Drug Development and Industrial Pharmacy, 2009; 35(8): 986–996

informa
healthcare

ORIGINAL ARTICLE

Development and mechanical characterization of solvent-cast polymeric films as potential drug delivery systems to mucosal surfaces

Joshua S. Boateng[1], Howard N.E. Stevens[1], Gillian M. Eccleston[1], Anthony D. Auffret[2], Michael J. Humphrey[2] and Kerr H. Matthews[3]

[1]Department of Pharmaceutical Sciences, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK, [2]Pfizer Limited, Sandwich, Kent, UK and [3]School of Pharmacy, The Robert Gordon University, Aberdeen, UK

Abstract

Solvent-cast films from three polymers, carboxymethylcellulose (CMC), sodium alginate (SA), and xanthan gum, were prepared by drying the polymeric gels in air. Three methods, (a) passive hydration, (b) vortex hydration with heating, and (c) cold hydration, were investigated to determine the most effective means of preparing gels for each of the three polymers. Different drying conditions [relative humidity – RH (6–52%) and temperature (3–45°C)] were investigated to determine the effect of drying rate on the films prepared by drying the polymeric gels. The tensile properties of the CMC films were determined by stretching dumbbell-shaped films to breaking point, using a Texture Analyser. Glycerol was used as a plasticizer, and its effects on the drying rate, physical appearance, and tensile properties of the resulting films were investigated. Vortex hydration with heating was the method of choice for preparing gels of SA and CMC, and cold hydration for xanthan gels. Drying rates increased with low glycerol content, high temperature, and low relative humidity. The residual water content of the films increased with increasing glycerol content and high relative humidity and decreased at higher temperatures. Generally, temperature affected the drying rate to a greater extent than relative humidity. Glycerol significantly affected the toughness (increased) and rigidity (decreased) of CMC films. CMC films prepared at 45°C and 6% RH produced suitable films at the fastest rate while films containing equal quantities of glycerol and CMC possessed an ideal balance between flexibility and rigidity.

Key words: *Carboxymethylcellulose; drying rate; films; mechanical properties; plasticizer; tensile testing*

Introduction

Films are widely used in pharmaceutical dosage forms and as drug delivery systems. They are widely used as packaging materials and as tablet coatings to protect drugs from environmental factors such as light, moisture, and air[1,2]. They also form gastro-resistant (enteric) film coatings that are resistant to gastric acids and are used for targeted drug delivery to the intestinal portion of the GI tract[3,4].

Films prepared from bioadhesive polymers are also used as formulations for delivering drugs[5] to moist surfaces such as wounds, vagina, nasal, and buccal cavities[5–8]. They have particularly wide applications for wound surfaces, for example, it has been proposed that films might be used to deliver genetic- and protein-based macromolecules to wound sites[9,10]. In addition, bioadhesive polymeric films containing antibiotics may be used to treat wound infections where they provide increased local concentrations of the antibiotics[11,12].

The advantages of film dressings include ease of application (due to flexibility) around joints and other difficult areas[13,14], and their transparency enables examination of the wound bed without the removal of the dressing. However, they also present major disadvantages including difficulty in handling, and wound exudate sometimes collects beneath the

Address for correspondence: Joshua S. Boateng, Department of Pharmaceutical, Chemical and Environmental Sciences, School of Science, University of Greenwich at Medway, Central Avenue, Chatham Maritime, Kent ME4 4TB, UK. E-mail: j.s.boateng@gre.ac.uk

(Received 25 Oct 2008; accepted 12 Jan 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.1080/03639040902744704

dressing encouraging skin maceration[15]. The requirements for wound management products with ideal characteristics have necessitated the need for novel formulations having improved physical and mechanical properties and general performance[16].

Films are prepared by various methods including spray coating where the polymer solution is sprayed, and solvent casting[17] where solvent evaporates from a solution or dispersion (gel) of polymer, leaving a continuous layer of polymeric film. There are two main types of films: solvent- and water-based films. In the past, most films were prepared in organic solvents, but these have been largely replaced by aqueous-based films[18]. Organic solvent-based films for pharmaceutical use are considered undesirable because of the difficulty in removing the solvents completely, stringent regulations on exposure to these organic solvents[19], and more severe guidelines on discharge of organic solvents due to increased environmental concerns[20].

The preparation conditions such as temperature and relative humidity critically influence the physical and mechanical properties of films prepared from polymers[21–24]. The mechanical properties of film dressings, in addition to affecting handling[25] and ease of application[26], also influence their clinical acceptability[15]. A hard and brittle film, for example, could destroy delicate newly formed tissue around a wound, leading to prolonged wound-healing times and the associated inconvenience to both patients and clinicians.

