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THE INFLUENCE OF DIFFERENT PLASTICIZERS ON SOME PHYSICAL AND MECHANICAL PROPERTIES OF HYDROXYPROPYL METHYLCELLULOSE FREE FILMS

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Coating has been widely used in pharmaceutical manufacture either as non-functional or a functional entity. The objectives of the present study were to investigate the effect of plasticizers such as PEG400, PEG1000 and triacetin on mechanical properties, glass transition temperature and water vapor transmission of free films prepared from HPMC and/or HPMC:PVA blends, to develop suitable coating system for tablets, and to determine the release profiles of the coated tablets. The tensile strength of plasticized HPMC films was generally lower than that of control HPMC film and could be attributed to increased crystallinity and segmental chain mobility of HPMC. This effect increased as the concentration of plasticizer increased. Generally the addition of both grades of polyethylene glycol (PEG400 & PEG1000) increased the moisture permeability of HPMC films but the films containing triacetin provided a more rigid barrier to moisture compared to unplasticized HPMC films. The dissolution profiles of paracetamol tablets coated with 7% w/v HPMC coating-solutions containing PEG400, PEG1000 and triacetin, and those containing PEG400 & PVA together showed that HPMC had weak water resistance. The presence of PEG400 and 1000 in HPMC films further weakened its resistance to solubility while the presence of triacetin caused a little increase in HPMC water resistance. From the results it was concluded that HPMC at 7%w/w concentration was suitable for film-coating intended for non-functional coating. Presence of the PEG 400, PEG1000 and triacetin as well as the presence of PVA and PEG400 together improved the coating properties of HPMC films and made it more suitable as a non-functional coating material.

Keywords: Plasticizers, hydroxypropyl, methylcellulose, tablet coating.

INTRODUCTION

Coating has been widely used in pharmaceutical manufacture either as non-functional or a functional entity. The non-functional coating is utilized to improve appearance or mask undesirable taste/odor and to provide additional protection whereas the functional coating is aimed at modifying release pattern of the drug. Both natural and synthetic materials have been used for coating. Sugar and film coating are the two most common types used in pharmaceutical manufacturing. The tablet dosage form is the most common dosage form to be coated.

During a film coating process, we must convert a liquid into an essentially dry solid. Dry films are those that resist blocking when two coated surfaces (e.g. two coated tablets) are brought into contact for two seconds under a pressure of 20psi. Such block resistance occurs when the viscosity of the coating exceeds 107 Pa.s (Burrell, 1962). A viscosity conducive to such blocking occurs when a coating is exposed to temperatures that exceed its glass transition temperature (T_g) by approximately 20˚C (William *et al.,* 1955). If the temperature of a product (during the coating process or storage of the coated product) exceeds the glass transition temperature of the modified polymer by more than 20˚C, tackiness becomes a problem. The presence of plasticizer and retained solvent may reduce the glass transition temperature of the polymer well below the normal value for the polymer.

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

1 Initial rapid evaporation of solvent from the atomized droplets of coating liquid cause an increase in polymer concentration and a contraction in volume of the droplets.
2 Further loss of solvent from the film at a slower rate which is now controlled by the rate of diffusion of solvent through the polymer matrix.
3 Immobilization of the polymer molecules at the solidification point, further solvent loss from the film at a very much-reduced rate and concurrent formation of shrinkage stresses within the film as a result of constrain imposed by the immobility of polymer molecules and the adhesion of coating to substrate.

According to Banker (1966) there are two sets of forces in film forming process; one operates between the film forming polymer molecules (cohesion force) and the other between the film and substrate (adhesion force). The degree of cohesion in film structure is fundamental to film properties. In order to obtain high levels of cohesion, it is necessary that the cohesive (autoadhesive) strength of the

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Table 1
Coating process conditions selected

Specification of coating apparatus/Pan	Conventional coating pan (10 kg capacity) with semi automatic coating spray machine
Tablet	
Formulation	Tablet containing 200 mg paracetamol, lactose monohydrate, corn-starch, CMC-Na, sodium and magnesium stearate.
Size	10 mm in diameter
Weight	400 mg
shape	deep convex
Hardness	9 – 10 kg
Disintegration time	35 sec
Coating solution	
HPMC (pharmacoat 606)	7 parts
Plasticizer	10 – 40 % w/w against HPMC
Sunset yellow	0.035 parts
Water	sufficient to make 100 parts
Coating conditions	
Batch size	400 gm (1000 tablets)
Pan revolution	14 rpm
Spray rate	20 ml/min
Spray cycle	spray 10 sec, interrupt 20 sec.
Spraying air pressure	4 kg/cm²
Drying air temperature	70 ºC
Tablet bed temperature	40 – 42 ºC
Coating time	120 min

material must be relatively high and the contiguous surfaces of the film material must coalesce on contact. Diffusion theory explains coalescence of polymer molecular layers or surfaces. According to this theory the movement of individual macromolecules or segment of macromolecules between and within film may occur under a variety of conditions, including during gelation, when polymers are deposited in solution over a previous polymer layer, or at elevated temperature corresponding to semisolid state (Banker, 1966).

Plasticizers are one of the most important additives that are used in coating formulations to modify film properties. Plasticization are of two types; the first is internal plasticization, and refer to a situation in which chemical change are made within the structure of the polymer itself. The second, termed as external plasticization, occurs when external additives (plasticizers) are added to the polymer. Plasticizers are commonly incorporated with the polymeric film formers, and change the flexibility, tensile strength and adhesion properties of the resulting film. Basically, any plasticizer added must first be compatible with the polymeric film formers to produce a good appearance and desirable physical properties of the finished film (Rowe, 1984). Plasticizers not only enhance flexibility and reduce the brittleness of the film but also may control the drug penetration through the polymeric film (Rowe, 1984; Okhamafe and York, 1987). Thus, plasticizers play an important role in the polymeric film coating. Coating formulations consisting of soluble polymeric film-formers, particularly the water-soluble cellulose ethers (Aldujaili *et al.,* 1986) are known to be tacky in nature. Anti-tack additives employed in sufficient quantities can reduce the tackiness of the film former, whilst also exerting a significant influence on the drug release behavior of sprayed films formed from water-soluble polymers (Lucy *et al.,* 1993). Examples of anti-tack additives used in film coating formulations include talc (Fukumori, *et al.,* 1987), silicon dioxide and kaolin (Ghebre-Sellassie *et al.,* 1986). Incorporation of plasticizers such as polyethylene glycol, triacetin, triethyl citrate and film formers Polyvinyl alcohol in HPMC solution have all reduced tack force (Heng *et al.,* 1996; Saringat *et al.,* 2004).

Mechanical properties of free films are measured to assess the strength or toughness of the films and their deformation characteristics. Parameters such as tensile strength, toughness and elongations can be measured to evaluate the film properties. These properties are an important characteristics which help to predict the stability and release property of film-coated dosage forms and also provide information concerning possible interaction between the components (such as polymer, plasticizer, pigment) in the coating films (Obara and McGinity, 1994; Baie and Sarwar, 1995).

