauric, oleic and palmitic acid, were investigated if the long carbon chains would retard the moisture permeation of HPMC films. As the long-chain fatty acids are insoluble in water, the concentration used was low, at 0.3% of the solid dry weight. They were first dissolved in ethanol and incorporated into the aqueous HPMC solution by using an emulsifier. In view of the low concentrations, a larger test surface area was used. The test was carried out using the moisture permeation cup that had a face opening of 4.91 cm² instead of the “bottle” method with a test surface of 1.13 cm². Due to the larger surface area, each test was carried out for a period of 100 h. The moisture permeation cup was filled with silica gel to form the gradient for moisture permeation across the film sample. Results indicated that the HPMC films incorporated with lauric acid had lower weight gained and was approaching constant diffusion by the 100 h. Those incorporated with oleic acid and palmitic acid had similar weight gained as that of the control, i.e. HPMC solution without additive (Figure 14). However, in view of the error levels of oleic and palmitic acids, there was little difference in moisture permeation rate before 80 h. Theoretically, longer carbon chain would retard water permeation as they are hydrophobic in nature. It has been reported that insoluble additives in film coating formulations may function as a barrier to moisture permeation and thus provide greater protection for moisture sensitive drugs (Felton & McGinity, 2002). Oleic acid with the most alkyl groups would have the lowest weight gained. However, this trend was not shown in the results. The length of the alkyl group did not affect the moisture permeation properties significantly. In view of their

insolubility, long-chain fatty acids were unsuitable as additives for HPMC coating solutions.

HPMC films containing a salt of oleic acid, namely sodium oleate, resulted in HPMC films which were not only hazy and spotty in appearance, but were also brittle and non adhesive (Table 5) to be used in film coating.

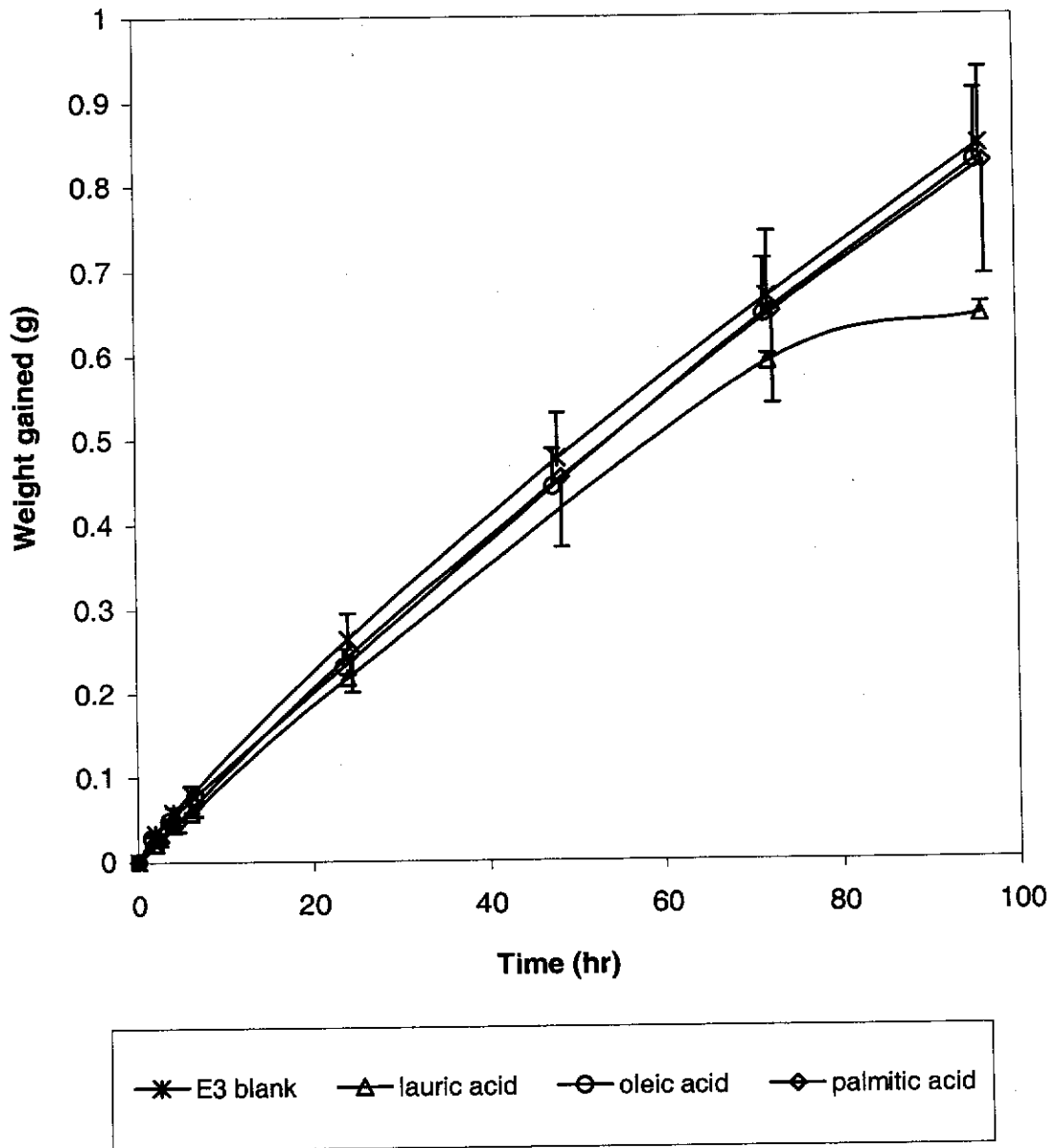


Figure 14. Weight gained by HPMC films incorporated with 0.3% of different types of fatty acids. (Bars are +1 s; n = 3)

D. Surface Roughness Analysis

HPMC produced very smooth films. Quantification of the surface roughness of 8% solid HPMC films was determined using a scanning probe microscope. After evaluating the scan parameters, it was found that the roughness of the films was best represented by the arithmetic mean surface roughness (R_a) and the maximum height surface roughness (R_y) values in nm as shown in Figure 15. From the R_y values, the lowest height in roughness was from HPMC films with S630. The external surface that was exposed to the environment was smoother than HPMC films without any additive, an improvement from 345 nm to 94 nm. There was a large increase in maximum height roughness for HPMC-PEG films from the 10% to 20% concentration. From the R_a values, it appeared that S630 was most compatible with HPMC as there was hardly any change in the surface roughness for such films. Both the external surface exposed to the environment and the inner surface against the glass plate, were equally smooth. Surface roughness increased for films containing PEG and PVA. In the case of PEG, there was a very pronounced increase in surface roughness above the 10% concentration, as shown by both the R_a and R_y values. This could be due to its hygroscopic nature. Films containing 10% PEG and above became moist and sticky during both sample preparation and testing. The films containing 20% PEG appeared moist and sticky rapidly when exposed to the environment. The hygroscopic PEG could dry poorly and in the process, became separated from the HPMC film when the moisture level in the partially dried film was low. PEG is a commonly used plasticizer for HPMC films.

However, if the film coating is intended for the protection of moisture sensitive core, this additive is not recommended in the formulation.

The smoothness of a polymeric film coat is governed by its surface roughness. This in turn affects its appearance as a smooth surface tends to look more glossy. A film coat with rough surface tends to appear dull. Very rough films may even have an “orange-peel” look on its surface.

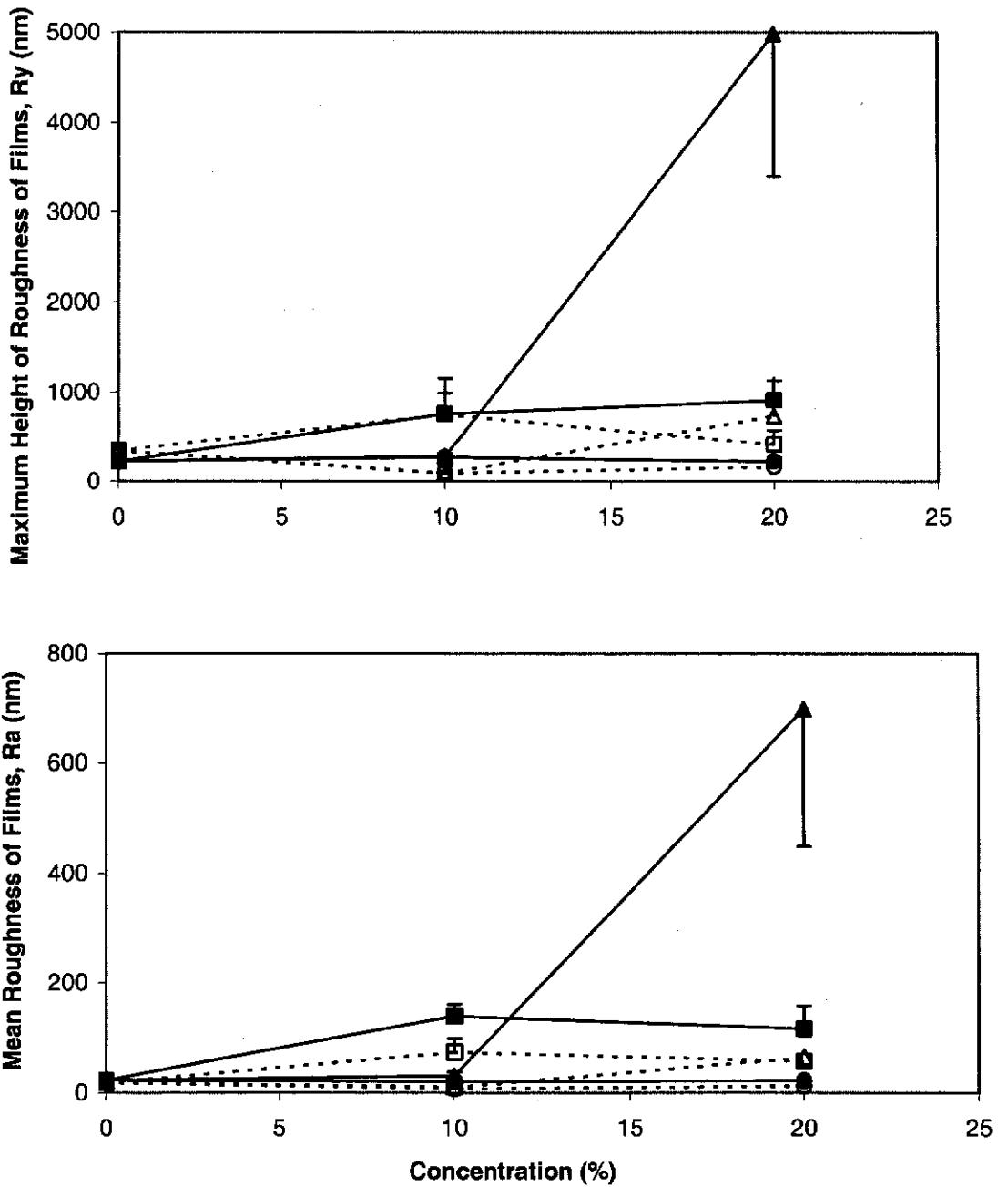


Figure 15. Maximum height roughness and mean roughness of HPMC films containing 10% additives of PEG (Δ), PVA (\square) and S630 (O). Lines show external lines (—) and internal (---) surface roughness.

(Bars are +1 s; n = 9)

E. Determination of Glass Transition Temperature

Glass transition temperatures (T_g) were determined for films dried from HPMC coating solutions containing 8% solid content. Solutions included those with 10% (based on the dry weight of solids) additives and those without additives. Generally, the T_g of HPMC varies from 170°C to 180°C (Wade & Weller, 1994). T_g of blank HPMC E3 films determined by differential scanning calorimetry in the study was 167.15°C as shown in Figure 16. The T_g of HPMC incorporated with PVA could not be detected. This could be attributed to the presence of a crystalline phase in the blend. Both PEG (T_g , 161.03°C) and S630 (T_g , 163.23°C) reduced the T_g of HPMC films by approximately 6°C and 4°C respectively. The glass transition temperature (T_g) has been described as the characteristic temperature at which a polymer changes from a state of relative molecular or segmental rigidity (glassy phase) to one of considerable chain mobility (rubbery phase). Plasticization lowers the T_g values and the incorporation of PEG in the HPMC formulation was proposed to increase the segmental mobility of the HPMC polymer. Incorporation of a plasticizer affects the glass transition temperature of the coating polymer and the more efficient the plasticizer, the greater the lowering of the T_g (Gutierrez-Rocca & McGinity, 1994). As S630 also lowered the T_g , though to a lesser extent than PEG, it demonstrated some plasticizing effect on HPMC films. T_g is known to influence the physical properties, such as viscosity of the coating solution and the mechanical properties and permeability of the film coat (Aulton, 1995).