This article discusses investigations into the influence of preparation methods on the formation of gels from three hydrophilic polymers, namely, carboxymethylcellulose (CMC), sodium alginate (SA), and xanthan gum (XG) using water as solvent. CMC and SA were chosen due to their good bioadhesive and film-forming properties as well as being known constituents of hydrocolloid and alginate dressings. Xanthan is known for its useful rheological properties[27] and has recently been investigated as a drug delivery system for the preparation of freeze-dried wafers for wound healing[28]. Recently, the mucoadhesive properties of xanthan have been investigated for use as topical mucosal drug delivery systems for wounds[29], buccal mucosa[30], and as buccal mucoadhesive tablets[31]. It has also been used in combination with other polymers to achieve specific controlled release profiles from matrix systems[32,33]. Three methods (passive hydration, vortex hydration with heat, and cold hydration) were investigated to identify the most suitable method of preparing the polymer gels used to make the films.

The second aspect of the work involved the influence of drying rate on suitable formulations (films) prepared by the best gel preparation method. The drying rates of the polymer gels were determined at different drying conditions (temperature and relative humidity). Suitable films obtained from drying the gels were characterized by measuring their tensile (mechanical) properties by stretching dumbbell-shaped films to break point. The results from the tensile characterization were used to identify formulations (films) for drug incorporation and subsequent drug delivery studies.

Materials and methods

Materials

Xanthan gum (Xanthural 180) was obtained as a gift from Pfizer Ltd. (Sandwich, Kent, UK), sodium CMC (Blanose 7H4XF, high viscosity grade) from Hercules (Hopewell, VA, USA), sodium alginate (Protanal LF 10/60) (SA-G), and Protanal LF 10/60LS (SA-M) with higher guluronic and mannuronic acid, respectively, were obtained as gifts from FMC Biopolymer (Drammen, Norway). Protanal LF 10/60 produces stronger gels due to its higher amounts of guluronic acid side chains (average guluronic/mannuronic ratio of 70:30) while Protanal LF 10/60 LS exhibits more flexible mechanical properties because of higher mannuronic acid content (average guluronic/mannuronic ratio of 40:60). Glycerol, calcium chloride, lithium chloride, and dried silica gel were purchased from Sigma (Gillingham, UK). Magnesium nitrate, potassium hydroxide, and potassium acetate were purchased from BDH (VWR, Poole, UK); ammonium nitrate was purchased from M&B Laboratory Chemicals (Dagenham, UK) and magnesium chloride from Aldrich (Poole, Dorset, UK).

Preparation of gels and films

Prior to the preparation of films, experiments were performed to produce 1–5% (wt/wt) aqueous gels for all three polymers to determine concentrations suitable for further experiments based on (a) ease of pouring, (b) release of air bubbles entrapped during stirring, and (c) clear uniform solutions with no lumps of undissolved polymer. Three different methods for preparing the polymer gels (solutions) were investigated and are described below:

1. *Passive hydration*: Gels were prepared by dispersing the polymer in distilled water at room temperature, left overnight to hydrate and dissolve, and stirred until a clear and uniform solution was obtained. By not applying heat, the risk of polymer decomposition was reduced.
2. *Vortex hydration with heat*: The second method involved dispersing the dry polymer into the vortex of vigorously stirred distilled water heated to 95°C. Stirring was continued until a uniform solution was obtained, covered and left to stand for about

10 minutes. This was the method of choice for subsequent experiments involving CMC and SA. Two of the films formulated were prepared containing glycerol as a plasticizer. In these, the glycerol was first dissolved in hot distilled water at a concentration of 5% and 10% (wt/wt). The glycerol solutions were then used in the preparation of the gels as above.

3. *Cold hydration*: This method was used to prepare XG gels as the use of the above methods produced gels that retained entrapped air bubbles. XG gels were obtained by initially cooling distilled water to about 4°C, then dispersing polymer evenly over the surface. The vessel was covered and left at 4°C for 24 hours. The swollen, hydrated gel was stirred gently until a homogenous dispersion was obtained.

The films were prepared by pouring 5 g (or 10 g for XG) of the gels prepared by the methods above into either 25-mL beakers to produce samples suitable for measuring the drying rates or into flat trays for tensile testing. The solutions were dried in sealed desiccators at relative humidities 3–52% and temperatures 25°C, 37°C, and 45°C. The relative humidities were achieved using saturated salt solutions (Table 1). Prior to drying, the desiccators containing saturated salt solutions were equilibrated for up to 7 days. To maintain constant humidity, the salts were added in excess so that they were visible at the bottom of the solutions. This provided assurance that the salt solutions remained saturated throughout the experiments.

Drying profiles

The drying profiles of the films were obtained by weighing the gels (contained in 25 mL glass beakers) every 24 hours to constant weight and the percentage water loss was plotted against time. The drying rates of the films were measured as a function of temperature, relative humidity, and glycerol content. The films produced were subjectively examined for their general physical appearance with the aid of digital photography.

Table 1. Drying conditions for production of films at different relative humidities (RH) and temperatures.