Table 2
DSC data (melting temperature (Tm) and enthalpy (ΔH)) of HPMC/PVA blends as cast run at 10°C min^{-1}

Blends ratio	Enthalpy as cast (ΔH) (Jg^{-1})	Melting temperature as cast (Tm)°C
9:1	1.582±0.0845	180±0.415
8:2	2.268±0.2211	180±0.2699
7:3	2.807±0.2138	180±0.294
6:4	3.827±0.2798	180±0.5496
5:5	5.855±0.5686	180±0.9046
9:1 blend Triacetin 10%	2.393±0.1915	174±0.2073
20%	2.062± 0.0725	174±0.5186
9:1 blend PEG1000 10%	0.804±0.0390	175±0.1608
20%	0.689±0.0935	174±0.7942
30%	0.646±0.0581	175±0.7423

Table 3
DSC data (melting temperature (Tm) and enthalpy (ΔH)) of HPMC/PVA blends after annealing (run 2) run at 10°C min^{-1}

Blends ratio	Enthalpy after annealing (run 2) (ΔH) (Jg $^{-1}$)	Melting temp. after annealing (run 2) (Tm)°C
9:1	4.797±0.3213	168±0.1589
8:2	6.946±0.3820	174±0.1632
7:3	6.518±1.2730	173±0.3555
6:4	7.536±0.5715	174±0.3605
5:5	7.316±0.5008	174±0.3007
9:1 blend Triacetin 10%	5.385±0.2506	163±0.8932
20%	5.853±0.2928	163±1.1481
9:1 blend PEG1000 10%	1.510±0.1273	169±1.2713
20%	1.684±0.0355	167±1.2724
30%	2.446±0.2246	166±1.071

Another parameter used to characterize free films is water vapor transmission. Studies that measure the transmission can be used to evaluate film integrity and the permeability of the film to water vapor which in turn provides useful information about the effect of the film on the stability of the coated product (Wang, 1994). Several workers have extensively reviewed the techniques and mathematical derivations and theories for calculating rates of moisture permeation (Banker *et al.,* 1981; Lieberman *et al.,* 1998). In this study, the water vapor transmissions of the formulations studied were evaluated as a function of plasticizer concentrations and types.

In a previous investigation (Saringat, *et al.,* 2004) of this series of our research work we evaluated the HPMC coating solutions for their tackiness and investigated the effects of interactions between the polymer and plasticizers on the tack behavior of HPMC film-forming coating solutions. The objectives of the present study are:

1. To study the effect of PEG400, PEG1000 and triacetin on mechanical properties, glass transition temperature and water vapor transmission of the HPMC free films.
2. To study blends compatibility in HPMC and polyvinyl alcohol blends using differential scanning techniques.
3. To study mechanical properties, glass transition temperature and water vapor transmission of HPMC:PVA blends free films and the effect of PEG400, PEG1000 and triacetin on these properties.
4. To develop a coat for tablets using HPMC and PEG400, PEG1000, triacetin and polyvinyl alcohol.
5. To determine the drug release profiles of the coated tablets.

MATERIALS AND METHODS

Materials

The materials used were hydroxypropyl methylcellulose (HPMC – Pharmacoat 606 (Shin-Etsu Chemical Co., Tokyo, Japan), polyvinyl alcohol (PVA) 86.5-89% degree of hydrolysis (BDH, UK), polyethylene glycols (PEGs) with nominal molecular weights 400 and 1000 g/mole (BDH, UK), triacetin (TA) (Sigma, Germany), microcrystalline cellulose NF (Avicel-101) (Asahi chemical, Japan), lactose monohydrate (MHS, Holland), paracetamol (Wenzhou Pharma, China). Carboxymethylcellulose-sodium (CMC-Na) (Sigma, Germany), potassiumdihydrogen phosphate (Riedel-dehaën, Germany), sodium hydroxide (Merck, Germany), zincsulphate hepta-hydrate (R & N Chemicals, USA) and sodium dichromate (BDH, UK).

Equipment

The equipment used were model AA-160 analytical balance (Denver Instrument, USA), torsion balance (White electric), Vacuum pump (Buchi B169, Switzerland), Ubbelohde Viscometer (Cannon instrument, USA), glass plates, hot air ovens, micrometer (Mitutoyo, Japan), type 814 Hygrometer (Gebrauchsanleitung fur, Germany), TA-XT2 texture analyzer (TA, England), glass vials with open top screw cap (Borosilicate, USA), differential scanning calorimeter (Perkin Elmer, USA), 5 kg mixer (Tylore, Taiwan), FGM/500 granulator (Erweka, Germany), model FBD/L72 fluid-bed drier (Mostyn Flintshire, UK), LP16 LOD moisture analyzer (Mettler, Switzerland), single punch tablet machine (Kosch, Germany), TA 3R friability tester (Erweka, Germany), TB 24 hardness tester (Erweka, Germany), conventional coating pan (Khotary Pharma, India), dissolution apparatus (Pharma test, Germany) and model U-2000 spectrophotometer (Hitachi, Japan).

Table 4
DSC data for plasticized HPMC/PVA blends after annealing (run 2) run at 10°C min^{-1}

Blend ratio	Glass transition temperature (Tg) °C
HPMC/PVA blends (unplasticized) 9:1	68.631±0.47674
8:2	68.592±0.78644
7:3	68.460±0.75846
6:4	69.026±0.59109
5:5	68.430±0.42499
9:1 blend Triacetin 10%	65.339±0.40398
20%	65.835±1.27341
9:1 blend PEG1000 10%	65.836±1.08480
20%	61.948±0.16901
30%	55.417±0.88002

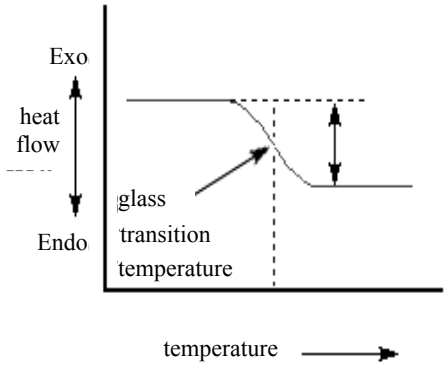


Fig. 1a: Schematic diagram for calculation of glass transition temperature.

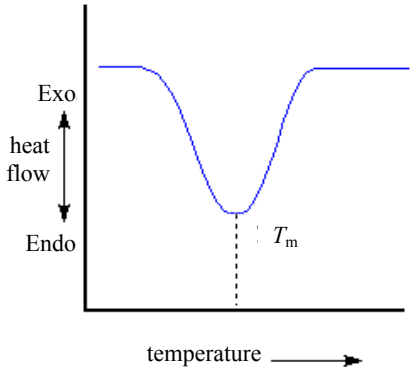


Fig. 1b: Schematic diagram for calculation of melting temperature.

Methods
Viscosity measurement, preparation of coating solutions and tack measurement of coating solutions were performed as described in our previous paper (Saringat, *et al.,* 2004).

Preparation of free films
All free films were prepared using cast method. Clean glass plates with boundaries on the edges were used to prepare free films for the testing of tensile strength, water permeability and glass transition temperature. The plates were leveled by spirit level to ensure uniform film thickness. 25 ml of each filtered solutions was poured in the glass plate and the solvent was allowed to evaporate at 60ºC for 2 hours in a hot air oven at 75%±2 relative humidity (RH) and then kept for 48 hrs at ambient temperature. Dried cast films were cut by knife and kept in a desiccator at ambient temperature and 75%±2 RH until required.

Measurement of mechanical properties
Mechanical properties of free films were measured using a TA-XT2 Texture Analyzer with 50 N load cell and constant cross head speed of 5mm/min. The film specimens with a uniform thickness (6 x 1 cm) were cut and film thickness measured at five different points. The initial length of the film specimens was 30 mm. Readings of minimum four samples from each system were recorded. The temperatures were held constant for all mechanical tests. The stress-strain curves were recorded for each sample and the tensile strength at breaking point and the percent elongation-at-break were calculated as following:

Tensile strength = Break force/AB
where, A and B are width and thickness of the test film respectively.
%elongation-at-break (%EB) = (L / Lo) X 100
where, Lo = original length of the sample, and
L = difference in the length at breaking point

Differential scanning calorimetry
Polymers have a higher heat capacity above the glass transition temperature than they do below it. Due to this change in heat capacity occurring at the glass transition, we can use differential scanning calorimetry (DSC) to measure the glass transition temperature of polymers. DSC studies were performed over a temperature range of 0 to 270ºC using a Perkin Elmer DSC (USA) equipped with a refrigerated cooling accessory (RCS). The purging gases used were dry nitrogen and helium, both at the flow rate of 20ml/min. The DSC was calibrated for baseline using empty pans of matched weight, and for temperature using zinc and indium. The instrument was also calibrated for the enthalpy of fusion using indium. The pan type used was aluminum pan for non-volatile sample (Perkin Elmer, USA). 10 mg of sample was accurately weighed (up to 0.01mg) in the pan using model AA-160 analytical balance (Denver, USA) and the lid was crimped onto the pan. The samples (as cast)

were held at 125ºC for 5 min prior to analysis to remove water. Samples were then cooled at 40ºC min^{-1} to 0ºC and held at this temperature for 1 min, and then re-run from 0 to 270ºC at 10ºC min^{-1} heating rate. Three measurements were performed for each system. The glass transition temperatures, melting temperatures and enthalpies associated with endotherms of the samples were determined. The glass transition was determined as the midpoint temperature of the heat capacity endothermic change (half cp extrapolated) (fig. 1a). The peak temperature of the melting endotherm was taken to be the melting temperature (T_m) of the polymer (fig. 1b). The software used for analysis of data was DSC Pyris 6.