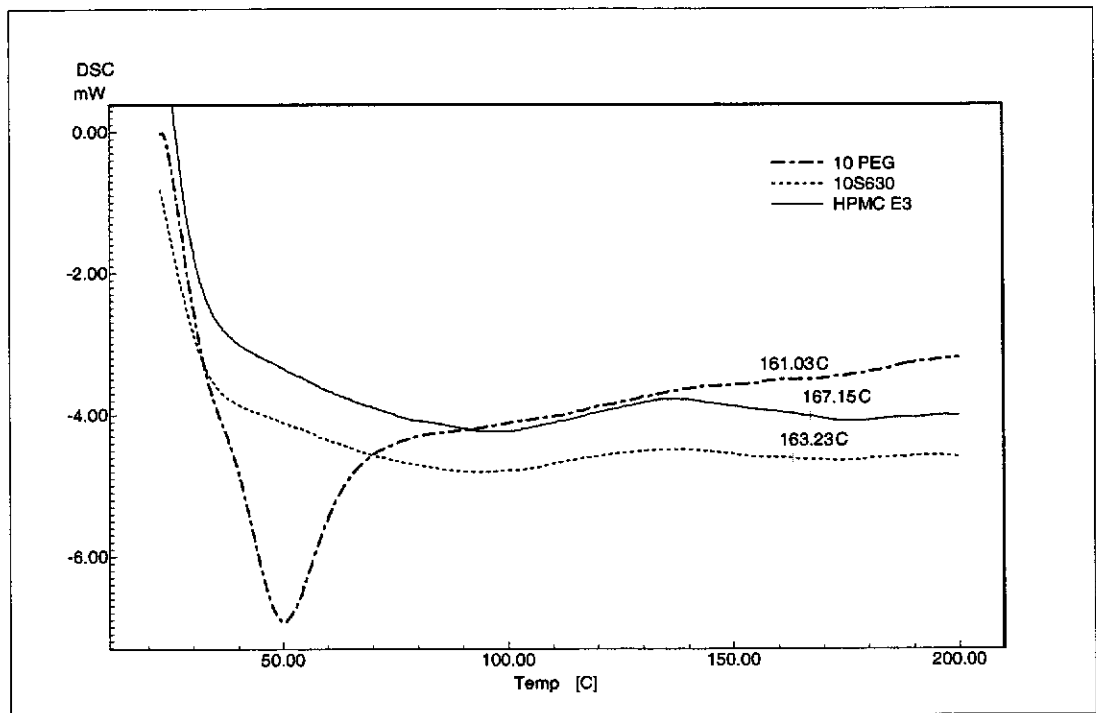


Figure 16. Glass transition temperature of HPMC E3 films with and without 10% additive heated to 160°C, cooled and reheated to 200°C at 20°C min⁻¹. (161.03°C) E3+PEG; (163.23°C) E3+S630; (167.15°C) E3

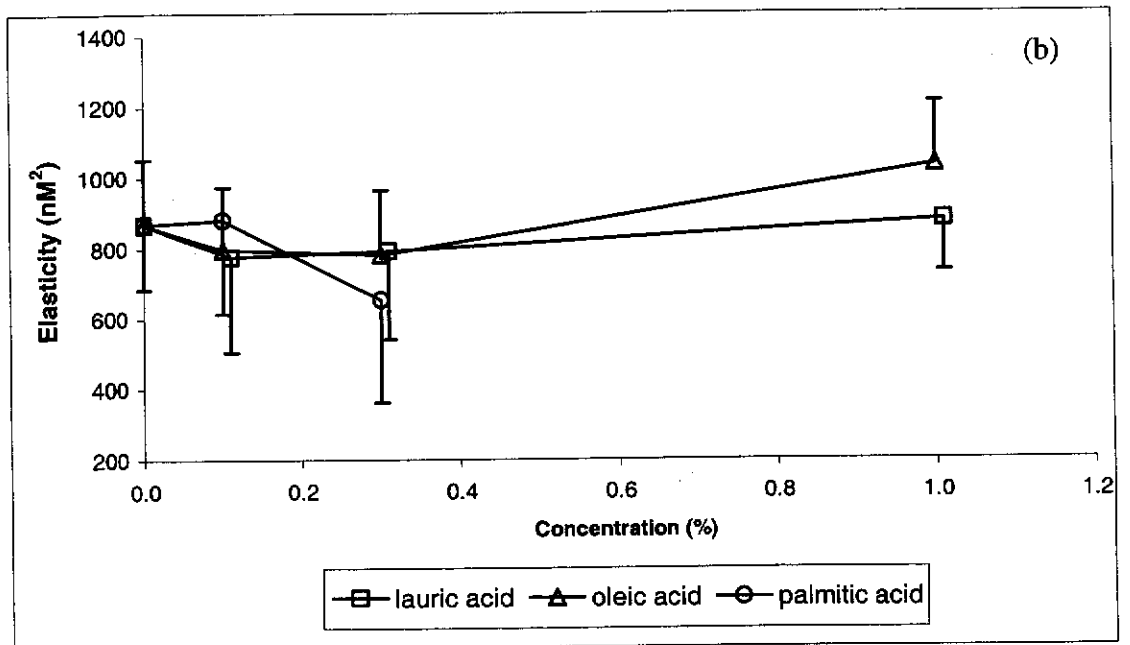
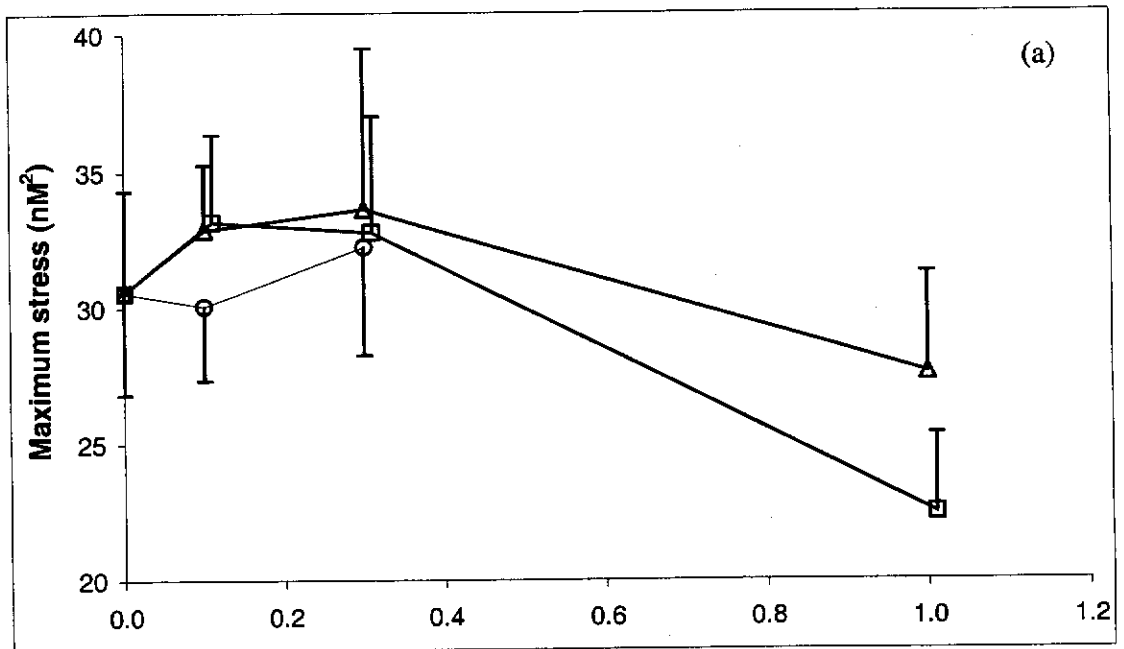
F. Evaluation of Mechanical Properties of Cast Films

Film coatings must have suitable mechanical properties so that they will not crack, split or fail in use. It should be strong and tough as indicated by high maximum stress and work of failure. Elastic modulus is an index for stiffness and rigidity. The higher the value of elastic modulus signifies a stiffer film. Elongation and tensile strength results obtained with free films were used to indicate the risk of film cracking (Johnson et al., 1991). Ideally, the film should be of sufficient stiffness without being brittle. In this study, mechanical tests on free cast films of HPMC E3 with a total solid content of 3% were carried out for films incorporated with (i) fatty acids, (ii) 10% of different additive and (iii) various concentrations of PEG, PVA and S630.

F.(i) HPMC films with lauric acid, oleic acid and palmitic acid

The mechanical properties of HPMC films including 0.1%, 0.3% and 1.0% of fatty acids are shown in Figure 17, (a) tensile strength, (b) elastic modulus, (c) % strain or elongation and (d) work of failure. Tensile test for palmitic acid at 1% concentration was not tested because the films became fragmented upon drying. There were inconsistencies in the results from those with 0.1% fatty acids. This could be due to experimental factors as it was very difficult to incorporate and distribute evenly the small quantity of fatty acids in the aqueous HPMC solution. After a slight increase in tensile strength at 0.3%, the fatty acids reduced the tensile strength of HPMC films, with lauric acid being the most influential in this aspect. Both lauric acid and oleic acid increased the elastic modulus gradually after the minima at 0.3% whereas palmitic acid

reduced the elastic modulus of HPMC films. Lowered elastic modulus values means that the additive may have a plasticizing effect, resulting in the film being less stiff and more flexible. Break strain indicates the percentage elongation at yield point. Except for slight increases in elongation at concentrations below 0.3% for lauric acid and oleic acid, the fatty acids reduced the elongation of HPMC films. Work of failure, measured in joules, is obtained from the area under the curve for work done. Besides oleic acid that caused a minor increase in the work of failure at the 0.3% concentration, all the other fatty acids reduced the toughness of HPMC films as shown by the decrease in energy in the work of failure. Above 0.3%, oleic acid also reduced the toughness but not to the same extent as the others. Overall, the results showed that long-chain fatty acids reduced the mechanical properties, such as tensile strength, elongation and work of failure of HPMC films. Except for palmitic acid, fatty acids increased the elastic modulus, i.e. the stiffness of the films, showing that they do not have any plasticizing effect. Hence, long-chain fatty acids are not suitable as additives for HPMC film coating solutions. When used above a concentration of 0.3%, they had a detrimental effect on the mechanical properties of HPMC films and at 0.5%, the physical appearance of the films was also affected.



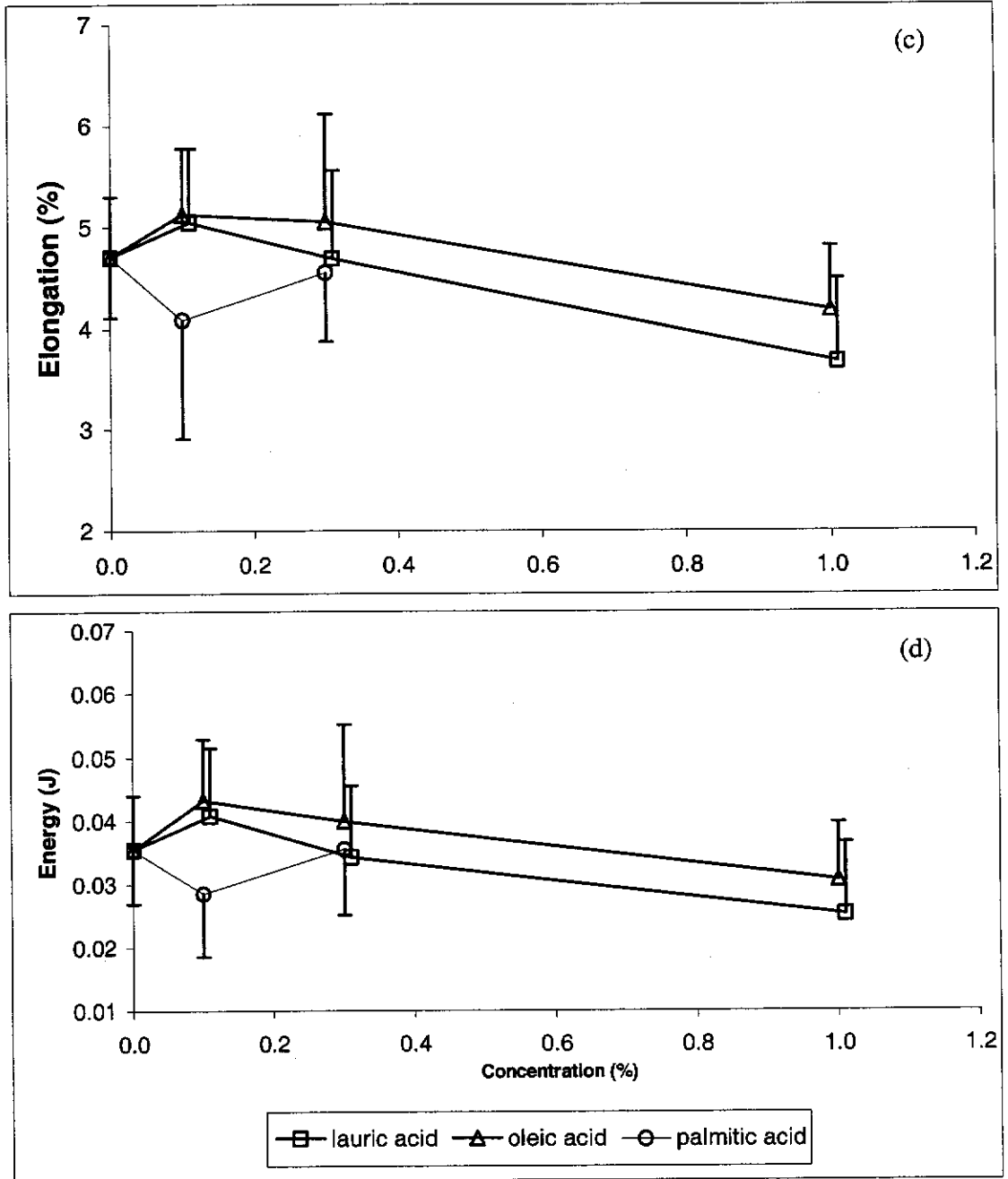


Figure 17. Mechanical properties of HPMC films incorporated with various concentrations of different fatty acids: (a) tensile strength, (b) elastic modulus, (c) % elongation and (d) work of failure. (Bars are +1 s; n = 10).

F.(ii) HPMC films with 10% concentration of different additives

A concentration of 10% was selected because some additives were not compatible with HPMC solution when used above this concentration. Sodium oleate, for example, when incorporated above 10% concentration, resulted in an unstable HPMC dispersion. HPMC films with more than 10% of some additives were too adhesive or had a poor physical appearance. Films with $\geq 15\%$ S630 were omitted from the tests because they adhered to the surface of the glass plate, making it impossible to remove suitable sized samples. For the same reason, both C15 and K90 were not used above 5% and 10% respectively, for testing the mechanical properties of HPMC films.

The results from the mechanical testing of HPMC films containing 10% additives are shown in Figure 18 for tensile strength and Figure 19 for the elastic modulus. In the stress-strain profile, maximum stress at break is a measure of the tensile strength, an indicator of the film strength. Polyvinylpyrrolidone (C15 and K90), sodium carboxymethylcellulose (Cekol 30 and 300) and sodium oleate reduced the tensile strength of HPMC films, with Cekol 300 and C15 to a greater extent than Cekol 30 and K90. At a low concentration of 5%, both citric acid and PVA increased the tensile strength sharply. However, the effect subsequently declined after the maxima at 5% and both had approximately a similar moderate increase at 10%. S630 increased the tensile strength gradually and at the 10% concentration, was the most effective in increasing the tensile strength of HPMC films.