Temperature	Relative humidity (%)	Salt solution (desiccant)
25°C	3	Dried silica gel
	9	Potassium hydroxide
	15	Lithium chloride
	22	Potassium acetate
	52	Magnesium nitrate
37°C	3	Dried silica gel
	10	Lithium chloride
	20	Potassium acetate
	50	Magnesium nitrate
45°C	3	Dried silica gel
	6	Lithium chloride
	10	Potassium hydroxide
	31	Magnesium chloride
	47	Ammonium nitrate

Tensile testing of CMC films (ASTM)

The films used for investigating the tensile properties were prepared by casting hot polymeric gels (as prepared above) in large trays and drying at 6% RH at 45°C. The proportions of CMC and glycerol by weight were 2:1, 1:1, and 2:3. The films were cut around a standard template (dumbbell) as defined by the ASTM test criteria for thin films. The tensile properties of the films were evaluated by stretching the dumbbell-shaped sections to break using a Texture Analyser (TA.XTi2, Stable Microsystems, Surrey, UK). The time to break(s) (TB), percent strain at break (SB), linear elastic region (mm), elastic modulus (mPa), and work (J) in breaking the films (WB)[34] were compared at stretching speeds 0.1–4 mm/s.

Results

Gel preparation and physical appearance of films

Working polymeric gel concentrations (easily handled) obtained were 1% and 2% (wt/wt) for CMC, 1–5% (wt/wt) for both grades of SA, and 1% (wt/wt) for XG. The passive and cold hydration methods for preparing solutions were unsuccessful with CMC and SA. The vortex method was, however, successful, and was the method of choice for preparing CMC and SA films. The cold hydration method was only successful in preparing 1% (wt/wt) XG gel.

All the polymers (except unplasticized SA-G) produced clear transparent films. Unplasticized films appeared brittle and often difficult to remove from the mould without breaking. Unplasticized XG film was so thin and difficult to remove from the containers in which they were cast even when initial weight of solution was doubled from 5 to 10 g. SA-G appeared to produce the strongest films with the unplasticized films showing stress fractures and were not transparent (Figure 1A). Drying their gels at a lower temperature and higher relative humidity (slower rate of drying) produced films that were hard and opaque but with no cracks (Figure 1B). SA-M films on the other hand appeared strong and tough but more flexible with no cracks (Figure 1C). CMC and XG both yielded clear transparent films with or without glycerol but the unplasticized films were hard, brittle, and deformed while films containing an equal proportion of glycerol and polymer were flexible and tough (Figure 2).

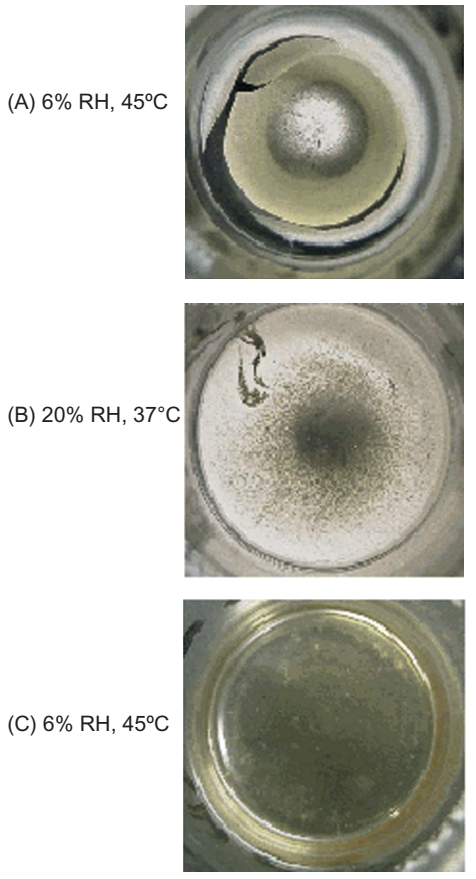

Figure 1. Unplasticized SA films produced by drying 5% (wt/wt) solutions of SA-G at (A) 45°C at 6% RH; (B) 37°C at 20% RH; and (C) 5% SA-M solutions at 45°C at 6% RH.

Figure 2. CMC films prepared from (A) 2% (wt/wt) solution (6% RH, 45°C). (B) 2% (wt/wt) solution containing equal proportions of CMC and GLY (6% RH, 45°C).

Drying of unplasticized CMC and ALG films

The drying profiles of the gels used to prepare the films were generally similar, showing a sigmoidal curve when percentage water loss was plotted against time. The rate of drying of unplasticized films of CMC prepared from drying 5 g of a 2% (wt/wt) solution of CMC in distilled water is shown in Figure 3. Drying profiles and rates of films prepared at different relative humidities and temperatures showing the effect of glycerol, and drying conditions are shown in Figures 4–6 and Table 2. The drying rates generally increased with increasing temperature, decreasing relative humidity, and at lower glycerol content. At temperatures of 25°C and 37°C, there was a decrease in drying rate with increasing relative humidity. Higher temperatures also resulted in lower residual water content of the films (Table 2).