Permeability studies

The measurements of water vapor permeation through the films were carried out using 50 ml glass vial with open metallic cap containing supersaturated zinc sulfate-heptahydrate solution, which gave an internal relative humidity of 90% at 25±2ºC. The method was modified from that of Guo *et al.* (1993). A schematic diagram of permeability cell is given in fig. 2. Films of a known thickness were mounted on the opening of vials containing zinc sulfate-heptahydrate as a desiccant. The films were 0.095-0.12 mm thick and the exposed surface area for water vapor transmission was 0.95 cm^2. Metal seals (with open top) were put over the film to make a tight joint between the film and the vial. The original weight of each vial was measured and then placed in a desiccator at 25±2ºC and 55%±2 RH over 72 hours. The pre-weighed vials were removed from the desiccator, weighed, then returned back to the desiccator every 12 hours. Zero time was considered after the first 12 hours of an equilibrating period. The experiment was performed three times on any free film formulation. The moisture transmitted through the film was given by the decrease in the total weight of the permeability cell.

Tablets preparation

Both placebo and paracetamol tablets were prepared by wet granulation method (Saringat *et al.,* 2004). Placebos were used for the optimization of coating process parameters such as batch size, solution spray rate, atomizing air pressure and temperature of drying air. The tablets were compressed to 9 kg hardness by means of deep concave punches and dies in a single punch tablet machine (Kosch, Germany).

Coating process

Paracetamol is used as a model drug (cheap, available and easy to analyze) to evaluate films with respect to stability and integrity of the tablet coats, the physico-chemical characteristics of the coated tablets and drug release. A conventional coating pan (Khotary Pharma, India) was used to coat the tablets. It uses the principle of tablets/granules tumbling and moving because of rotary momentum of the pan. It is also equipped with a hot air blower and a semi

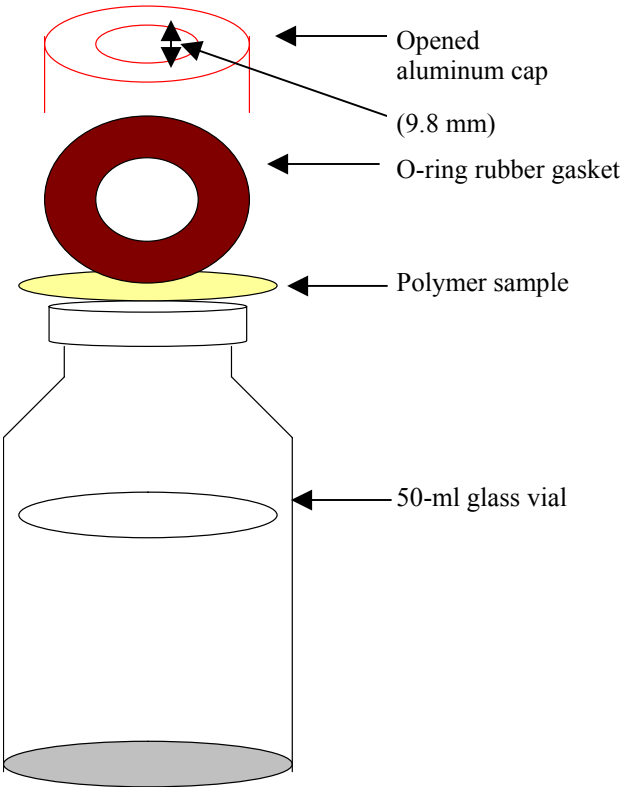


Fig. 2: Schematic diagram of permeation cell.

automatic spray coating machine. The suitable volume of coating liquid to be used to develop 0.05 mm thick film onto the substrate was found to be 250 ml of 7% w/v coating solution. The coating solution delivery equipment (pressurized container) supplied with the pan coater has a capacity of 10 liter. Since it was difficult to prepare this quantity of coating solution at a laboratory scale, a modified delivery container was used to enable the reduction of the volume of the coating solution to be prepared to 250 ml/batch.

Using placebo tablets, process parameters were optimized, and then the selected process conditions were used to coat paracetamol tablets. The tablets bed was warmed up at the required temperature for 15 min then the coating solution were sprayed onto the tumbling tablets bed. After the completion of spraying, coated tablets allowed to tumble in the coating pan for 10 minutes to ensure complete drying.

Dissolution studies

The release properties of coated and uncoated 200mg paracetamol tablets were studied using basket method (method II, USP XXII; basket vessel apparatus model, 900ml, 37ºC, 50 rpm. Distilled water was used as a dissolution medium for all measurements. Six tablet of each sample were studied.

5-ml of samples were withdrawn at pre-selected intervals, then replaced with an equal volume of dissolution medium pre-equilibrated at the same temperature, using automated sampler. Sampling took place halfway up the basket at mid point between the basket and the wall of the dissolution vessels. Samples removed were automatically filtered with a filters attached to sampler probe and the absorbance of the sample solution was measured using model U-2000 Hitachi spectrophotometer (Japan) operated at the wavelength of 242.8 nm.

The drug concentrations of the samples were determined by interpolation from standard curve of solutions of paracetamol powder in a medium similar to the dissolution medium used for samples test. The standard curve consisted of five different concentrations of paracetamol powder ranging from 5 to 175µg/ml.

RESULTS AND DISCUSSION

Coating process conditions

Process variables such as minimum-optimum batch size, appropriate spray rate, atomizer pressure and the temperature of drying are of great importance regarding the final coating properties and quality. Proper distribution of coating material, uniformity of the film and surface smoothness are correlated to batch size. Spray rate used is governed by drying temperature, rotation per minute (rpm) of the coating pan, atomizing air capacity and viscosity of solution. For aqueous based solution, comparatively high drying temperature is required. Beside this a high atomizing pressure is also required to achieve small droplet size that affects the wetting. However too small droplet size causes spray drying. A series of experiments were carried out using placebo tablets as a coating substrate in order to obtain an optimum coating process using conventional coating pan with aqueous film coating. Table 1 presents the process conditions adopted for subsequent experiments.

Mechanical properties of fee films

Mechanical properties of polymeric film included tensile strength, Young's modulus, elongation, hardness, stress crack resistance, and incidence of cracking and edge splitting. Percentage elongation at break and tensile strength are two of the most commonly measured mechanical properties. Thus the work in this section duly focused on these two properties.

Microstructure as well as physicochemical properties (features such as polarity, crystallinity, chain stiffness and cross-linking) of the film affect the mechanical properties (Okhamafe and York, 1983). Microstructure depends upon formulation factors such as presence of other film formers (plasticizers and insoluble additives), solvent system, film thickness and operating conditions. Presence of plasticizer enhances the segmental mobility of polymer chain resulting in loose structure; hence reduced tensile strength and increased elongation (Okhamafe and Yourk, 1983, 1987). Presence of insoluble additives, crystallinity and cross-linking hinder the mobility of polymer chain resulting in higher tensile strength and lower elongation (Okhamafe and Yourk, 1983, 1985a). Therefore, the structural and formulation factors exert effects on mechanical properties.