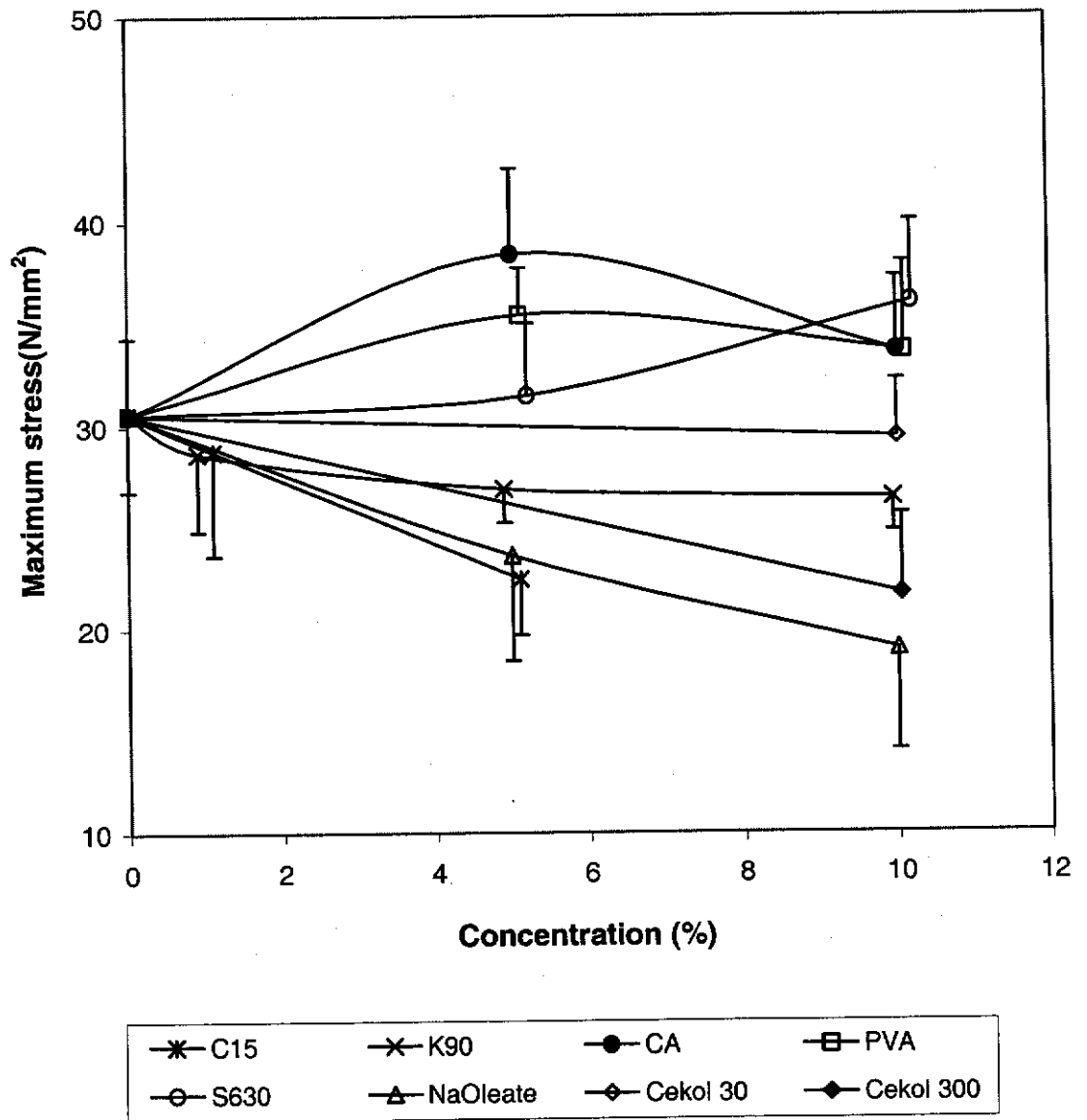


Figure 18. Tensile strength of HPMC films incorporated with different additives at a 10% concentration of the solid dry weight. (Bars are +1 s; n = 10).

Often, additives that increase the tensile strength of HPMC films would decrease the elastic modulus and vice versa. As shown in Figure 19, citric acid caused a drastic reduction in the elastic modulus. PVA decreased the elastic modulus sharply at 5% but increased subsequently to a moderate level by the 10% concentration. Polyvinylpyrrolidone (C15 and K90) and sodium carboxymethylcellulose (Cekol 30 and 300) increased the elastic modulus of HPMC films with K90 and Cekol 30 to a higher extent than C15 and Cekol 300 respectively. However, the influence of K90 declined after a maximum at 5% to a moderate increase at the 10% concentration. The influence of S630 was exceptional. It increased both the tensile strength and the elastic modulus of HPMC films. Films containing 10% S630 had the highest elastic modulus values among the additives. From the mechanical test results, it appeared that S630 had the greatest influence by increasing both the tensile strength as well as elastic modulus in HPMC films. Ideally, a desirable film coat should be hard, tough and extendible (Okhamafe & York, 1983), characterized by high tensile strength, high elastic modulus and moderate elongation. In view of the potential in improving the mechanical properties of HPMC films, S630 was further investigated to understand its role as an additive for HPMC film coating formulations. It was compared with PVA, a commonly used copolymer and PEG, a commonly used plasticizer.

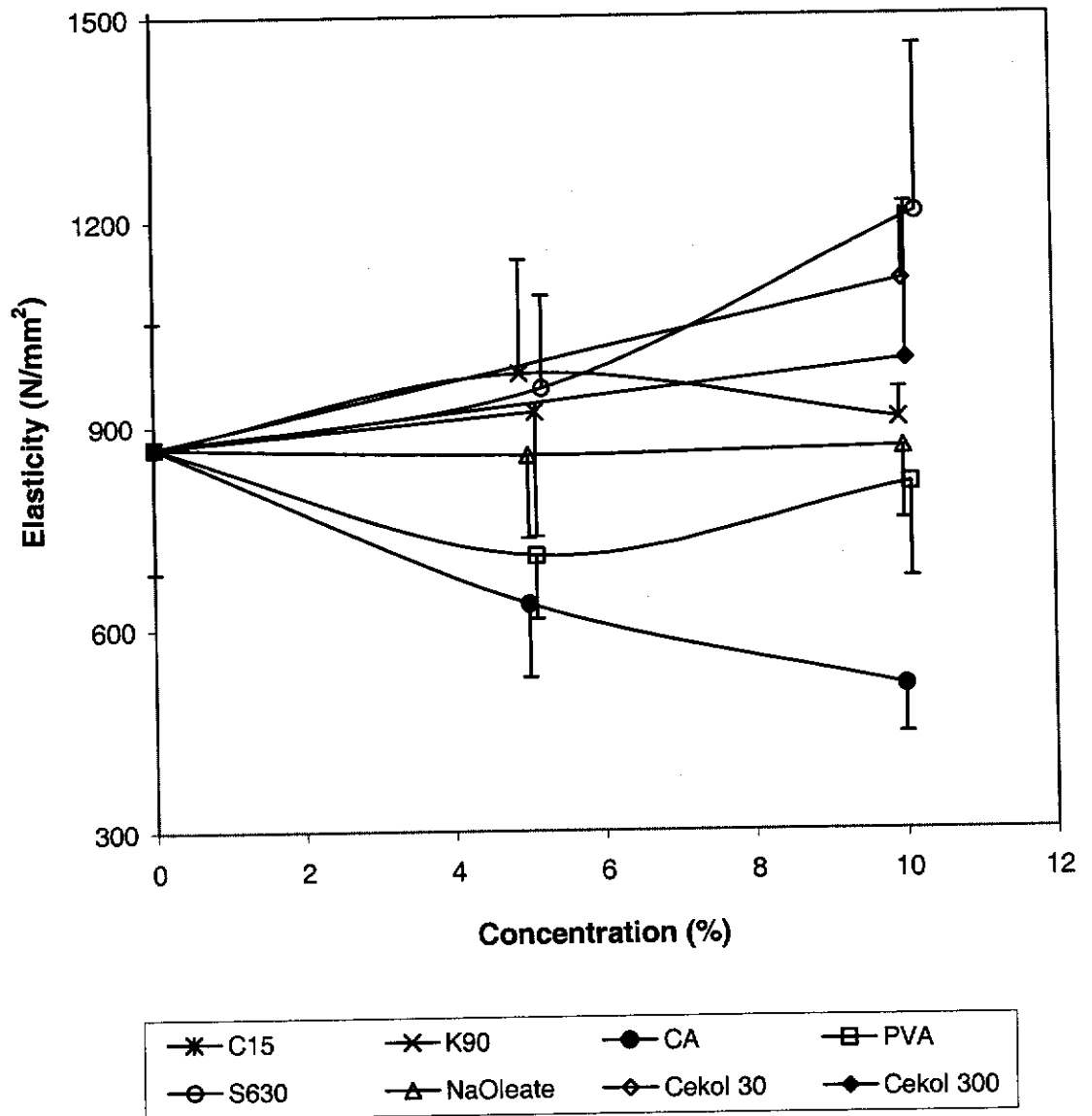
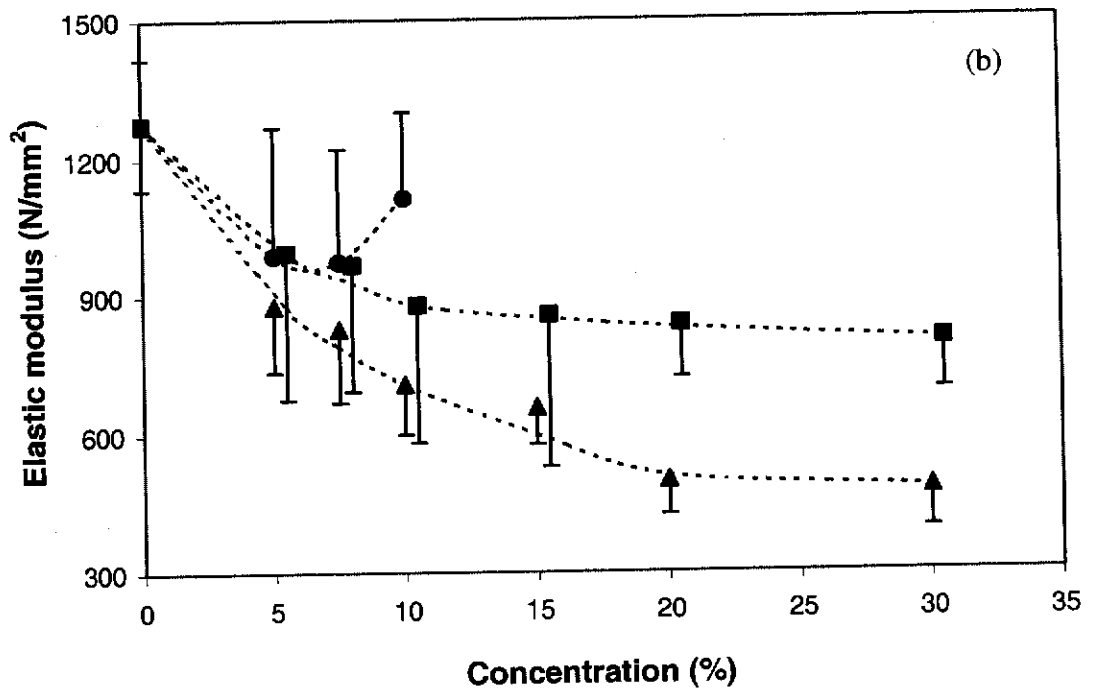
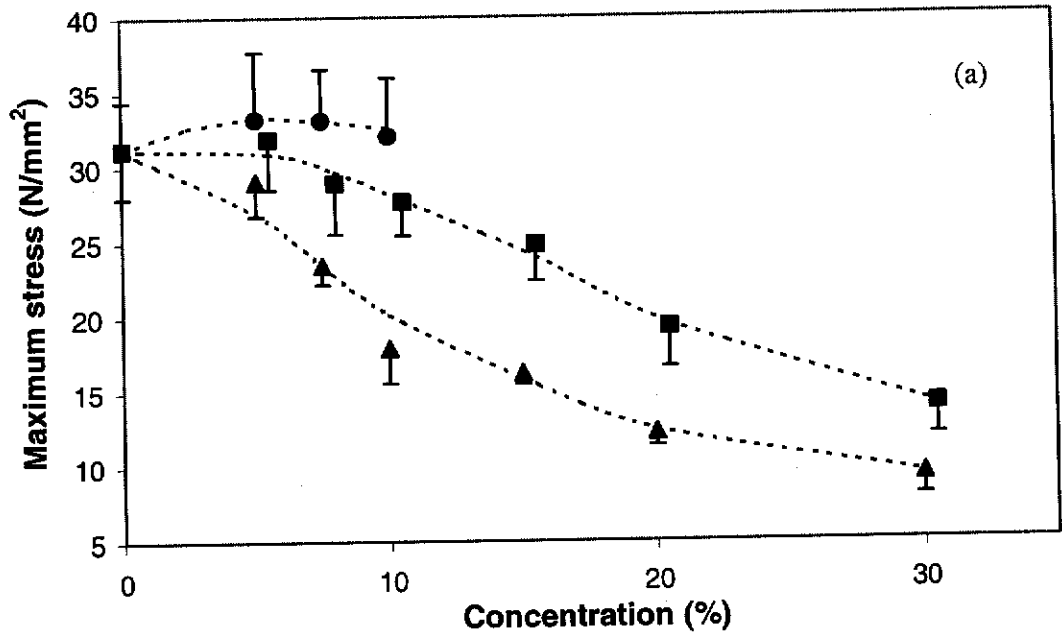


Figure 19. The elastic modulus of HPMC films incorporated with different additives at a 10% concentration of the total solid dry weight. (Bars are +1 s; n = 10).

F.(iii) HPMC films with various concentrations of PEG, PVA and S630

Results of the mechanical tests on HPMC films incorporated with 5%, 10%, 20% and 30% of copolymer PVA, plasticizer PEG, and S630 (up to 10% only) are shown in Figure 20 (a) tensile strength, (b) elastic modulus, (c) elongation and (d) work of failure. The maximum stress results showed that both co-polymers, S630 and PVA, increased the tensile strength of HPMC films slightly when incorporated at the 10% concentration or below. Above this level, HPMC-PVA films showed a downward trend with the tensile strength inversely proportional to the concentration of PVA. This trend was not apparent in HPMC-S630 films as the tensile strength was higher than those without additive. PEG affected the tensile strength of HPMC films adversely, reducing the tensile strength of the films by more than 60% when 30% PEG 1500 was incorporated. Figure 20b shows that the additives used in this study reduced the elastic modulus of HPMC films, with PEG showing the most pronounced effect. While the effect of PVA stabilized gradually above a 10% concentration, S630 appeared to have an upward trend in increasing the elastic modulus after an initial drop at 5% concentration. Figure 20c shows a moderate increase in percentage elongation at break when the additives were incorporated in the HPMC films at low concentrations. PVA produced the highest increase at concentrations of 10% and below, after which there was a decrease. PVA decreased the elongation of HPMC films when used above 20% and at the 30% concentration, HPMC-PVA films had the lowest elongation. PEG increased the elongation, reaching a maximum at 20%, followed by a decline. However, both PEG and S630 showed a positive influence in extending the elongation of HPMC films. From the

results in Figure 20d, the work of failure was initially increased at low concentrations of additives of less than 10%. At concentrations of 10% and above, there was a decline in work of failure for HPMC films incorporated with PEG or PVA. This trend was not pronounced in HPMC films with S630 as the decline in work of failure from the 5% to 10% concentration was moderate and gradual compared to the other additives. As no sample of HPMC-S630 films above the 10% concentration was evaluated, its effect on the mechanical properties at higher concentration was not verified. As shown from these results, PVA and S630 were most influential in increasing the percentage elongation in HPMC films at low concentrations at 10% and below. S630 was also the best in improving the film toughness. In addition, S630 had the least effect in reducing the tensile strength and elastic modulus of HPMC films. While PEG enhanced the percentage elongation of HPMC films at higher concentration, the other mechanical properties such as tensile strength, elastic modulus and work of failure deteriorated. The effect of PEG was in line with the effect of plasticizers in reducing the mechanical properties of HPMC films.