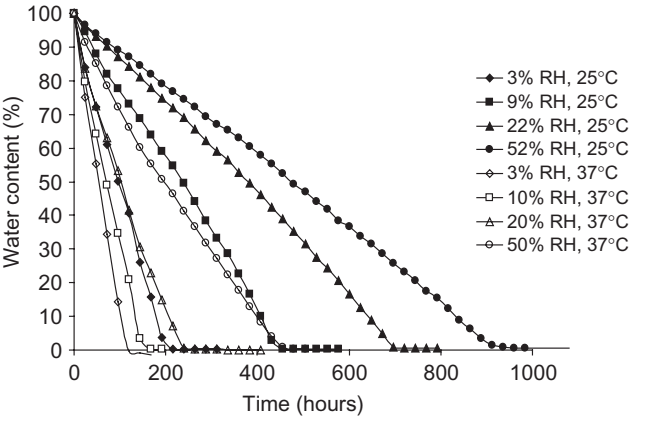

Figure 3. Effect of relative humidity on drying profiles (water content as a function of time) of 5 g CMC solutions (2%, wt/wt) for preparing films at 25°C and 37°C.

Tensile properties

Generally, unplasticized films and films containing lowest amounts of glycerol (CMC : GLY, 2:1) were hard, brittle, and broke easily during removal. On the other hand, films containing the highest glycerol content (CMC : GLY, 2:3) were elastic, sticky, and very difficult to handle, making them unsuitable for application and difficult to test. These observations were reflected in the results obtained from the tensile testing. The variations in % strain (SB) and elastic moduli with increasing glycerol content and stretching speed are illustrated in Figures 7 and 8. The SB (ratio of the elongation to the gauge length per unit of original length expressed as a percentage) did not vary appreciably at different stretching speeds. A summary of the effect of increasing glycerol content on the tensile properties of CMC films is shown in Table 3. Generally, time to break (TB), percent strain at break (SB), and work done to break the films (WB) increased while tensile strength and elastic modulus decreased as the glycerol content increased. The WB increased with higher glycerol content to a maximum value and then decreased again (CMC : GLY, 2:3) but remained higher than the unplasticized films.

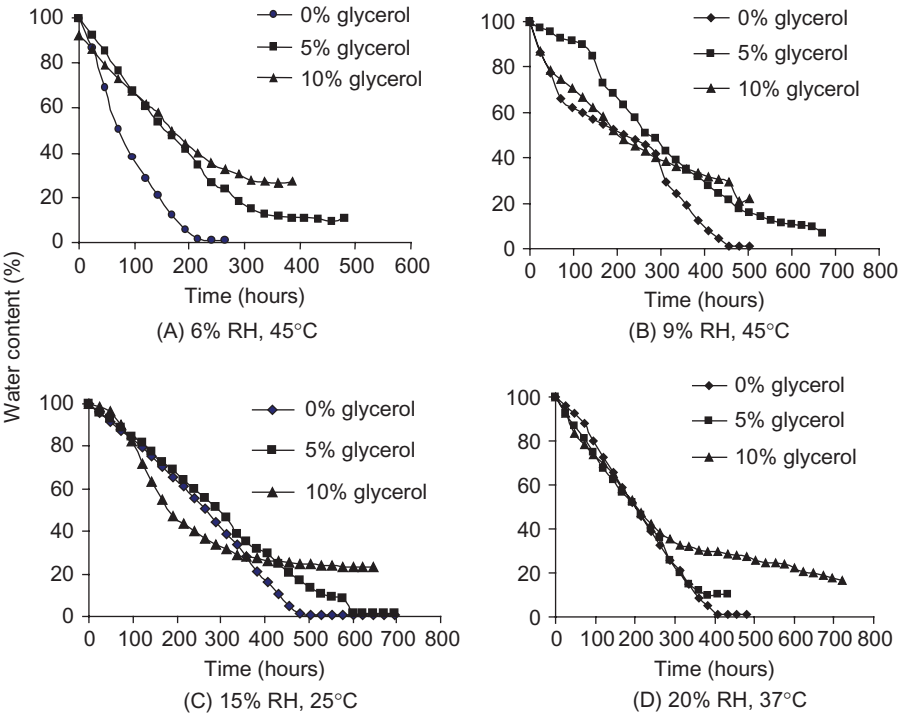

Figure 4. (A–D) Effect of glycerol on drying profiles of 5 g CMC solutions (%, wt/wt) during film preparation at different relative humidities (6-20%) and temperatures (25–45°C).