Tensile strength at break

The mechanical properties of cast films were examined by tensile testing. The effect of different plasticizers and additives (PEG400, PEG1000, triacetin and PVA) on tensile strength of HPMC films is presented in table 1 and figs. 3a and b. Since triacetin levels greater than 20% caused blooming in films prepared by casting method, no tensile strength or elongation study was performed above this level. The tensile strength of plasticized HPMC films was generally lower than that of control HPMC film. This effect increased as the concentration of plasticizer increased. Incorporation of PEG400 and PEG1000 up to 30% w/w level, decreased the tensile strength of HPMC films significantly and when increased above this level no further significant change in the tensile strength was observed (fig. 3a). Triacetin at 10 and 20% level also decreased the tensile strength of HPMC films at breaking point but to a lesser extent compared to that of PEG400. The decrease in tensile strength of plasticized HPMC films is attributed to increased segmental chain mobility of HPMC. Plasticizers react with HPMC, and this reaction involves hydrogen bonding between adjacent segments of the HPMC film in which plasticizer becomes sandwiched. The result is a loose structure in which reduced links between the segments of HPMC film leads to enhanced segmental mobility characterized by increased water diffusion and lower resistance to stress and to deformation characterized by decrease in the tensile strength and increase in the elongation.

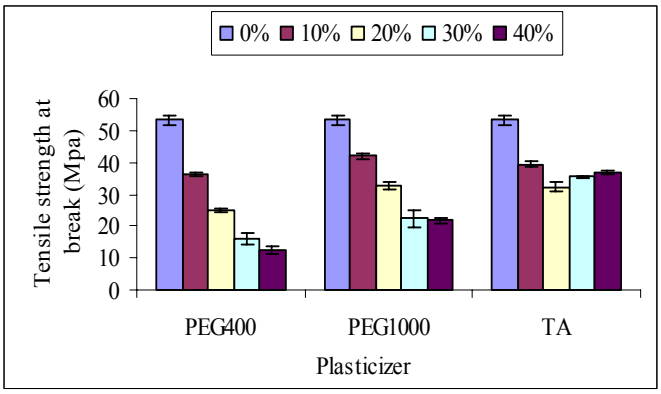


Fig. 3a: Comparison of ultimate tensile strength at break for HPMC films plasticized with 10-40% w/w PEG400, PEG1000 and triacetin.

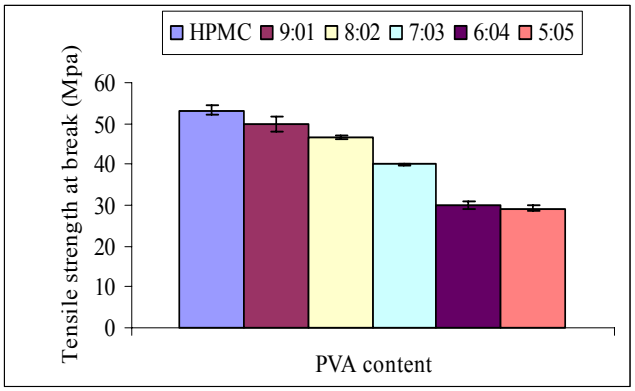


Fig. 3b: Comparison of ultimate tensile strength at break for HPMC cast films blended with PVA at ratios 9:1, 8:2, 7:3, 6:4 and 5:5

Honary & Orafai (2002) reported that the reduction in tensile strength of HPMC films when plasticized with PEG could be explained by gel theory. This theory assumed that active center forces attract polymer molecules in solution to each other. The formation and breakage of these bonds are in a dynamic equilibrium in solution form. As they break, water molecules are in competition for the active sites. Plasticizers will also be in competition for the same sites and will thus reduce the number of active centers and the number of polymer-polymer contacts, so they could decrease the rigidity of the three dimensional structure formed on drying. From the result, PEG400 was a more effective plasticizer than PEG1000 and this is in agreement with Okhamafe & York, 1983 and Honary & Orafai, 2002. This can be explained by the fact that there will be more molecules (in case of PEG400) and therefore more chances of competition for active sites, per gram of added PEG (Honary & Orafai, 2002).

Polyvinyl alcohol (PVA) lowered the tensile strength of HPMC films (fig. 3b). However, the decrease in tensile strength is much less as compared to that of plasticizers used in this work. This can be explained by the proposed increase in crystallinity of HPMC/PVA films which prevented a large drop in tensile strength at break compared to plasticized HPMC films. The blends of HPMC/PVA increased the crystallinity of the films and consequently, more compact films were obtained. Crystallinity indicates a state of higher molecular order with little or no polymer chain mobility that will, therefore, have the effect of increasing the mechanical properties of the film.

Tensile strength of 9:1 & 8:2 HPMC: PVA film blends containing 400, PEG1000 and triacetin are presented in figs. 4 and 5. The results show that the tensile strength of plasticized HPMC: PVA blends was generally lower than that of unplasticized control (HPMC 606) films. The tensile strength of 9:1 blends containing PEG400 and triacetin at concentration of 10% were found to be significantly lower than that of the control HPMC film. Further increase of concentration of these plasticizers up to 20% and 30% levels resulted in a further decrease of the tensile strength. In the case of PEG1000 the significant decrease in tensile strength was recorded at 10 and 20% and when the concentration increased from 20 to 30 and 40%, no further significant change was observed.

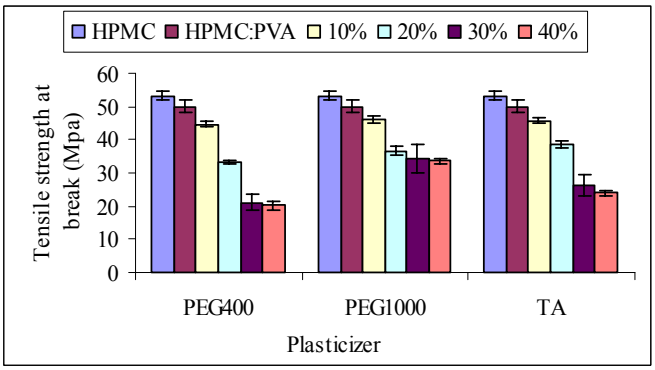


Fig. 4: Comparison of ultimate tensile strength at break point for control HPMC films and (9:1 HPMC/PVA blends) cast films containing different concentrations of polyethylene glycol 400 (PEG400), polyethylene glycol 1000 (PEG1000) and triacetin

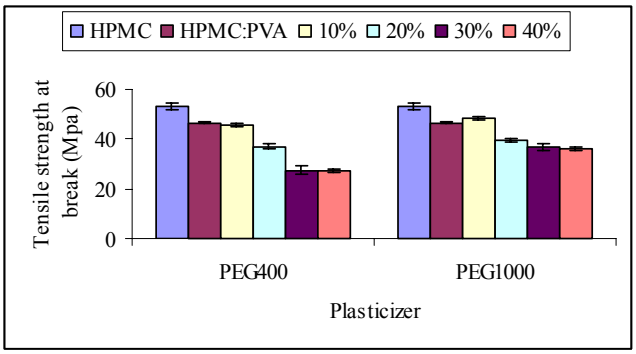


Fig. 5: Comparison of ultimate tensile strength at break point for control HPMC film and (8:2 HPMC/PVA blends) cast films containing different concentrations of polyethylene glycol 400 (PEG400) and polyethylene glycol 1000 (PEG1000).

When the ratio of PVA in the blends increased from 9:1 to 8:2, the tensile strength for films containing PEGs significantly decreased to a lesser extent compared to that of 9:1 ratio blends. In addition, the films containing triacetin at all levels showed unsatisfactory appearance so that no tensile strength or elongation studies were performed for such films. When added to HPMC/PVA blends, both polyethylene glycol grades preferentially plasticized HPMC.

Furthermore these plasticizers were relatively not compatible with PVA as observed in thermal studies. The effect of PEGs on film blends may be attributed to a decrease in the crystallinity of film blends and to an increase in film flexibility.