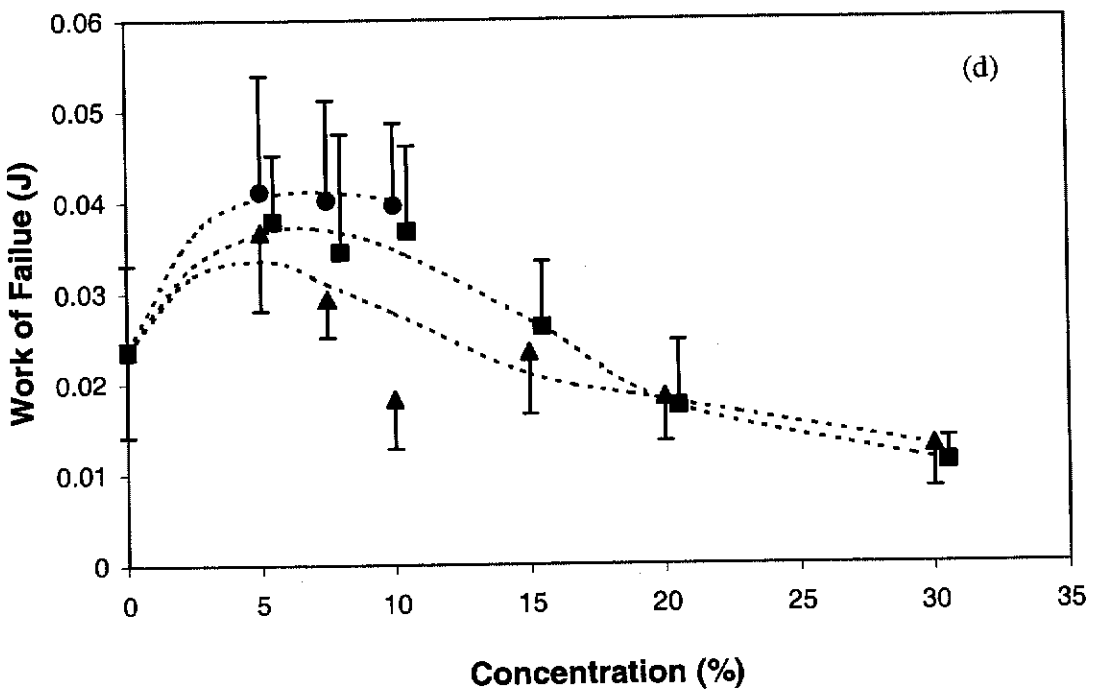
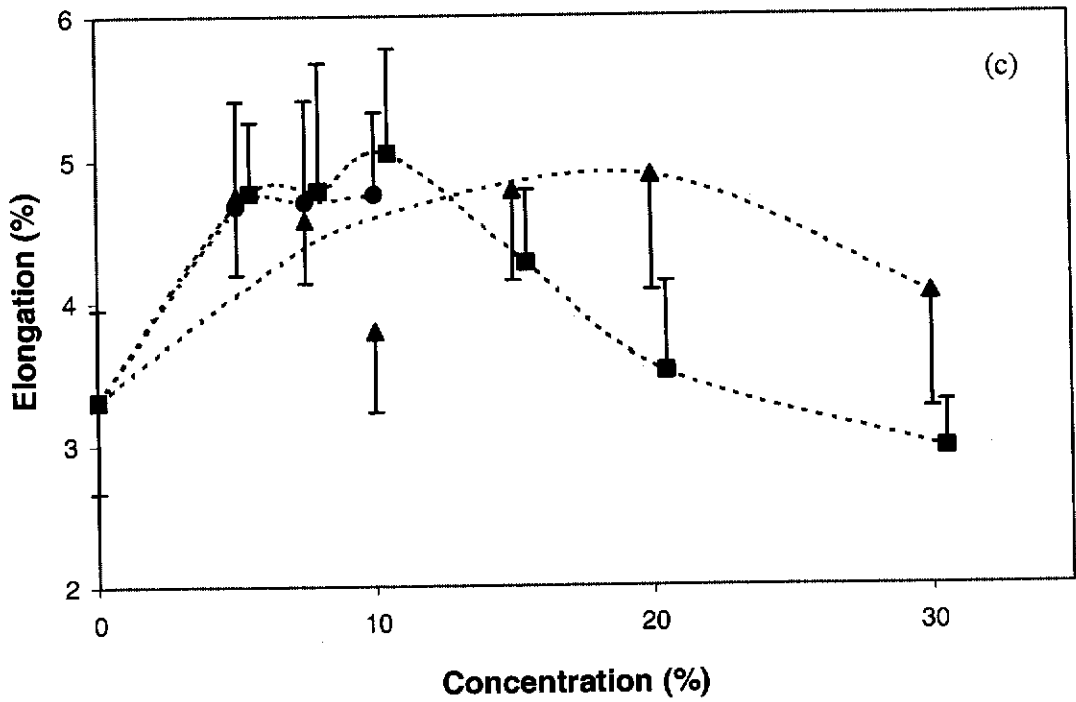


Figure 20. Effect of S630 (O), PEG (Δ) and PVA (\square) on (a) tensile strength, (b) elastic modulus, (c) % elongation and (d) work of failure of HPMC films. (Bars are +1 s; n = 10).

G. Film coating

Aqueous film coating was carried out with 3 kg of 8% w/w HPMC E3 solutions, with or without additives, on 5 kg of caplets. Each coating process was carried out for about 3 h, using the ultra-coater under selected conditions. Minor adjustments to the operating settings had to be made during the pre-coating, coating and post-drying phases. Delivery of the coating liquid by means of a peristaltic pump was consistent as the coating solutions were of a suitable viscosity for aqueous film coating. Hence the process parameters were optimized for film coating the HPMC formulations without much difficulty. The only disadvantage in the design of the ultra-coater is the two-fluid nozzles set at 40° from the normal in the direction of tablet flow. The angle makes it difficult to coat small batches of tablets. A minimum load of 4 kg was required but the coating process was best carried out at the optimum load of 5 kg of the tablets. The tablets were coated in less than three hours and the film coats were uniform and had a good appearance. The observations on the effect of the coating process conditions are listed in Table 8.

Table 8. Effect of process conditions and settings on the film coating process using the ultra-coater.

Process	Optimal	Observations when other settings were used.
Conditions	Setting	
Load (kg)	5 kg	For the ultra-coater, the minimum coating load must be at least 4 kg. Due to the angle of the spray nozzles, the size of the rotating disk, the capacity of the container and the diameter of the perforated coating pan, the spray droplets could not reach the tablet cores efficiently when the load is too small. The optimum load for uniform spraying and distribution of coating fluid was 5 kg.
Pump flow rate (%)*	12 & 13	When the flow rate was too high, the coating solution could not dry quickly leading to the formation of a fluid layer on the table cores. The drying efficiency was affected and the outlet humidity rose to above 70%. Sticking of tablets and peeling of film coats were seen. High fluid pump rate and insufficient air flow resulted in the sticking and disintegration of tablets, leading to the clogging of the spray nozzles.
Disk rotating speed (rpm)	22	High rotating speed results in breaking of tablets. The speed was drastically reduced to around 15 rpm during the post-drying phase in order to minimize attrition.

Process	Optimal	Observations when other settings were used.
Conditions	Setting	
Atomizing pressure (bars)	3.0	Too low an atomizing pressure affected the spray coating efficiency. 2.5 bar was not efficient for optimal spraying of the coating fluid.
Air flow rate ($\text{m}^3 \text{hr}^{-1}$)	70	Air flow was introduced while preheating the tablets to remove the dust simultaneously. When $60 \text{ m}^3 \text{hr}^{-1}$ was used, the low rate of air flow affected the drying of spray solution. Larger air quantity was required to maintain drying efficiency. When the tablets took too long to dry, the fluid layer on the tablet cores resulted in surface roughness or picking.
Inlet air temperature ($^{\circ}\text{C}$)	80	Inlet air temperature had to reach 80°C before the start of the coating process. The tablets had to be preheated to the desired temperature to prevent severe wetting upon introduction of the coating solution. The temperature was maintained throughout the process, otherwise the drying efficiency would be compromised, leading to picking and in some instances, severe wetting and sticking of tablet cores.

H. Determination of Film Coat Thickness

Aqueous film coating with 3 kg of 8% w/w HPMC E3 solution on 5 kg of caplets produced a film coat with uniform thickness of 0.084 ± 0.007 mm (Table 9). Those with additives had film coat thickness ranging from 0.082 to 0.086 mm. Different additives in the HPMC E3 solution did not play a significant role in the film coat thickness. PEG had no effect while PVA increased and S630 reduced it by approximately 2.4%. Hence, the quantity of solid content was a major factor in determining the thickness of film coat.

Table 9. Film coat thickness of different HPMC E3 formulations.

Film Type	HPMC E3	E3+S630	E3+PVA	E3+PEG
	Thickness (μm)			
Mean	84	82	86	84
S.D	7	5	5	6

I. Evaluation of Adhesive Properties of Film Coats

Investigations were carried out to evaluate the adhesiveness of film coats onto tablet cores and the influence of various additives on coat-substrate adhesion. The method used was a modification of the Butt adhesion technique using a custom-made tablet holder fitted to the tensile tester. To verify that the failure of the film was adhesive in nature, the weight of the adhesive tape for peeling the film coat was weighed before and after the adhesion test. The weight of material adhering to the tape was determined. The adhered material comprising of the peeled film coat plus any substrate particles removed during the peel test was found to be from 18 to 20 mg (Table 10).

Table 10. The weight of substances (film coat and substrate particles) adhering to the adhesive tape after the butt adhesion test.

Film Type	HPMC E3	E3+S630	E3+PVA	E3+PEG
	Mean weight and S.D. (mg)			
Adhesive tape before test	100.9 ± 1.0	101.4 ± 1.1	98.4 ± 1.0	100.4 ± 0.0
Adhesive tape after test	120.2 ± 1.5	120.7 ± 1.5	118.1 ± 1.7	118.6 ± 1.4
Adhered film coat & particles	19.3 ± 1.2	19.3 ± 1.1	19.7 ± 1.5	18.2 ± 1.1

Based on the following calculations, the weight of substance adhering to the adhesive tape was mainly from the film coat and the amount of particles removed during the peel test was minimal.

Weight of 8% w/w solid coating solution used	=	3000 g	
Weight of solid in film coating	=	$8/100 \times 3000$ g	= 240 g
Weight of caplets per coating operation	=	5000 g	
Weight of each caplet	=	0.65 g	
Weight of film coated on each caplet	=	$0.65 \times 240/5000$ g	= 0.0312 g
Approximate surface area of each caplet	=	300 mm ²	
Approximate area of peeled film coat from test	=	23.5 mm x 8.5 mm	= 200 mm ²
Approximate weight of peeled film coat	=	$200/300 \times 0.312$ g	= 0.0208 g

The theoretical weight of film coated on each caplet was 31.2 mg and that of the peeled film coat from the truncated caplet was estimated to be 20.8 mg. However, there is an inherent loss of some coating material incurred during the process (Bauer et al., 1998) as a result of deposits in the pan, abrasion and fines extracted with the drying-air, the actual weight of the film coat would be less. Hence, the weight of 18 to 20 mg of material adhering to the tape would mainly be from the peeled film coat rather than any adhering particles from the solid substrate. It is also interesting to note that HPMC films incorporated with PVA not only had the highest weight of material adhering to the test tape but also the thickest film coat (Table 9). The minimal quantity of particles proved that failure of the film coat was adhesive and not cohesive. Cohesive failure would have

occurred if the bonds between the powdered particles within the tablet were not strong, resulting in the lamination of the tablet compact during the butt adhesion test (Felton & McGinity, 1996). When this happened, the weight of the adhered particles would be significant.

The film coating process should produce a film coat in intimate contact with the core substrate. The force of adhesion and area under the stress-strain curve can provide an accurate quantitative measure of film-tablet adhesion. Strong adhesion is evidenced by the increase in adhesive force. Adhesive force is the force required to remove the film coating from the surface of the tablet (Felton et al., 2000). The adhesive toughness is the work required to remove the film coating from the tablet (Felton & McGinity, 1997). Increased in adhesive toughness is reflected by the increase in the area under the curve or the work done to detach the film from the surface of the solid core. Thus, adhesive toughness of the polymer, in conjunction with the force of adhesion, provides a more complete understanding of the mechanisms involved in the adhesion process.

It is imperative that a good film coat has strong substrate adhesion in addition to good film properties. The measurement of adhesion is extremely difficult due to the limited surface area and geometry of tablets. A method to determine film coat adhesion was devised by the use of elongated caplets that, after truncating the two semi-circular ends, allowed a length of film coat for detachment and for measurement of the adhesion force. The film coat was cut transversely prior to detachment with an adhesive tape over the film coat. Both S630 and PVA enhanced the force of adhesion in HPMC film coats as indicated by the maximum stress in the stress-strain data obtained from the modified

butt adhesion technique (Figure 21). The increase was approximately $37\pm 1\%$ higher than the film coat comprising of HPMC without any additive.