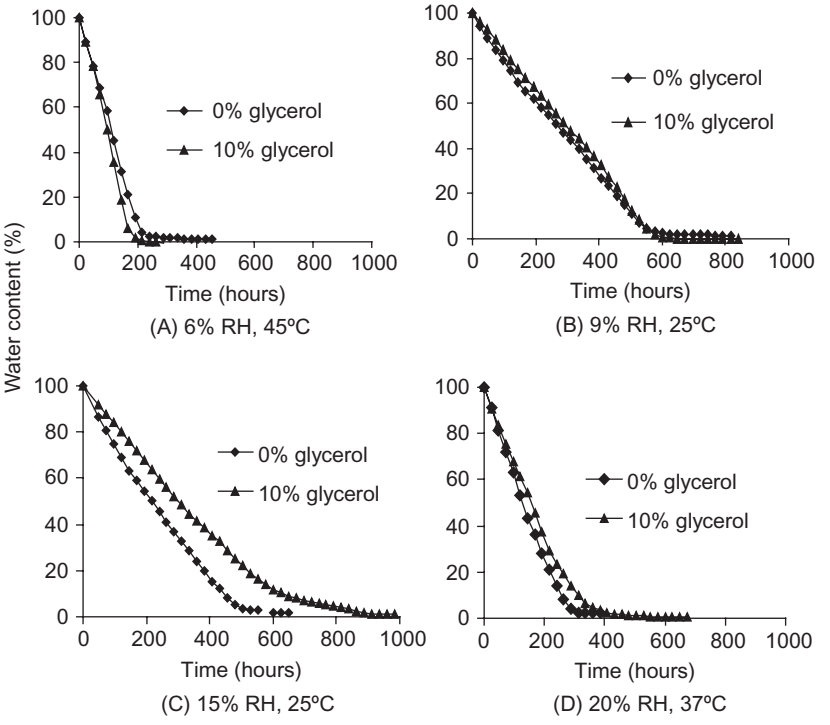

Figure 5. (A–D) Drying profiles of 5 g ALG-G solutions (%, wt/wt) during film preparation at different relative humidities (6–20%) and temperatures (25–45°C) showing the effects of glycerol.

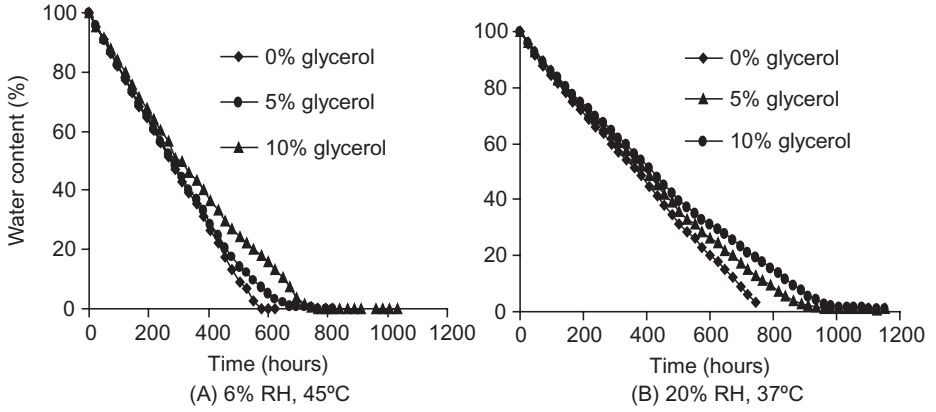

Figure 6. (A and B) Effect of glycerol on drying profiles of 10 g XAN solutions (%, wt/wt) during film preparation at different relative humidities (6% and 20%) and temperatures (37°C and 45°C).

Table 2. Effects of temperature (25°C and 37°C) and relative humidity (3–52%) on the drying rates, total drying times, and final moisture contents (gravimetric method) of 2% CMC solutions and 5% ALG solutions dried to afford films.

Formulation	RH (%)	Temperature (°C)	Drying rate (% water loss/cm^2/h)	Drying time (hours)	Final moisture content of dried film (%)
CMC	3	25	0.07	200	15.25
	9	25	0.03	450	17.01
	22	25	0.02	696	20.63
	52	25	0.01	930	25.92
	3	37	0.12	120	11.50
	10	37	0.09	150	13.41
	20	37	0.05	240	17.69
	50	37	0.03	456	22.17
ALG-G	3	25	0.07	200	3.10
	9	25	0.03	456	4.21
	22	25	0.02	710	8.42
	52	25	0.01	984	14.67
	3	37	0.10	144	4.94
	10	37	0.10	144	15.25
	20	37	0.06	220	6.71
	50	37	0.03	485	11.03
ALG-M	3	25	0.06	216	4.90
	9	25	0.03	438	5.66
	22	25	0.02	650	11.03
	52	25	0.01	944	14.38
	3	37	0.09	144	9.42
	10	37	0.09	144	15.54
	20	37	0.06	222	10.07
	50	37	0.03	460	7.41

Discussion

This study concerned the development and characterization of films as drug delivery system to moist surfaces. To achieve ideal results, the preparation method and mechanical properties should be optimized. Polymeric gels for preparing the various formulations were required to be easily poured from the container. In addition, they must not retain air bubbles entrapped during stirring without the use of a vacuum pump for degassing. Different concentrations, 1–2% (wt/wt) for CMC, 1–5% (wt/wt) SA, and 1% (wt/wt) XG solutions satisfied the above criteria. Films produced by drying 2% (wt/wt) CMC and 5% (wt/wt) ALG gels were selected because they were easier to remove from the containers than those prepared from lower concentrations (1–4%, wt/wt).