Elongation at break

Elongation is referring to the maximum extension gained by the film at break. Plasticizers are often added to the coating polymer to enhance their film forming characteristics by interposing themselves between the polymer chains and affect the forces which hold chains together, thereby extending and softening the polymer matrix (Entwistle & Rowe, 1979). The PVA, when incorporated into HPMC film, significantly reduced the elongation. In addition, this effect became more pronounced with increasing PVA concentration, as shown in and fig. 6a. The decrease in elongation by addition of PVA is attributed to the increased crystallinity and reduced chain mobility.

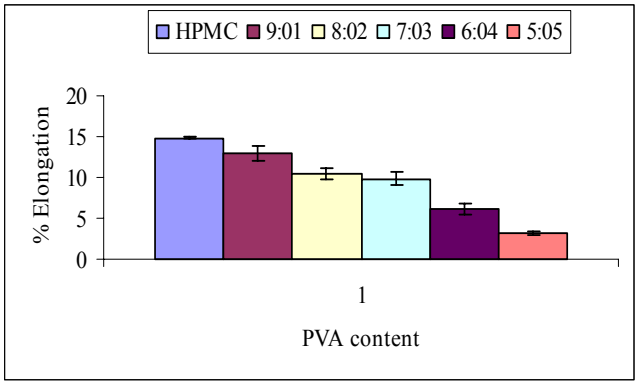


Fig. 6a: Percentage elongation of HPMC films containing PVA. The ratios were 9:1, 8:2, 7:3, 6:4 and 5:5 w/w HPMC: PVA.

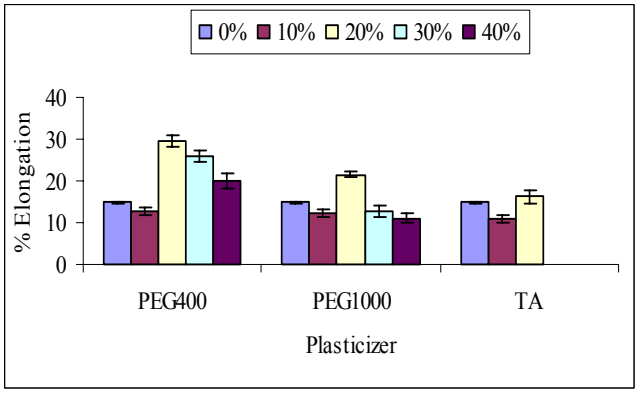


Fig. 6b: Percentage elongation of HPMC films containing 0, 10, 20, 30 and 40%w/w PEG400, PEG1000 and triacetin.

Values for percentage elongations calculated from stress strain profiles of HPMC films having different Plasticizers at different concentrations are presented in fig. 6b. These values show that addition of plasticizers (PEG400, PEG1000 and triacetin) increased the elongation at break of HPMC films. At the concentration of 10% w/w, PEG400 caused a slight decrease in elongation of HPMC and the highest elongation obtained when concentration rose to 20%. Further increase in the concentration to 30 and 40% w/w caused a drop in elongations but still were significantly above that of HPMC films. Similarly, the elongation of HPMC films decreased slightly when 10%w/w PEG1000 was added and a significant increase in elongation was observed when the concentration was raised to 20% w/w. Above this concentration, no significant change in the elongation was observed. Films containing 10 and 20% w/w triacetin showed a significant increase in the elongations. In terms of elongation, the efficiencies of the plasticizers were ranked as PEG400 > triacetin > PEG1000. Improved elongation at break of HPMC films by incorporating PEG400, PEG1000 or triacetin could be attributed to the interaction of plasticizer with HPMC which result in decreased molecular order and enhanced chain mobility of HPMC. These results are in agreement with those of the Johnson *et al.* (1991) who reported that both triacetin and PEGs increase chain mobility of HPMC films.

Percentage elongations values for 9:1 and 8:2 HPMC:PVA blends plasticized with 0 to 40% w/w PEG 400, PEG 1000 and triacetin are presented in figs. 7 and 8. For the 9:1 blend containing 20% PEG grades, higher values for the percentage elongation were observed, compared to the control HPMC. However, the films containing triacetin did not increase the elongation. At all levels of PEG400 and PEG1000, no significant increases were recorded for 8:2 blends compared to control HPMC.

An ideal tablet film coat should be hard, tough and extendible. Hard and tough polymer is characterized by high tensile strength and moderate elongation at break. Plasticization usually decreased tensile strength at break and increase elongation at break of HPMC (Okhamafe and Yourk, 1983). Films prepared with incorporation of PEGs at 30% concentration were soft and tough, while those prepared from 20% PEGs and 10 and 20% triacetin were comparatively hard and tough. Films prepared from 9:1 blend of HPMC:PVA and plasticized with 20% PEG400 were also hard and tough. The films that were plasticized with triacetin were hard and brittle. All films prepared from 8:2 blends were hard and tough even after addition of PEG400, PEG1000 and triacetin and at all concentration levels.

Thermal properties

Aqueous film coating techniques are of current interest in pharmaceutical industry. Despite their wide applications

little is known about the thermodynamic properties of these systems. A property that can be well defined and measured for polymers is the glass transition temperature (Tg). This is a function of chain mobility and, since the purpose of plasticizer is to increase chain mobility, it offers an experimental method for evaluating the efficiencies of plasticizers. A polymer-polymer compatibility or miscibility may also be evaluated from Tg data. While above its Tg polymer film is brittle, it is rubbery blow their Tg. The knowledge of the glass transition of a coat is important, because attempting to dry films at temperature lower than their Tg result in cracking and loss in integrity of the film (James and Timmins, 1989). Since the Tg of most polymers used in film coating is above the coating temperature it is essential that a plasticizer be incorporated into a coating fluid formulation to decrease the Tg of these polymers. The thermal analysis will give information regarding polymer interaction with plasticizer and other additives.

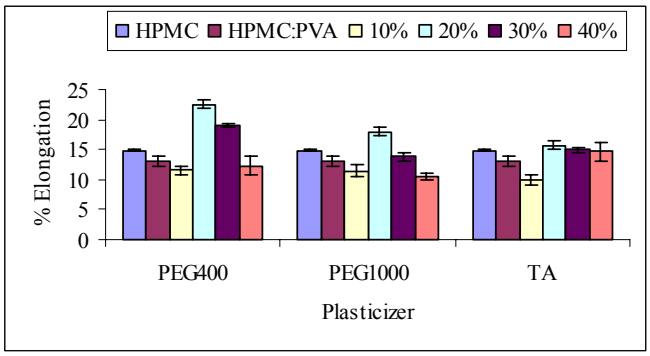


Fig. 7: The percentage elongation at break of 9:1 HPMC/PVA blends plasticized with 0 to 40% w/w PEG 400, PEG 1000 and triacetin compared with that of control HPMC 606.

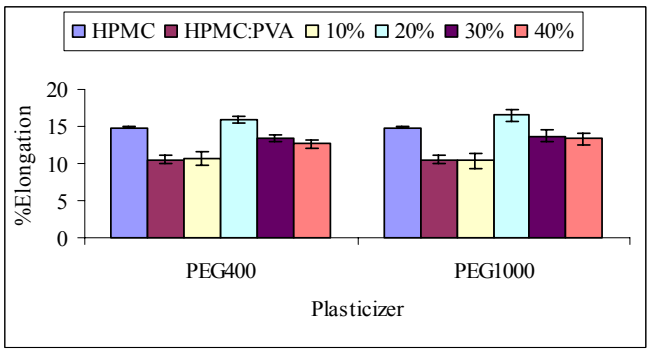
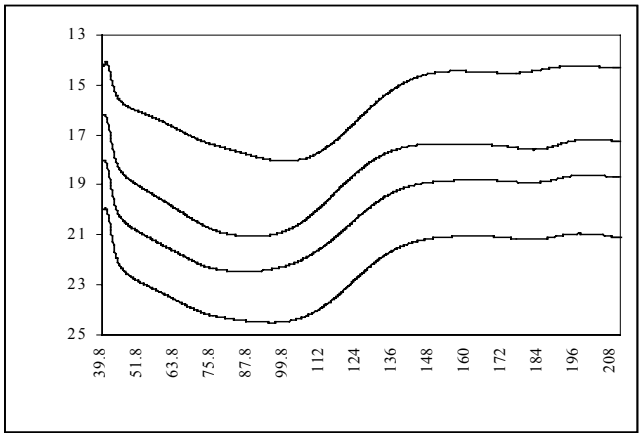