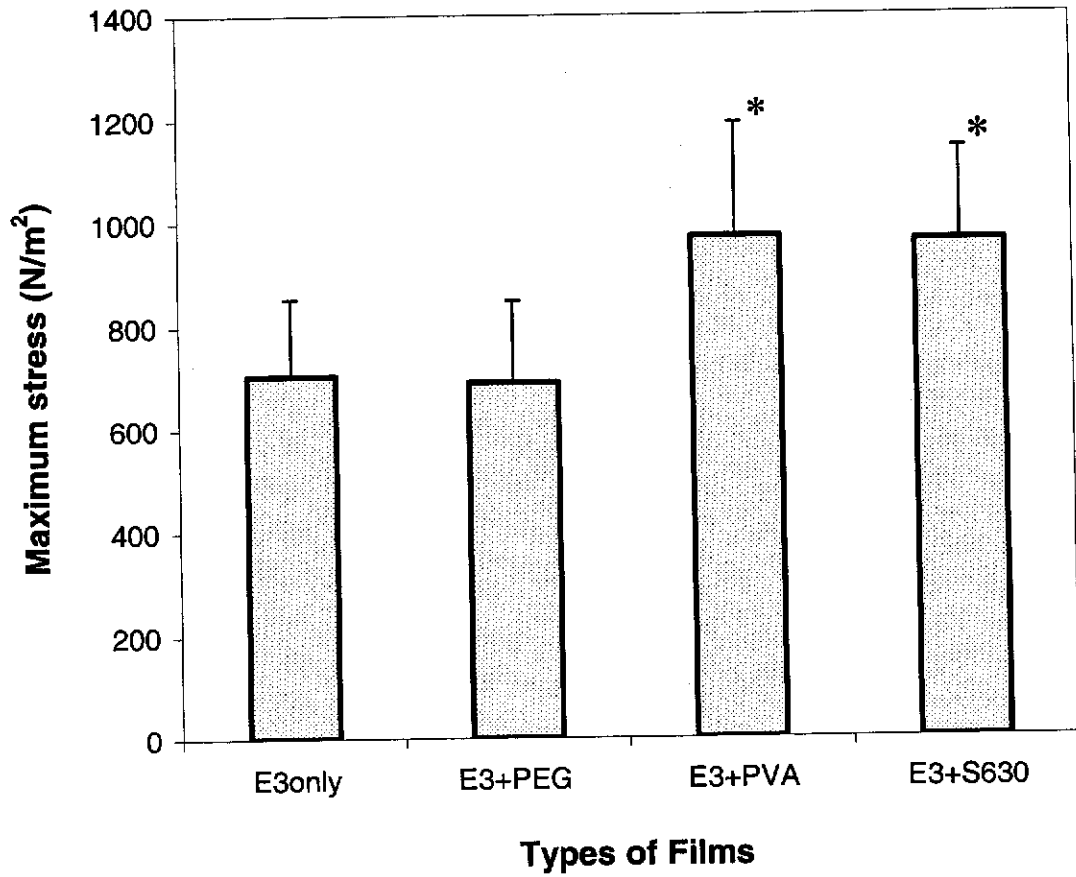


Figure 21. Adhesive strength of HPMC film coat without and with PEG, PVA and S630.

*: significant difference with HPMC film (ANOVA, $p < 0.05$).

(Bars are ± 1 s; $n = 20$)

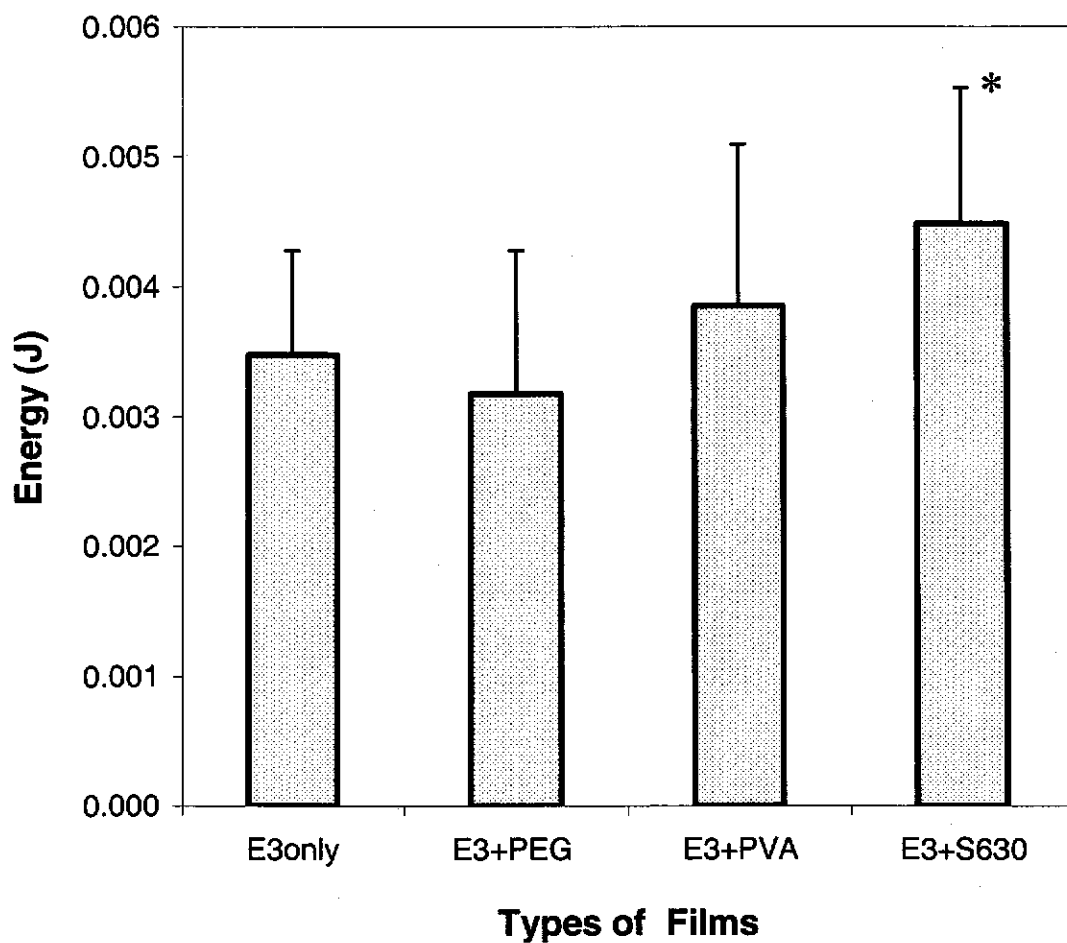


Figure 22. Adhesive toughness of HPMC film coat without and with PEG, PVA and S630. *: significant difference with HPMC film (ANOVA, $p < 0.05$).

(Bars are $+1$ s; $n = 20$)

Adhesive toughness, indicated by energy for the work of failure (area under the stress-strain curve) or work done to detach the film from the caplet core, was highest for HPMC-S630, followed by HPMC-PVA films (Figure 22). However, only S630 enhanced the toughness HPMC film significantly. This indicated that more work was required to remove the film from the surface of the tablet compact (Felton & McGinity, 2002). Both adhesive force and toughness were reduced in HPMC films containing PEG. From the results obtained on the tensile test of cast films and adhesion test of film coats, films plasticized with PEG were adversely affected, with reduction in both the mechanical and adhesive properties of HPMC film whereas PVA and S630 enhanced these properties. Clearly, S630 showed an overall advantage in the force of adhesion as well as adhesive toughness of HPMC E3 films when compared to the other two additives evaluated.

CONCLUSION

HPMC produced smooth, clear and colourless film coatings. Similar appearances were observed for HPMC of various degrees of substitution and viscosity designations. However, films from high viscosity grades of HPMC were hard and stiff and hence, unsuitable for film coating.

Rheological investigations on low viscosity grades of HPMC (Methocel E series) showed that the flow properties were non-Newtonian as the shear stress increased with shear rate. The increase in viscosity was significant with increase in concentration, with those at 6% concentration having a four-fold to seventeen-fold increase in viscosity compared to those at 2% concentration. HPMC E3 appeared to be an ideal polymer for film coating, having the lowest viscosity and being the least affected by increased concentration. Low viscosity grade polymer is more suitable for film coating. Honary et al. (2000) have reported that compared to E5, the high viscosity of E50 solution resulted in decreased geometric mean diameter of spray droplets and would cause less spreading of droplets on the substrate surface. It was noted, however, that HPMC E3 films were not strongly adhering and could be easily detached from the surface of the casting plate. The viscosity of an aqueous HPMC solution is related to the molecular weight of the polymer, hence, the low viscosity grade HPMC was brittle, lacked good physical properties and were not very adhesive.

Different additives, including plasticizers and copolymers, were included to modify the film properties. It was found that HPMC films with water-soluble additives, such as polyvinylpyrrolidone, sodium carboxymethylcellulose, S630 and citric acid, produced films with good clarity similar to those without additives, whereas those with hydrophobic additives, such as sodium oleate, PVA and most of

the long-chain fatty acids, had a patchy or hazy appearance. Besides the physical appearance, the addition of insoluble additives to film coating formulations can influence both the internal stress and degree of thermal stress in the film (Felton & McGinity, 2002). The concentrations used for fatty acids were not more than 1%, yet clarity was impaired, especially in HPMC films containing palmitic acid. The effect could be attributed to the poorly water soluble substance being separated from the system after it had exceeded the level at which it was miscible in aqueous HPMC solutions. Spots seen on some films containing high concentrations (20% and above) of soluble additive, such as PEG and Plasdone K90, could be due to the additive's solubility having been exceeded, causing the excess substance to be separated and reassembled as tiny spots on the surface of the film. Phase separation was seen in some HPMC solutions containing Plasdone K90 and lauric acid. Felton and McGinity (2002) have reported that an incompatibility or chemical interaction between the polymer and insoluble additives may result in coagulation or flocculation of the coating formulation. HPMC-PEG films appeared satisfactory initially but upon exposure to a more humid environment at a relative humidity of 60% or higher, HPMC-PEG films turned hazy and had an oily feel. This could be due to the hygroscopic nature of PEG facilitating the uptake of water vapour, making the films soft, flexible and moist.

There was a sharp increase in viscosity when sodium carboxymethylcellulose and Plasdone K90 were used with HPMC. Plasdone C15 and PVA, also resulted in an increase in viscosity but not to the same extent. However, these copolymers had different influences on the moisture permeation of HPMC films. PVA was able to reduce moisture permeation but the other copolymers, polyvinylpyrrolidone, sodium carboxymethylcellulose and S630, did not reduce the moisture permeation of HPMC

films. Generally, a copolymer increases the viscosity whereas a plasticizer like PEG for example, reduces the viscosity and Tg but increased the permeability of HPMC films. S630 appeared to have a plasticizing effect as it had the same influence on viscosity, Tg and moisture permeation as PEG. However, the increase in moisture permeability was reduced at concentrations above 20%. The plasticizing effect on the viscosity and Tg of HPMC coating formulations was beneficial for the aqueous film coating process. Long-chain fatty acids, namely lauric, oleic and palmitic acids, did not have significant influence in moisture permeation. The hydrophobic nature of these fatty acids made it difficult for them to be incorporated in the aqueous HPMC system. Citric acid, though established to be a suitable plasticizer for HPMC (Okhamafe & York, 1987), was most effective in retarding moisture permeation among all the additives studied.

The most prominent influence of S630 was adhesion where the HPMC-S630 films adhered tightly to the glass surface of the plate. This strong adhesion was not observed in films containing PEG or PVA. For this reason, tensile tests to evaluate the mechanical properties of HPMC-S630 films were limited to concentrations of 10% and below. When compared to PEG and PVA at a 10% concentration, S630 increased the tensile strength of HPMC films, whereas both PVA and PEG reduced it, with PEG to a greater extent than PVA. At the same concentration, PEG had the highest reduction in elastic modulus and S630, the lowest. This is in accordance with the report of Okhamafe and York (1983) that PVA decreased film hardness and elastic modulus but to a smaller extent than HPMC-PEG films. It was noted that citric acid reduced the elastic modulus but increased the tensile strength of HPMC films. Work of failure was found to increase initially at concentrations of additives below 10%, with S630 showing the highest increase, compared to PEG and PVA.

Work of failure or energy used in straining the sample to failure is related to film toughness and is important in film coating as it relates to the ability of the coating to withstand shock loads without affecting adversely the integrity of the film. Overall, it could be seen that S630 had the best influence on mechanical properties of HPMC films compared to PEG, a plasticizer and PVA, a copolymer. PEG, often used in HPMC formulations to enhance film flexibility, significantly reduced the mechanical properties, including tensile strength, elastic modulus and work of failure. From this study, S630 has shown to have multiple beneficial roles in HPMC film coating formulations. Like a plasticizer, it reduced the viscosity and glass transition temperature, yet like some copolymers, it increased the mechanical strength and toughness of HPMC films. Besides evaluating the mechanical properties of free films, the properties of the film coatings have to be evaluated as the value of the data generated from free (cast) films is questionable since the method of manufacture is different from the film coat of a tablet (Li, Marteliucci, Bruce, Kinyon, Hay & Higgins III, 2002).

The tensile tester fitted with a custom-designed tablet holder was suitable for evaluating the adhesive properties of HPMC film coats. Results from the butt adhesion technique showed S630 was able to enhance the adhesive toughness of HPMC films significantly. Both PVA and S630 enhanced the adhesive strength but PEG decreased the adhesive strength as well as toughness of HPMC film coatings. In conclusion, S630 has shown to enhance both the mechanical properties of HPMC films (from cast films) and adhesive properties of HPMC film coatings. Though it has been proven that increase plasticizer concentration caused an increase in adhesive toughness of the acrylic polymer (Felton et al., 2000), PEG did not have similar influence on HPMC films. In accordance to the report that the inclusion of

additives in a basic film coating formulation would markedly influence the adhesion of the film coat to the tablet core (Khan et al., 2001), the three additives included in the HPMC film coating solutions in this study had significant influence in the film coat – substrate core adhesion.

Early studies on the adhesion of polymeric film coatings to tablet cores had used flat- faced tablets (Okhamafe & York, 1985). Recent studies involved flat-faced tablets with beveled edges (Felton & McGinity, 1996, 1997, 1999; Felton et al., 2000; Khan et al., 2001) to overcome the difficulties created by the sharp edge of the flat-faced tablets during the coating process and to lower the internal stresses within the film. The use of capsule-shaped tablets (caplets) is recommended for the ease of the coating process and to facilitate the peeling of the film coat during the butt adhesion test.

The ultra-coater has effectively combined the use of a perforated coating pan with fluidised bed technology to give high drying capacity and short processing time. Process variables, including air flow rate, temperature, humidity and atomizing air pressure, were easily monitored and controlled. The large amount of energy from the heated air was effectively used for drying the core bed. The film coating processes could be performed efficiently, resulting in an elegant and uniform coating when operated under optimal conditions, especially with regard to the spraying of the coating fluid and optimization of air flow. In conclusion, the ultra-coater (hybrid coater) was an effective equipment for aqueous film coating.

Hence this study indicates that S630, as an additive to HPMC, significantly enhances its properties as a polymer for film coating and warrants further evaluation on a range of tablet matrices.