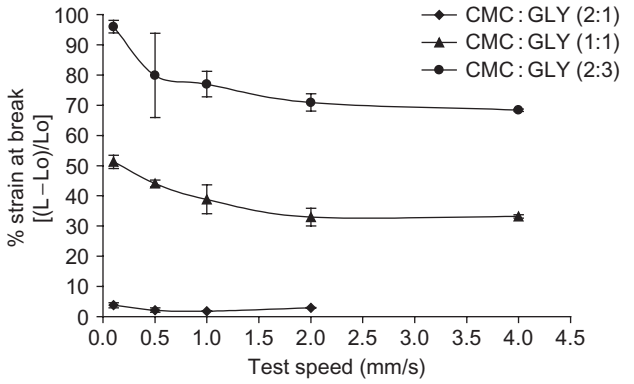

Figure 7. Percent strain at break of CMC films stretched at speeds of 0.1–4.0 mm/s showing the effects of glycerol content extent of stretching.

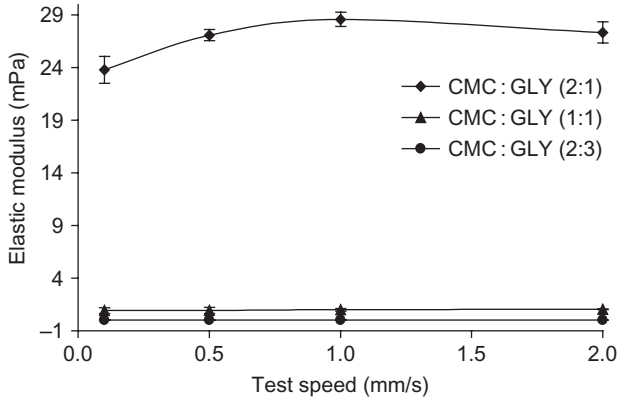

Figure 8. Changes in elastic moduli with increasing glycerol content for CMC films stretched at speeds of 0.1–4.0 mm/s.

The passive hydration method for preparing gels did not achieve the desired results for CMC and SA. This was due to the difficulty in removing air bubbles generated during stirring. The cold hydration method was also unsuitable for both polymers because of incomplete dissolution (hydration) at the low temperature (4°C). The cold hydration method was, however, the method of choice for preparing XG gels because the gels produced using heat and stirring resulted in entrapped air bubbles that can only be removed under reduced pressure. As a result of these observations, vortex hydration with heat was the method of choice for preparing all the gels with the exception of XG. The vigorous stirring in the vortex of the water quickly dispersed the powder, preventing formation of lumps and resulted in easy dissolution of polymer in the hot water. At the concentrations used, the hot solutions were less viscous and therefore readily released entrapped air bubbles, resulting in clear, transparent solutions that were easily poured into moulds before the gels set at lower temperature.

As water evaporated from the gels during film formation, there was an increase in viscosity due to a higher concentration of polymer. At the same time, there was a reduction in weight while the gel collapsed in the container with a resultant decrease in thickness. This corresponds to the initial linear portion of the drying curve where there was rapid loss of water resulting in the formation of a thick semisolid mass. The exponential portion of the drying curve represents a slower loss of water that culminated in a fully formed solid film. At this point, most of the water had evaporated with the film finally losing residual amounts of water through its surface. The flat portion of the curve and the change in weight approaching zero reflect this. The various stages in the drying process and the shape of the drying curve have been discussed by different authors for other polymeric solutions[35,36].

The results obtained by drying the gels under different conditions indicated that the drying rate and the residual water content were a function of temperature, relative humidity, and concentration of glycerol in the films. Drying rates increased while water content of the films decreased at high temperature and low RH. Temperature appeared to have a greater influence on drying rate than relative humidity as shown by the faster drying times for films prepared at 20% RH at 37°C than those at the lower relative humidity of 9–15% and lower temperature of 25°C (Figure 4). This was also observed in Figure 3 where films prepared at high temperature (37°C) and high relative humidity (20% and 50%) still dried faster than those prepared at low temperature (25°C) and low relative humidity (9% and 10% RH). Similar observations have been made for whey protein isolates films plasticized with glycerol[37] and chitosan films[38]. These authors also observed that films dried at higher temperatures showed stiffer, stronger, and less extendable properties (because of lower water content) than films dried at lower temperatures, confirming the observation made for an unplasticized film prepared at higher temperature being more brittle and exhibiting cracks.

Table 3. Effect of glycerol content on tensile properties of CMC films at stretching speed of 0.5 mm/s ($n = 2$).

Film CMC : GLY	Time to break (seconds) (±SD)	% Strain at break (±SD)	Tensile strength (N) (±SD)	Elastic modulus (mPa) (±SD)	Work to break (J) (±SD)
2:1	4.8 (1.6)	2.2 (0.7)	48.0 (4.9)	27.1 (0.5)	0.1 (0.08)
1:1	97.1 (2.4)	44.0 (1.1)	26.4 (3.9)	1.2 (0.2)	1.2 (0.20)
2:3	175.0 (0.7)	80.0 (13.9)	7.9 (0.7)	0.6 (0.02)	0.6 (0.02)

Higher glycerol content on the other hand slowed down the drying and resulted in higher levels of residual water in the films at a given temperature/relative humidity as shown in Figures 4–6. For example, the drying rates for CMC films prepared at 6% RH at 45°C decreased from 0.07 (% water loss/cm^2/h) for unplasticized film to 0.03 (% water loss/cm^2/h) for a film containing 10% glycerol. The ability of glycerol to retain water is exploited in topical (pharmaceutical and cosmetic) formulations where its humectant properties keep skin moist. The water content of starch films increased with increasing glycerol concentration at constant humidity[39]. Furthermore, combination of glycerol and water can produce a synergistic plasticizing effect with its associated effects on the mechanical properties, i.e., to depress the glass transition temperature. Increased rates of water loss caused increased stresses within the film as they formed. The presence of glycerol then alleviates these stresses compared with the unplasticized states.