Fig. 8: The percentage Elongation at break of 8:2 HPMC/PVA blends plasticized with 0 to 40% w/w PEG 400, PEG 1000 compared with that of HPMC 606

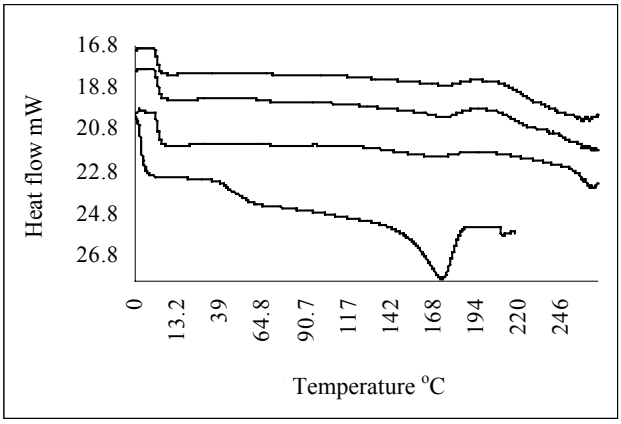
In this work the glass transition temperature (Tg), melting temperature (Tm), and the enthalpy (ΔH) associated with the melting endotherms of plasticized and unplasticized HPMC/PVA blends cast from aqueous solutions were measured using differential scanning calorimetry (DSC) in order to study the compatibility of HPMC and PVA as well as the effect of different plasticizers (PEG400, PEG1000, and triacetin) on this blends. Triplicate measurements were made for each blend with satisfactory reproducibility.

DSC thermal properties profiles of unplasticized blends films presented in fig. 9a show two endotherms, the first broad endotherm was at around 100ºC which attributed to evaporation of water, obscuring the transition due to PVA-rich phase at 68.6ºC. The second endotherm was sharper, recorded at 180ºC (table 2) and attributed to melting of PVA which obscured the transition due to HPMC. The enthalpy (ΔH) associated with second endotherms, which is consistent with melting of PVA, increased with increase in PVA concentration (table 2) but its melting position remained constant (fig. 9a). On annealing (second run) the broad endotherm due to evaporation of water disappeared (fig. 9b). This enabled determination of glass transition due to PVA-rich phase which was located at 68.6ºC and remained constant through blend composition (table 4). This indicates absence of interaction between HPMC and PVA. In addition after annealing the melting endotherm has appeared at a temperature lower than 180ºC (table 3), suggesting the formation of another type of crystallites in these films under the condition employed (10ºC/min). The Tg of HPMC-rich phase could not be accurately resolved from the base line or may be obscured by the melting endotherm.

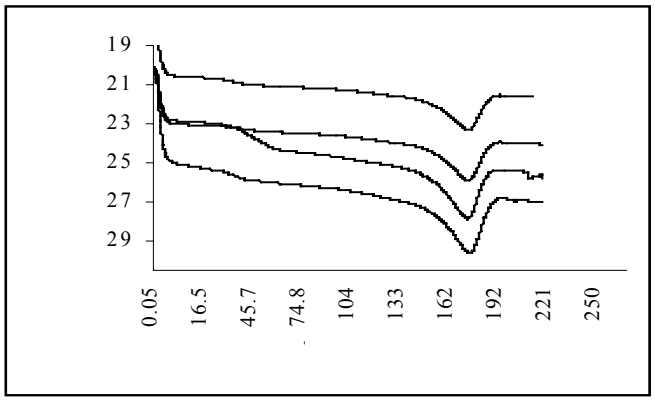
The thermal properties for plasticized 9:1 HPMC/PVA blends as cast are shown in figs. 9c, d and e. Similar to the unplasticized blends, two endotherms were recorded which were attributed to evaporation of water (that around 100ºC obscuring the transition due to PVA-rich phase) and melting point of PVA (at 174ºC which obscured the transition due to HPMC) (table 2) were recorded for the plasticized blends. On annealing (run 2) the broad endotherm due to evaporation of water disappeared (fig. 9f). This enabled determination of glass transition due to PVA-rich phase. Addition of plasticizers generally reduced to different extent both the values of Tm and Tg of PVA- rich phase, as well as the ΔH associated with the melting endotherm. Present at concentration of 10 and 20%, the triacetin decreased the Tg of the PVA-rich phase by 3.6 and 2.8ºC respectively (table 4) and Tm reduced by 6ºC for both concentrations (Table 2). While at 10, 20, and 30% levels of concentrations, the PEG1000 reduced the Tg by 2.8, 6.6 and 13.2ºC respectively (table 4) and (Tm) reduced by 5, 5 and 6ºC (table 2). In case of PEG400 the Tg of PVA-rich phase could not be resolved from the base line. In addition the Tg of HPMC could not be detected because the Tg of HPMC could not be resolved from the base line.



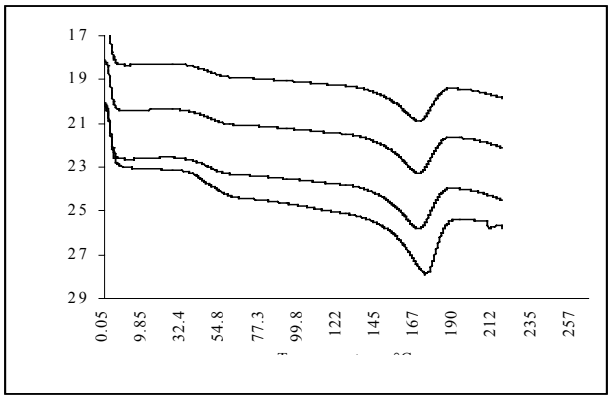
a. HPMC:PVA as cast



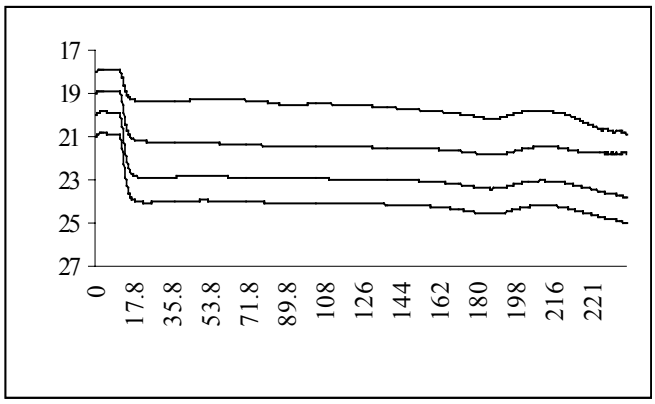
b. HPMC:PVA annealed



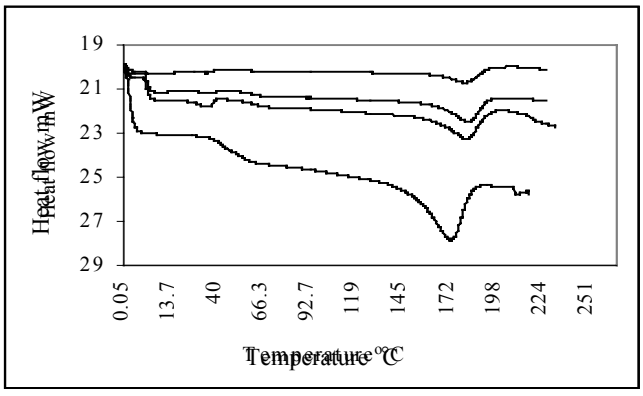
c. PEG 1000



d. Triacetin



e. PEG400



f. Annealed-plasticized HPMC : PVA blend

Fig. 9: DSC profiles for un-plasticized (a & b) and plasticized (c, d, e, and f) HPMC: PVA blends.