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APPENDICES

Appendix I

Abbreviation and information on polymers and additives

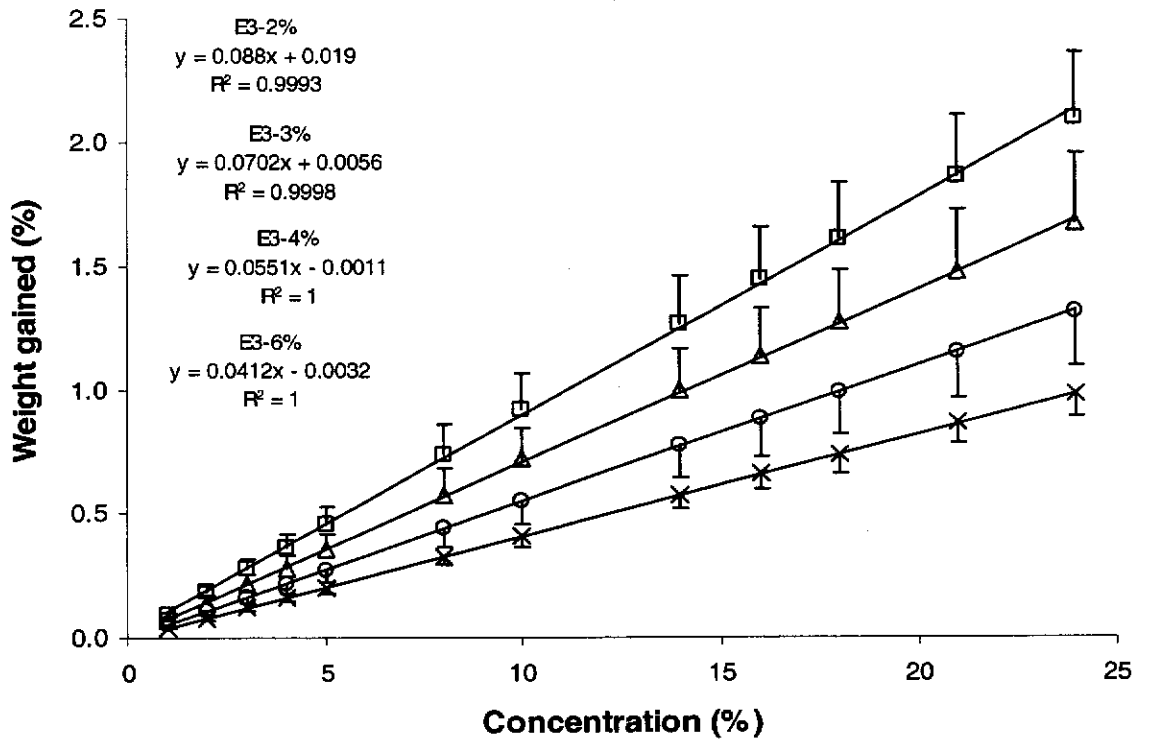
Product Name	Chemical Name	Composition	*Viscosity (mPa s) / K value
Cekol			
Cekol 30	Sodium carboxymethylcellulose	NaCMC: 99.5% Na glycolate: 0.5%	* ^a 4%: 200-500
Cekol 300	Sodium carboxymethylcellulose	Same as <i>Cekol 30</i>	* ^a 2%: 150-400
Plasdone			
C15	Polyvinylpyrrolidone	Aldehyde (%): 0.2% Vinylpyrrolidone (%): 0.2 Nitrogen (%): 11.5-12.8	K value: 16-18
K90	Polyvinylpyrrolidone	Same as <i>Plasdone C15</i>	K value: 85-95
S630	Ethenyl ester polymer with 1-ethenyl-2-pyrrolidinone or vinyl pyrrolidone / vinyl acetate copolymer		
Methocel E			
Prem LV			
E 3	Hydroxypropyl methylcellulose,	Methoxyl (%): 28-30 Hydroxypropyl (%): 7-12 Ash (%): 3 (max) Sodium chloride (%): 1.0	* ^b 2.4-3.6
E 5	Hydroxypropyl methylcellulose	Same as <i>Methocel E3</i>	* ^b 4-6
E6	Hydroxypropyl methylcellulose	Same as <i>Methocel E3</i>	* ^b 5-7
E15	Hydroxypropyl methylcellulose	Same as <i>Methocel E3</i>	* ^b 12-18
E50	Hydroxypropyl methylcellulose	Methoxyl (%): 28-30 Hydroxypropyl (%): 7-12 Ash (%): 1.5 (max) Sodium chloride (%): 0.5	* ^b 40-60
PEG 1500	Polyethylene glycol, MW = 1500	Polyethylene glycol polymers Average mol wt: 1300-1600	
PVA	Polyvinyl alcohol, 98-99% hydrolyzed	Vinyl alcohol polymer	

Viscosity:

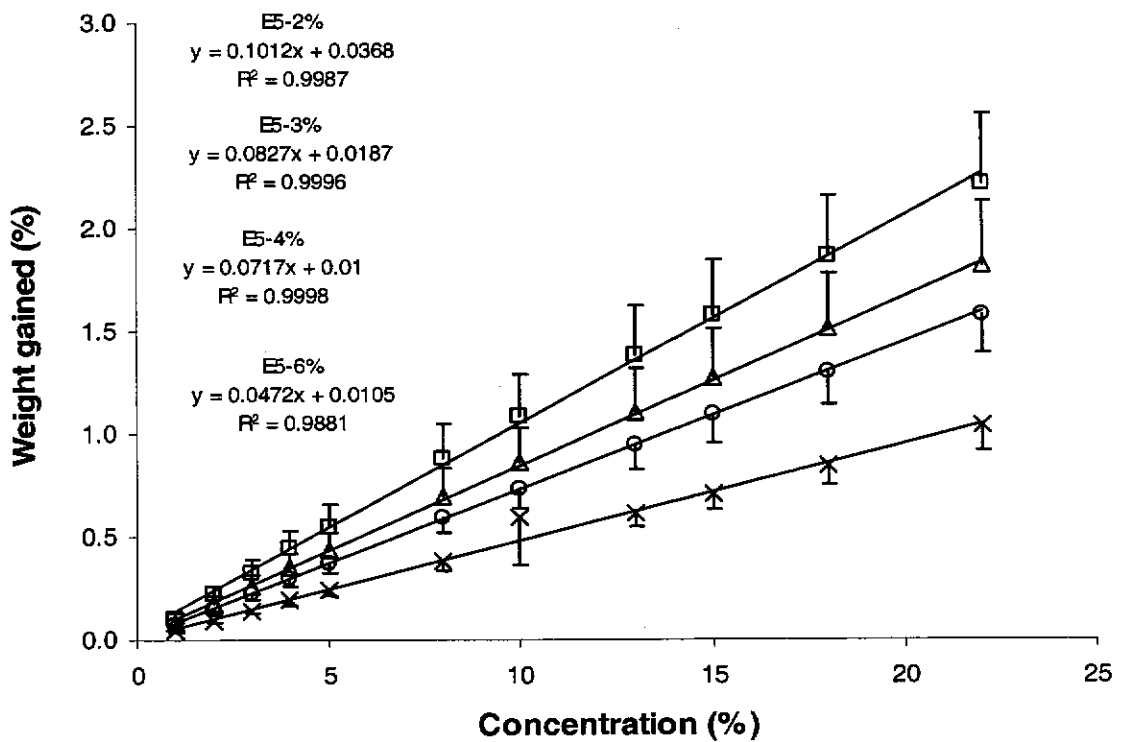
*a: At 25°C with a 4% (*Cekol 30*) and 2% (*Cekol 300*) solution in water calculated on a dry weight basis, using Brookfield LVF viscometer

*b: At 20°C with a 2% solution in water calculated on a dry weight basis, using Ubbelonde viscometers