Unplasticized XG films were difficult to remove from their containers unlike CMC and SA films. One of the requirements for pharmaceutical films is that they must be free from any substrates related to the moulds and therefore films should be easily removed from their casting containers[40]. As a result, the development of XG films was discontinued. CMC and SA have already been identified as good film formers[41] and were easier to handle than XG.

All the polymers (except unplasticized SA-G) produced clear transparent films. Among the wound-healing dressings, this property of films constitutes one of its major advantages as it allows inspection of wounds without removing the dressing[15]. Unplasticized SA-G produced the strongest films that were hard and split at high drying rates. This is because the high guluronic acid could not dissipate stresses generated during the evaporation of water from the films and the subsequent reduction in the volume between the polymer chains. The films of this alginate grade were also not transparent due to crystallization of guluronic acid segments as water evaporated from the film (Figure 1A). Drying the solution at a lower temperature and higher relative humidity (slower rate of drying), however, produced films that were hard but opaque, with no cracks (Figure 1B). This is because, at lower drying rates, smaller stresses were generated during solvent evaporation and the film was able to accommodate these stresses. Glycerol also improved the elegance of the films, producing transparent films that would otherwise have been opaque because of recrystallized guluronic acid. Unplasticized SA-M films on the other hand were strong and tough, but more flexible due to higher mannuronic acid content (Figure 1C). No cracks were produced because the more flexible mannuronic acid side chains were able to dissipate stresses generated during drying of the films even at the high rates of drying, apparent at higher temperatures.

Characterization of the mechanical properties of films required them to be easy to handle and yield smooth edges when cut, without any serrations that could act as lines of weakness. Determination of the tensile properties of the different CMC films prepared showed differences in behavior based primarily on the amounts of glycerol present. Highly plasticized films were very elastic stretching to more than 100% their original lengths before breaking while moderately plasticized ones were tough but broke with less elongation. At low glycerol levels, the films snapped with little stretching due to their brittle nature. Increasing the speed of testing resulted in a decreased time to break point for films while higher glycerol content resulted in an increase in TB of the films. Generally, there was about a 40-fold increase in time to break point with increasing glycerol content at each corresponding stretching speed. This indicated that glycerol reduced brittleness of the films by making them more flexible and able to extend over longer periods before breaking.

Figure 7 shows a gradual decrease in SB at speeds of 0.1 mm/s through to 2 mm/s after which it remained constant. For films containing CMC : GLY ratio of 2:1, the values decreased from 3.77% to 1.82% at stretching speeds of 0.1 and 1 mm/s, respectively. This increased to 2.91% at stretching speed of 2 mm/s. Similarly, the SB for films prepared from equal proportions of CMC and glycerol decreased initially from 51.27% to 32.95% at speeds of 0.1 and 2 mm/s, respectively, and remained constant at speeds above 2 mm/s. This could be explained in terms of the creep properties (time-dependent irreversible deformation under constant load) of the polymer[42]. At low stretching speeds, the films had enough time to respond to the deformation force and attempt to resist this force. The films therefore stretched to relatively longer distances before breaking. At higher stretching speeds, deformation forces were applied to the films at a faster rate and therefore appeared to stretch over shorter distance before breaking.

Glycerol increased the SB by many magnitudes (about 39-fold) at each stretching speed. For example, percent strain at break increased from 3.77 (for CMC : GLY, 2:1) to 96.00% of its original length (for CMC : GLY, 2:3) at a stretching speed of 0.1 mm/s. Glycerol served to increase the flexibility of the films therefore making them able to stretch over long distances. It should be noted, however, that films (CMC : GLY, 2:3) containing higher proportions of glycerol than CMC had the tendency to exhibit 'necking.' Necking occurs when the film elongation increases by several magnitudes above the original length and a corresponding decrease in surface area but with no corresponding increase in tensile

strength. Necking in films during tensile stretching is an indication of plastic yield, explained by the plastic flow of macromolecules[43]. This resulted in high values of 'percent strain at break,' but the results may be misleading especially when the values exceed 100%. This made the films prepared from CMC : GLY (2:3) not very useful for application and further development. Films prepared from equal proportions of polymer and glycerol were stretched to about 50% of their original length, which is ideal because film dimensions did not change significantly before breaking.