From the above results it can be concluded that blends of HPMC with PVA were incompatible when cast from aqueous solution at all levels of concentrations. Some compatibility might have occurred after annealing at temperature 210ºC and after addition of plasticizers (PEG and triacetin) as well. PVA-rich phase retained limited crystallinity during film casting and after annealed at 210ºC. PEGs were more effective plasticizers to the PVA-rich phase as they caused more reduction in its Tg compared to triacetin which had small effect on the Tg of PVA-rich phase.

Permeation properties

A film coating when applied to a particular solid dosage form will influence the transport of one or more molecular species into or out of that dosage form. The transport of the permeant (permeating species, e.g. water) across the film occurs in two stages:

(1) The permeant first dissolves in the polymer matrix (solubility stage). A fraction of the dissolved permeant will then probably interact with some of the functional groups of the polymer and any additives present; (2) The second stage (diffusion stage) involves the free or unbounded fraction of the permeant (referred to as diffusant) being carried along the diffusion channels and pores in the polymer matrix. Diffusivity plays a far more important role than solubility in determining permeability (Okhamafe and Yourk, 1983, 1987).

Microstructure as well as physicochemical properties of the film components that affect mechanical properties were also important in permeation process. Presence of plasticizer enhances the segmental mobility of polymer chain resulting in an increase in number, size and/or diffusion channels (Okhamafe and Yourk, 1983). Presence of insoluble additives, crystallinity and cross-linking hinders the mobility of polymer chain resulting in a decrease in the number and size of diffusion pathways and diffusivity (Michaels and Bixler, 1961; Okhamafe and Yourk, 1983, 1985a).

Water vapor permeability

Moisture permeability for films containing different blends ratio of hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA) (9:1, 8:2, 7:3, 6:4, 5:5) were studied (fig. 10). Films prepared in the ratio of 9:1 and 8:2 had satisfactory appearance. Incorporation of PVA above this ratio level produced films with irregular spots and patches. Both 9:1 and 8:2 blends significantly lowered the moisture permeability. Moreover, blend 8:2 showed higher effect on water permeability than 9:1 blend. As the amount of PVA in the blend increased to 7:3 ratio, a big drop in moisture permeability was observed and over this ratio the permeability remain unchanged (consistent). This is in agreement with Okhamafe and Yourk, (1983). At 8:2 blend the moisture permeability was lowered by a factor of 0.34 compared to the HPMC film; this large fall in water permeability may be attributed to its degree of crystallinity which is higher than that of HPMC film (Okhamafe and Yourk, 1983). The crystalline phase of a film is impermeable to water molecules because diffusion holes are either not present, or are too small to allow water passage. Michael and Bixler (1961) found that crystallinity level of 60-80% decrease diffusivity in some films to between 0.1 and 0.033 of values for equivalent amorphous films.

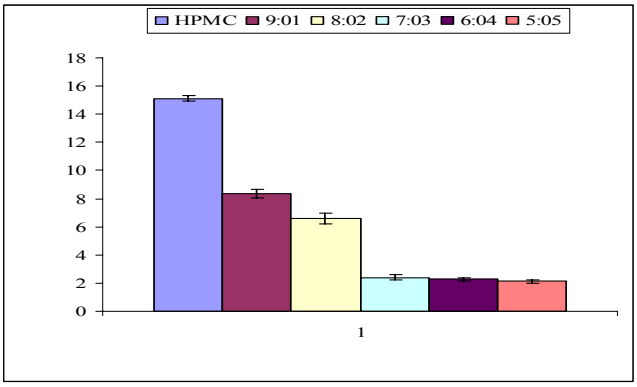


Fig. 10: Moisture permeability for HPMC blended with PVA at 9:1, 8:2, 7:3, 6:4, and 5:5 blends ratios.

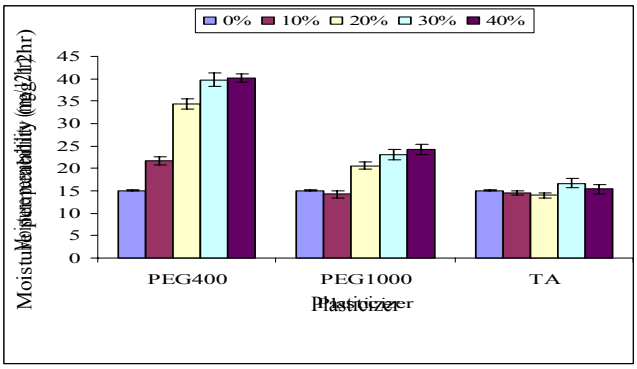


Fig. 11: Moisture permeability for HPMC (606) films containing (0--40%w/w) PEG400, PEG1000 and triacetin (TA).

The results of water vapor permeability for HPMC films plasticized with polyethylene glycol (400 & 1000) and triacetin are presented in fig. 11. Generally the addition of both grades of polyethylene glycol (PEG400 & PEG1000) increased the moisture permeability of HPMC films but the films containing triacetin provided a more rigid barrier to moisture compared to unplasticized HPMC films. The results show that films containing 10-30%w/w PEG400 and 20-30% PEG1000 significantly increase the water vapor permeability of HPMC films, and as amount of PEG in the blend increased over this ratio, the permeability remain unchanged (consistent). The increase of HPMC moisture permeability by incorporation of PEG was attributed to the interaction of PEG with HPMC causing a decrease in the molecular order of HPMC resulting in enhanced chain mobility. This may consequently enlarge the diffusion pathways and hence facilitate the permeation of the water vapor. In addition, films plasticized with PEG1000 showed lower water permeability than that of PEG400 probably due to the larger ethylene backbone of PEG1000 causing a reduction in hydrophilicity and moisture affinity of the film.

From the above results it was concluded that there was a clear relationship between the moisture permeability properties of plasticized HPMC films and the molecular weight as well as concentration of PEGs used.

Since triacetin levels greater than 20% caused blooming in films prepared by cast method; no permeability study was performed above this level. Films containing 10-20% triacetin showed a little decrease (not significant) in moisture permeability of HPMC films. Therefore, triacetin in a range of 10-20%w/w of HPMC could be more beneficial as a plasticizer against moisture permeability.

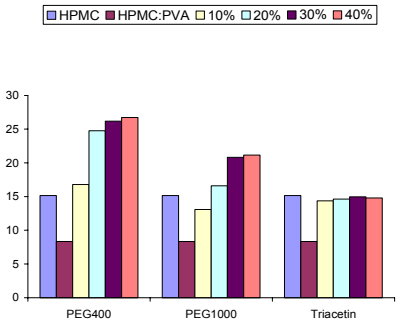


Fig. 12: Moisture permeability for (9:1) HPMC/PVA blends films containing different concentration of polyethylene glycol 400 (PEG400), polyethylene glycol 1000 (PEG1000) and triacetin compared with that of control HPMC.

Moreover, the addition of plasticizer increased the chain mobility causing the glass transition temperature (Tg) to decrease (Billmeyer, 1971). All types of plasticizers used (PEG400, PEG1000, and triacetin) are capable of lowering the Tg of HPMC and increasing its chain mobility (Johnson *et al.,* 1991). Thus, films containing triacetin are expected to cause some increase in permeability, however, experimentally it caused a little decrease in moisture permeability of HPMC films. Therefore, it indicates that chain mobility alone cannot explain the water vapor permeability data. The hydrophilicity property of a plasticizer plays an important role in water vapor permeability of the film. The significant differences in the permeability of PEG and Triacetin may be attributed to the lesser hydrophilicity of triacetin compared to PEG. While PEG is freely water-soluble, only 1 part of triacetin is soluble in 14 parts of water (Windholz *et al.,* 1983). Triacetin significantly lowered the ability of the HPMC film to absorb water but PEG has little effect (Johnson *et al.,* 1991). PEG 400 and 1000 are more hydrophilic plasticizer than triacetin. Moreover, PEG 400 and 1000 have a number of hydroxyl groups, so that they are capable of forming more hydrogen bonds with diffusing water molecules, thereby increasing the diffusion rate.