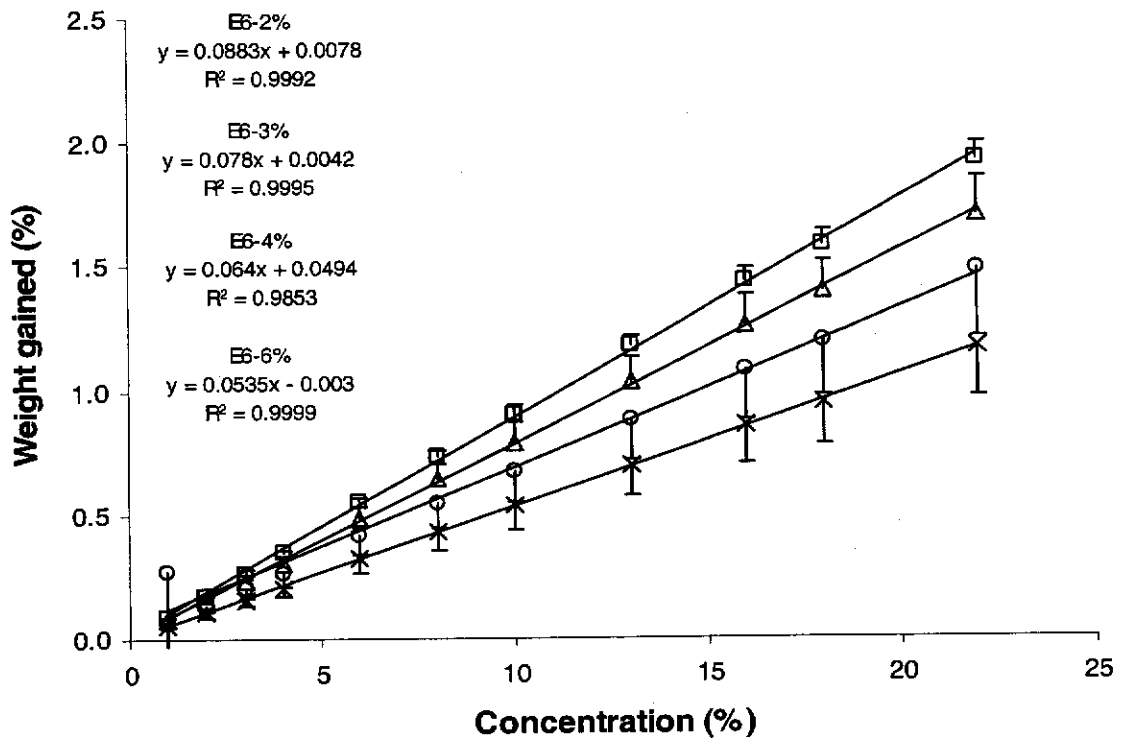
Appendix II



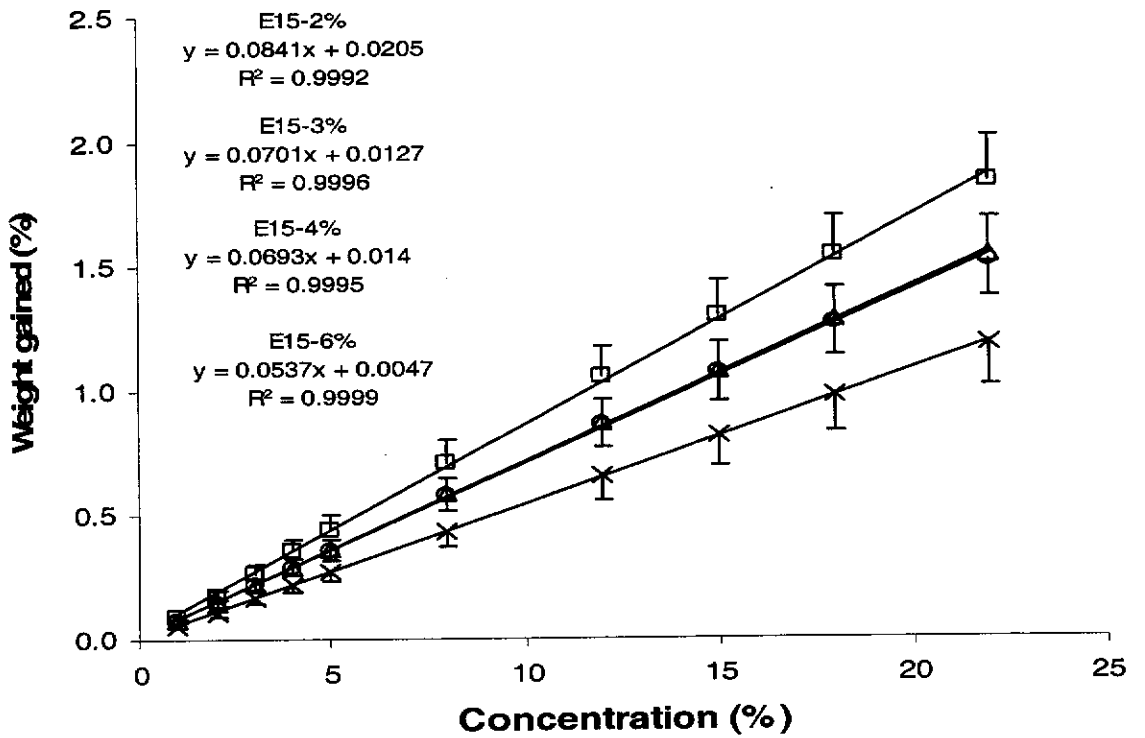
E3



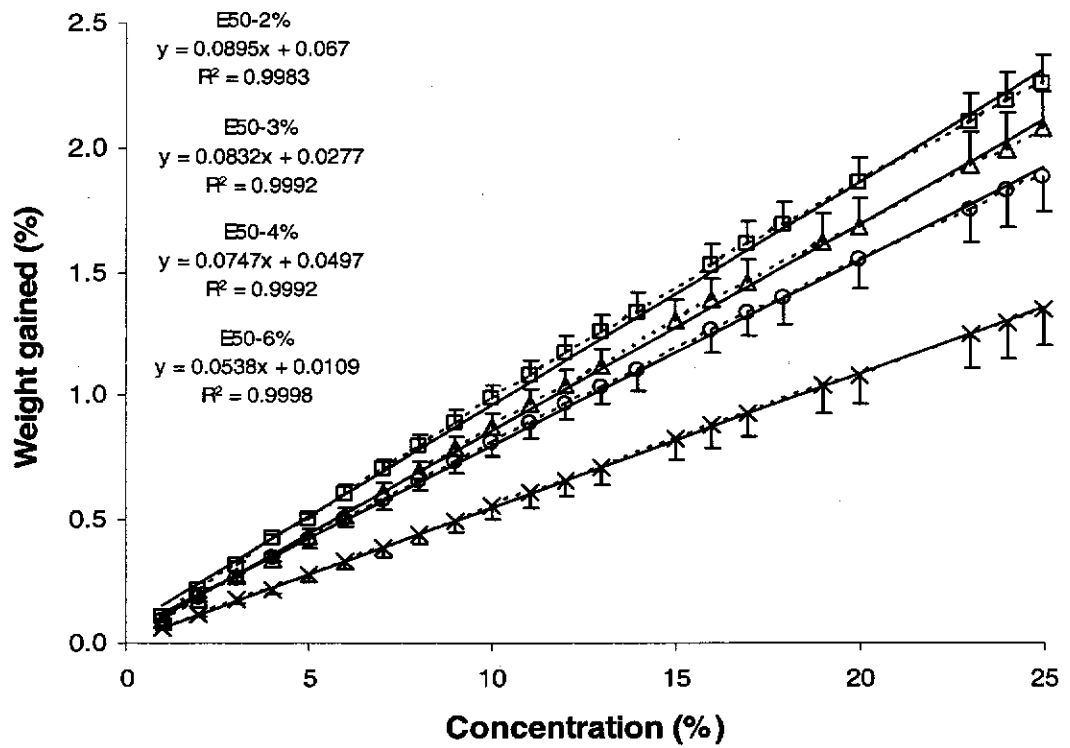
E5



E6



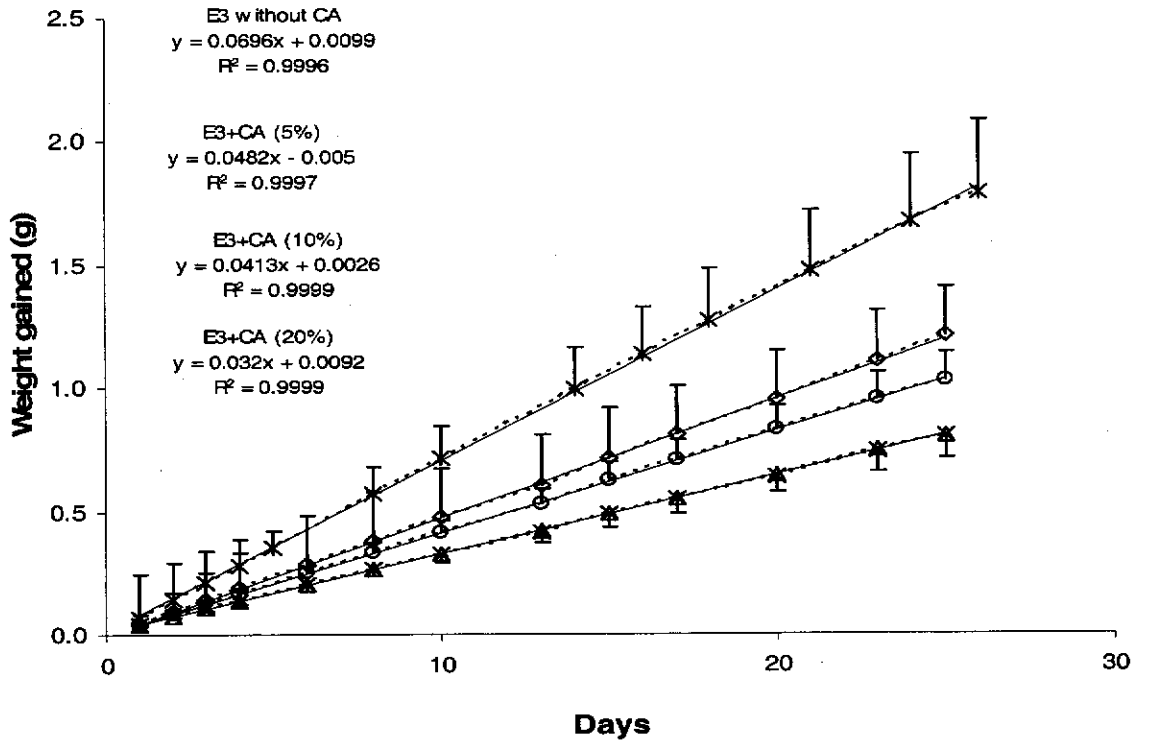
E15



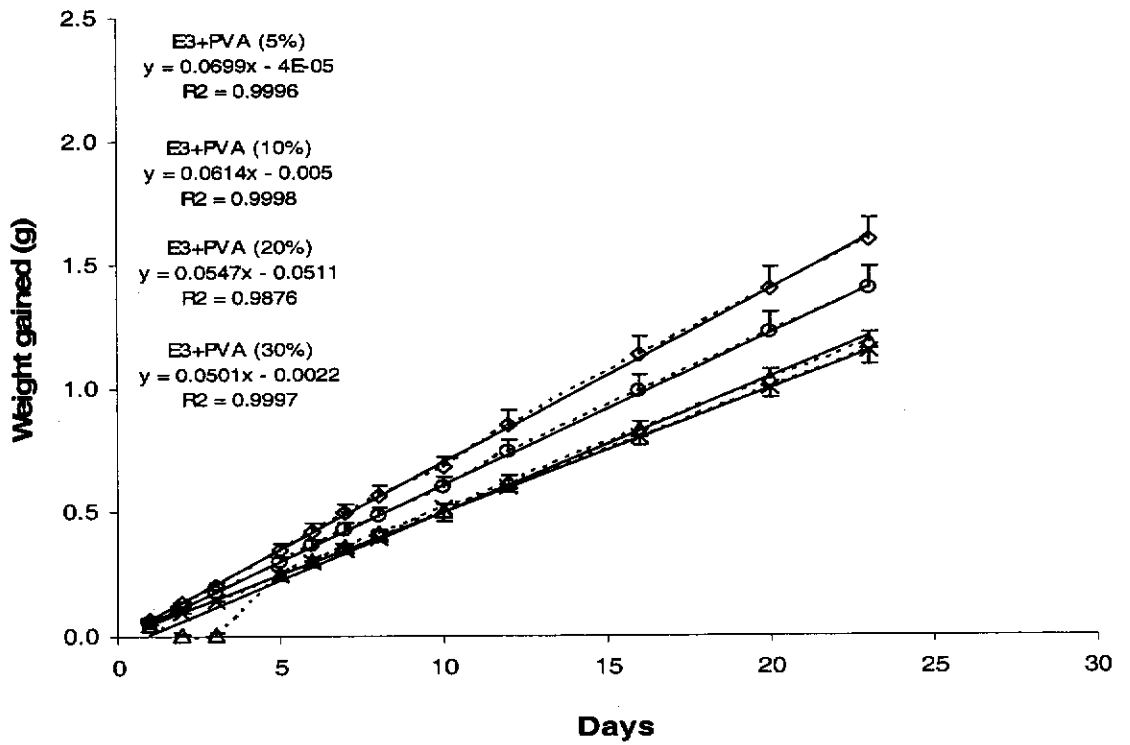
E50

Appendix II. Gradients from weight gained over test period (days) via different concentrations of HPMC E3, E5, E6, E15 and E50 films: (□) 2%, (△) 3%, (○) 4% and (×) 6%. Trendline equations are included.

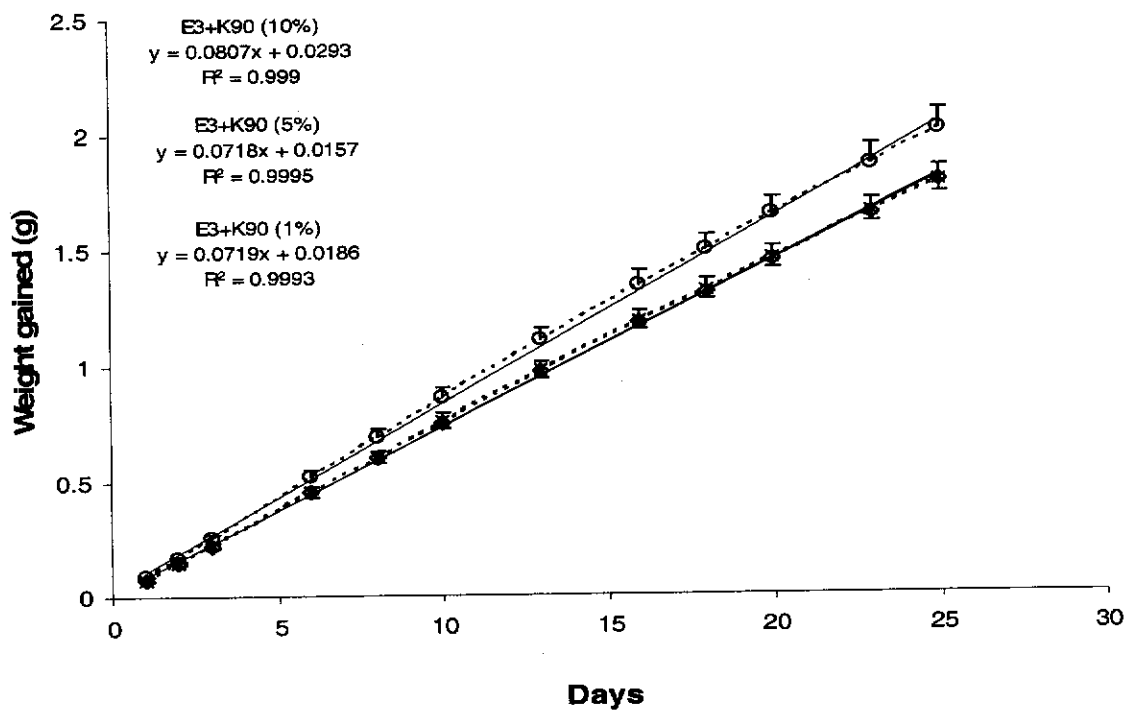
Appendix III



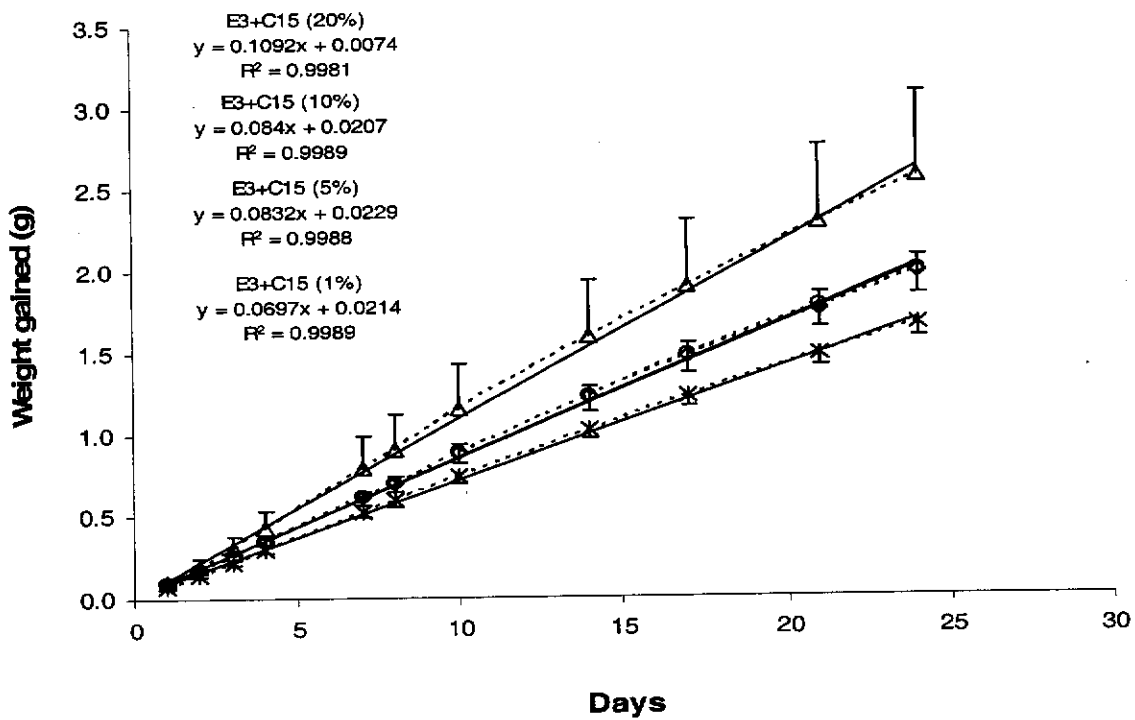
HPMC E3 with citric acid



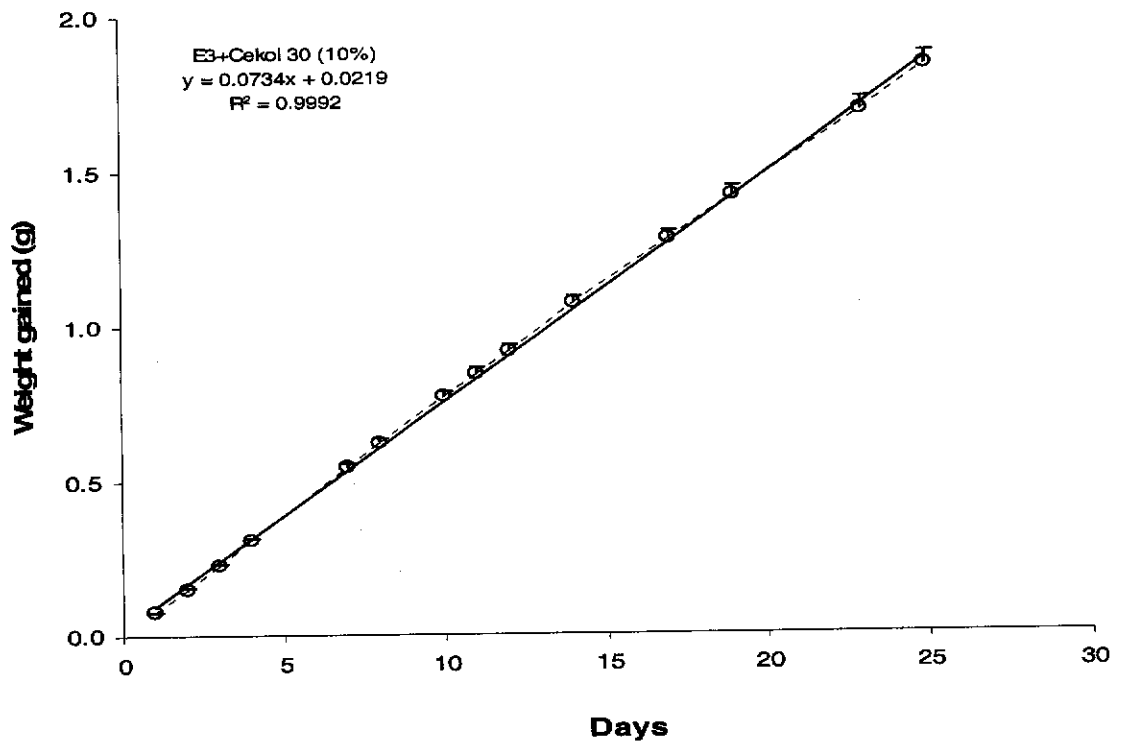
HPMC E3 with polyvinyl alcohol



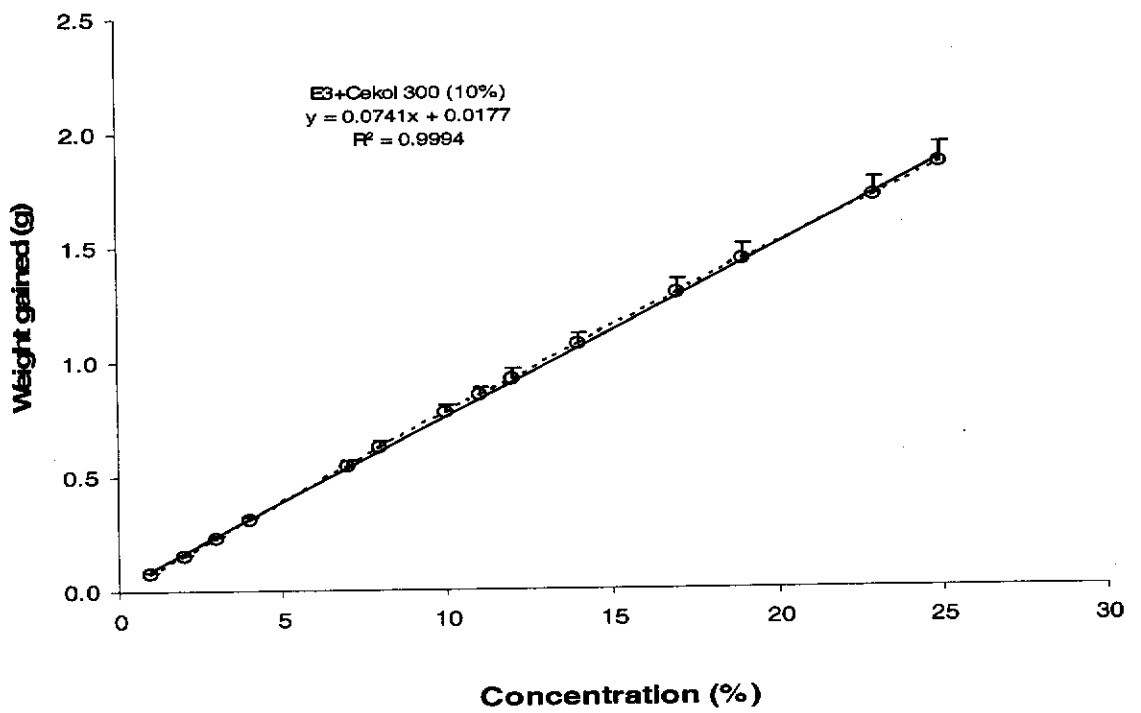
HPMC E3 with Plasdone K90



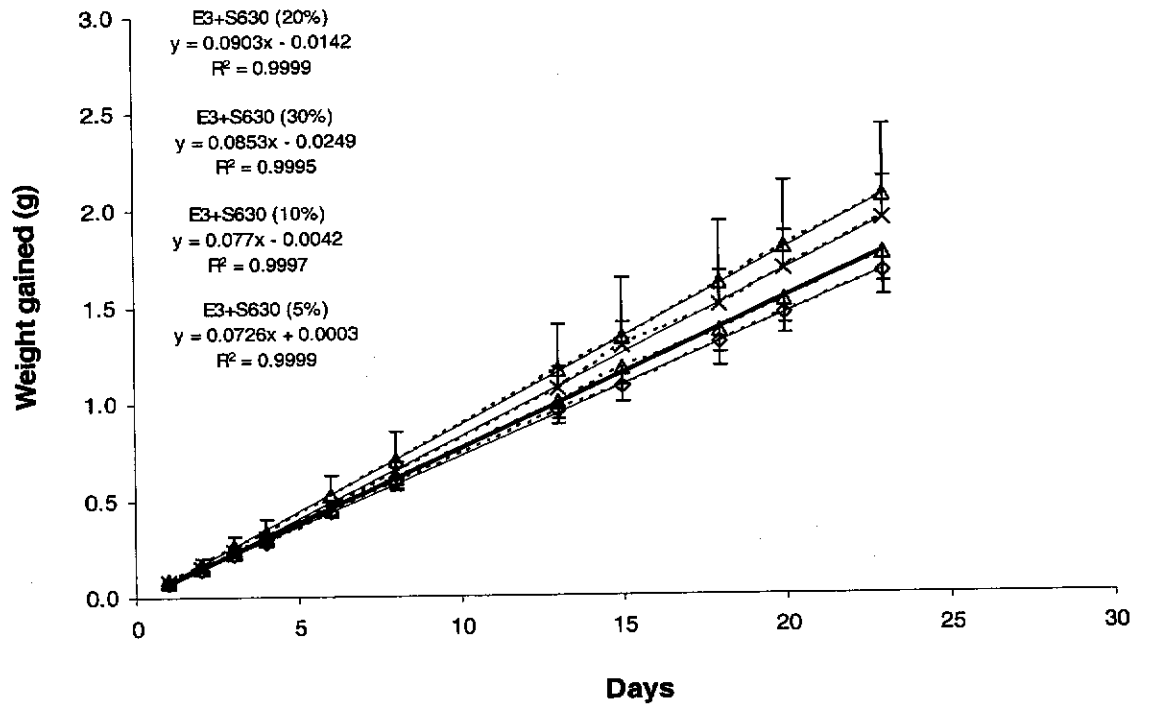
HPMC E3 with Plasdone C15



HPMC E3 with Cekol 30



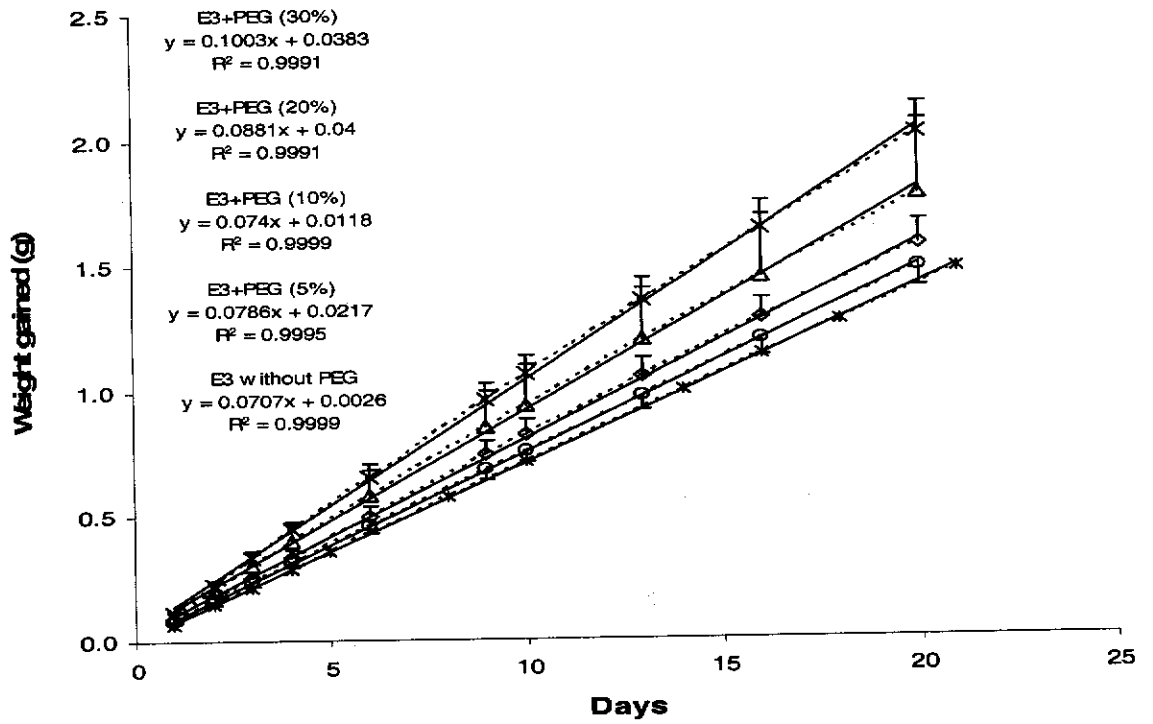
HPMC E3 with Cekol 300



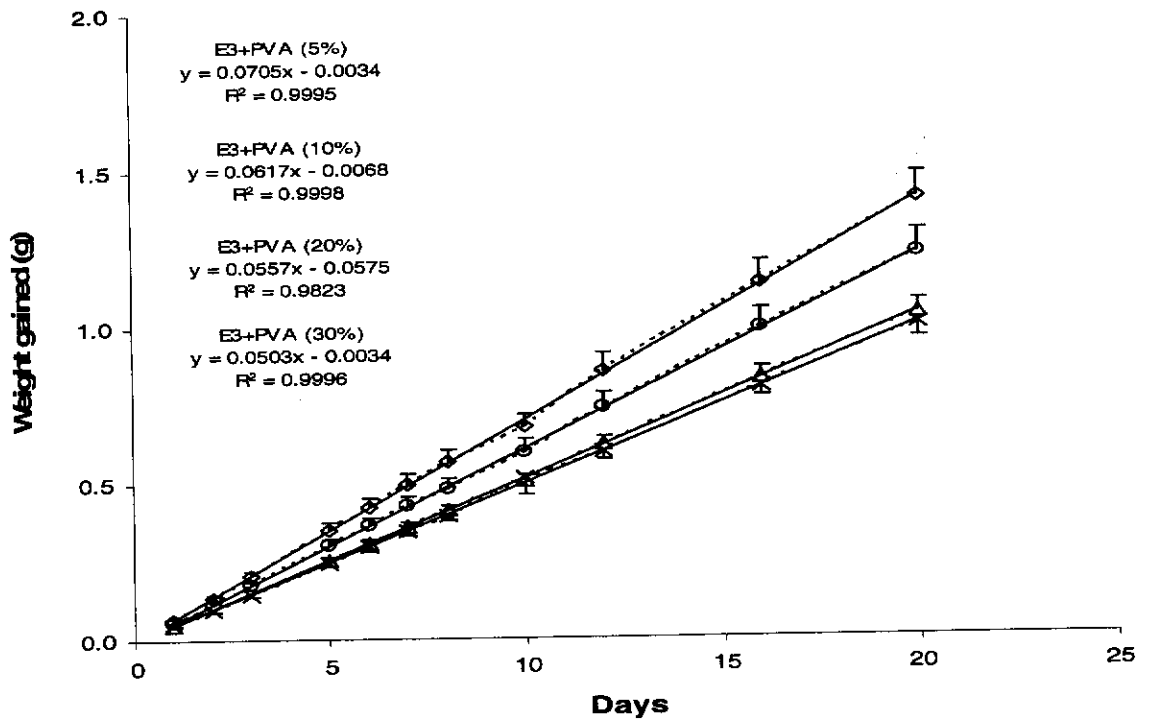
HPMC E3 with S630

Appendix III. Gradients of weight gained over test period (days) via HPMC E3 films with different concentrations of various additives: (□) 5%, (□) 10%, (□) 20% and (□) 30%. (Error bars are to 1 S.D.)

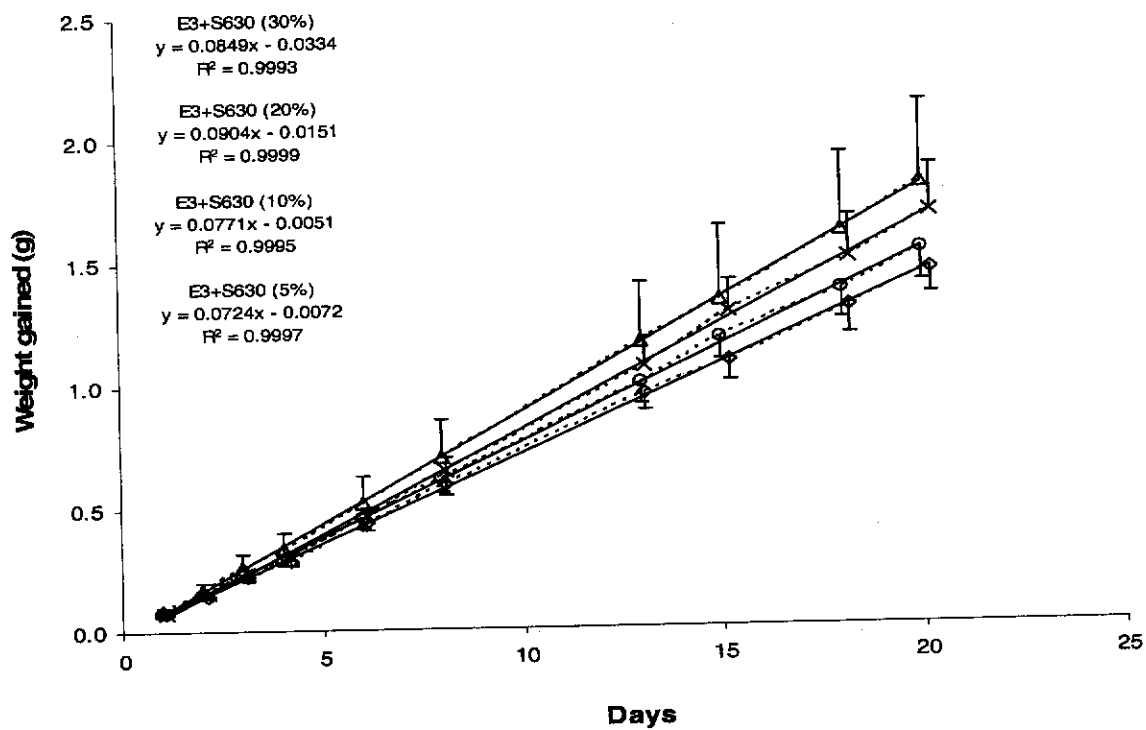
Appendix IV



HPMC E3 with PEG 1500



HPMC E3 with PVA



HPMC E3 with S630

Appendix IV. Gradients of weight gained over test period (days) via HPMC E3 films with different concentrations of PEG 1500, PVA and S630: (□) 5%, (◻) 10%, (◻) 20% and (◻) 30%. (Error bars are to 1 S.D.)

CONFERENCE PRESENTATION / PUBLICATION

Conference Presentation (Poster)

Kwok, T.S.H., Heng, P.W.S., & Sunderland, V.B. Evaluation of additives on substrate adhesion of coated HPMC film. American Association of Pharmaceutical Scientists annual general meeting, 26 to 30 October, Salt Lake City, Utah, USA.

Publication (Paper No. 103337, to be published in Chemical & Pharmaceutical Bulletin, Vol.52 No.7.)

Kwok, T.S.H., Sunderland, B.V., & Heng, P.W.S. An investigation on the influence of a vinyl pyrrolidone / vinyl acetate copolymer on the moisture permeation, mechanical and adhesive properties of aqueous-based hydroxypropyl methylcellulose film coatings.