From the results it was concluded that the more hydrophilic PEG significantly increased the permeability at 20 and 30% levels while the less hydrophilic triacetin had little effect on permeability.

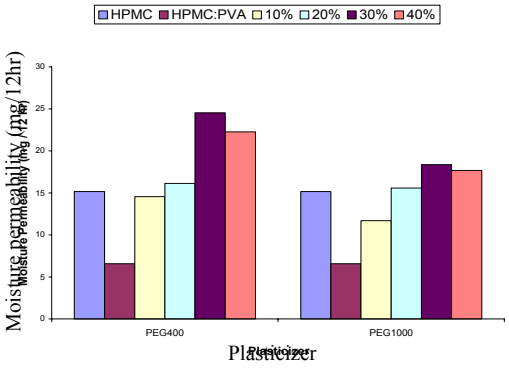


Fig. 13: Moisture permeability for (8:2) HPMC/PVA blends films containing different concentration of PEG400, PEG1000 compared with that of control HPMC.

Water permeability of 9:1 HPMC: PVA films blends plasticized with 0-40%w/w PEG 400, PEG1000 and triactin are represented in Figs. 12 and 13. The results show that PEG 400, PEG 1000 and triacetin prevented the large fall in HPMC film moisture permeability caused by PVA. Film blends containing PEG400 and PEG 1000 at concentrations of 20% and 30 %, respectively, were found to have moisture permeability significantly above that of control HPMC film. And no significant change was recorded in case of triacetin. As the ratio of PVA in the blends increased from 9:1 to 8:2, films plasticized with both grades of PEG had a satisfactory appearance but that plasticized with triacetin at all levels showed blooming, so no permeability study was performed for 8:2 blend films containing triacetin. At the range of 10-20% w/w PEG, a significantly decreased moisture permeability compared to control HPMC was observed (Fig. 11). However, their moisture permeability was significantly above that of unplasticized 8:2 blend.

When added to HPMC:PVA blends, both PEG grades interacted with HPMC and reduced the number of HPMC-PVA contacts, so that the PEGs could decrease the crystallinity usually caused by PVA. In addition, at higher plasticizer concentrations, the excess plasticizer may interact with PVA, and as a result the total crystallinity of the blend may be decreased. Therefore, the increased moisture permeability for plasticized film blends compared to unplasticized blends may be attributed to the decrease in crystallinity and the increase in films flexibility.

From mechanical properties and moisture permeability studies, it was concluded that PEG400, PEG1000 and triacetin were efficient as plasticizers for HPMC films. For

9:1 HPMC:PVA films, the PEG400 at 20% w/w level gave the best plasticizer characteristics for satisfactory mechanical properties and moisture permeability resistance. Therefore, drug release studies were performed using tablets coated with 9:1 blend plasticized with 20% w/w PEG400 and that coated with HPMC containing PEGs and triacetin as plasticizers.

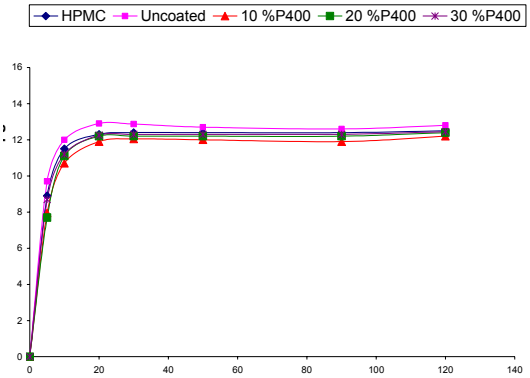


Fig. 14: Release profile of Paracetamol tablets coated with 7% HPMC (Pharmacoat 606) containing 10-30% PEG400.

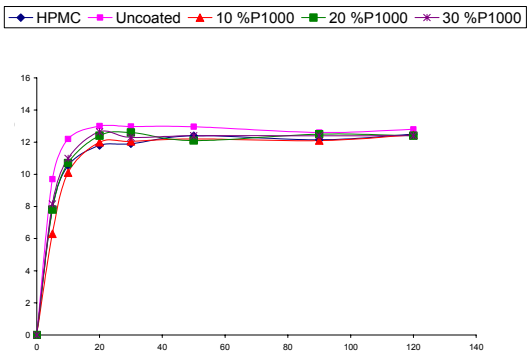


Fig. 15: Release profile of Paracetamol tablets coated with 7% HPMC (Pharmacoat 606) containing 10-30% PEG1000.

Dissolution studies

Dissolution properties of paracetamol tablets coated with 7% w/v HPMC (pharmacoat 606) coating-solutions containing PEG400, PEG1000 and triacetin, and those containing PEG400 & PVA together are shown in Figs. 14-17. It was found that HPMC had weak water resistance and this was evident from the close profile of drug release of tablets coated by HPMC to the profile of the uncoated tablet. The presence of PEG400 and 1000 in HPMC films further weakened its resistance to solubility while the presence of triacetin caused a little increase in HPMC water resistance.

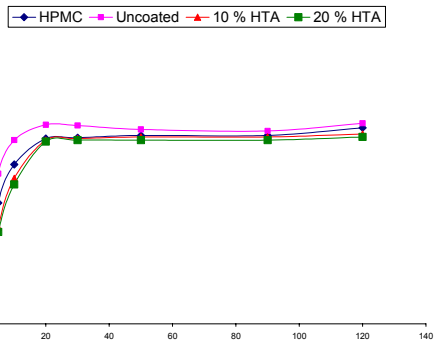


Fig. 16: Release profile of Paracetamol tablets coated with 7% HPMC (Pharmacoat 606) containing 10-20% triacetin.

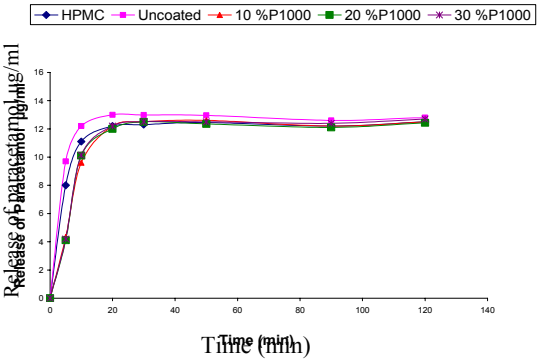


Fig. 17: Release profile of Paracetamol tablets coated with 7% HPMC/PVA (9:1 blend ratio) containing 10-30% PEG400.

In general, it was found that the presence of more hydrophilic additives (PEG) (figs. 14 and 15) in HPMC coating of cores resulted in a rise in the release rate of drug from the coated tablet compared with that coated with HPMC without additives. The presence of less hydrophilic triacetin (fig. 16) in HPMC coating of cores caused a little reduction in the release rate of drug. In the case of coatings containing HPMC, PVA and PEG400 all together (fig. 17) a little reduction in release rate of drug was found, too.

From the results it was concluded that HPMC at 7%w/w concentration was suitable for film-coating intended for non-functional coating (to mask taste and odor, improve elegance and integrity of the tablets without significant change in drug release rate compared to uncoated ones). Presence of the PEG 400, PEG1000 and triacetin as well as the presence of PVA and PEG400 together improved the

coating properties of HPMC films and made it more suitable as a non-functional coating material.

CONCLUSIONS

- The more hydrophilic PEG significantly increased the permeability at 20 and 30% levels while the less hydrophilic triacetin had little effect on permeability.
- PEG400, PEG1000 and triacetin were efficient as plasticizers for HPMC films.
- HPMC at 7%w/w concentration was suitable for film-coating intended for non-functional coating (to mask taste and odor, improve elegance and integrity of the tablets without significant change in drug release rate compared to uncoated ones).
- Presence of the PEG 400, PEG1000 and triacetin as well as the presence of PVA and PEG400 together improved the coating properties of HPMC films and made it more suitable as a non-functional coating material.

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