The tensile strength (maximum force per unit area applied to a point at which the film specimen breaks) of the CMC films decreased considerably with increasing glycerol content at all stretching speeds. For example, at a stretching speed of 0.5 mm/s, tensile strengths for the three formulations (CMC : GLY, 2:1; CMC : GLY, 1:1; and CMC : GLY, 2:3) stretched were 47.90, 26.38, and 5.66 N/mm^2, respectively (Table 3). Glycerol as a plasticizer increased the free volume between the polymer chains by reducing the interactions between the chains, thereby making the polymer more flexible, and the polymer chains easily slide past one another to yield lower values of tensile strength with reduced brittleness. The variations in elastic modulus with stretching speed and the effect of glycerol content of the films on elastic modulus are shown in Figure 8. The elastic modulus is a measure of film stiffness and rigidity, and for materials that obey Hooke's law, the elastic modulus is calculated from the slope of the initial linear portion (region of linear elastic deformation) of a stress–strain curve. The results showed that the elastic modulus was not significantly affected by the stretching speed. However, glycerol content had significant effects on the elastic modulus for the films investigated. Films with low glycerol content were harder, stronger, and stretched over shorter distances before breaking and therefore yielded high tensile strength (stress) and low percent strain values. This resulted in higher elastic moduli than films containing higher quantities of glycerol that had high percent strain values because of their increased elasticity and flexibility but lower tensile strength values.

Glycerol had a peculiar effect on the work done to break the film (WB) of the films (toughness of the films). There was an initial increase in the WB with increasing glycerol content followed by a sharp decrease with further increase in glycerol content. The WB values for CMC : GLY (2:1, 1:1, and 2:3) at a speed of 0.5 mm/s were, respectively, 0.1, 1.2, and 0.6 J (Table 3). This observation could be explained from the two parameters (stress and elongation) that comprise the WB. Increasing the glycerol content largely affected the elongation of the film and therefore yielded higher values of WB. However, as the glycerol content was further increased, the film stretched over long distances with no corresponding increase in tensile stress because the film behaved more as a 'fluid' than a solid due to increased chain mobility, resulting in a decrease in toughness.

Plasticizers such as glycerol are added to polymeric films to reduce brittleness, improve flow, impart flexibility, and increase toughness. The mechanism of action of a plasticizer generally involves interposing its molecules between the polymer chains. The plasticizer molecules also interact with the functional groups of the polymer chains. Plasticizer and polymer are held together by intermolecular secondary valence forces leading to formation of molecular aggregates. This results in a reduction in the interaction and the intermolecular forces between the polymer chains (reduces cohesion) and an increase in spaces between polymer chains. The overall effects include increased polymer chain mobility and flexibility and a reduction in the glass transition temperature. The lowering of glass transition temperature leads to the conversion of a rigid glassy polymer into the rubbery state. The increase in mobility is termed relaxation and dissipates stresses generated as solvent evaporates from the polymer solution.

It will be useful to observe the decrease in glass transition temperature of CMC films with increasing glycerol concentration. Though that was not achieved, this may be reflected in the increased flexibility of the films with glycerol and the corresponding decrease in tensile strength and elastic modulus as well as increase in the work done to break the films for the tensile measurements. These properties are known to be related to the glass transition temperature of most polymers. Changes in the local movement of polymer chains at the glass transition temperature (T_g) may lead to large changes in physical properties including mechanical modulus[44]. Such changes are exploited in determination of the glass transition temperature using various techniques[45–47]. For example, dynamic mechanical/thermal analysis (DMA/DMTA) measures the effect of a sinusoidally varying stress on dynamic moduli[48].

It has been observed that the efficiency of a plasticizer is related to its chemical structure and the interaction between its functional groups and those of the polymer[49,50]. Bodmeier and Paeratakul[51] investigated factors influencing plasticizer uptake such as polymer type and concentration. It has also been reported that film adhesion increased when the concentration of plasticizer in dried Eudragit™ acrylic films was greater than 25%[52]. Aulton and coworkers[53] demonstrated that plasticizers increased the ease of Hydroxypropylmethylcellulose (HPMC) film deformation, with a decrease in tensile strength and a reduction in the modulus of elasticity.

Careful selection of the type and amount of plasticizer ensures a uniform and reproducible film[54].

A plasticizer will need to be miscible with the polymer in order to be compatible, and most plasticizers usually resemble closely the polymer it will plasticize. For example, water-soluble cellulose ethers such as HPMC and CMC with a high hydroxyl ratio are best plasticized by hydroxyl-containing compounds such as glycerol. Use of plasticizers that are physicochemically associated with the polymer reduces the possibility of plasticizer loss through leaching and evaporation.

The mechanical properties of the films have several important implications. For example, film dressings are required to be durable, stress resistant, soft, flexible, pliable, and elastic to be able to cope with the stresses exerted by different parts of the body having varying contours, especially around the joints such as knees and elbows[13]. Mechanical properties also affect the lag time of swelling for controlled release dosage forms[55]. A film coating for tablets is expected to have sufficient tensile strength to avoid damage during manufacturing processing, storage, and transportation. A low elastic modulus has also been found to be advantageous in preventing initiation and propagation of cracks which can lead to rapid release of drugs from slow release formulations[56].

Conclusions

Solvent-cast films from three hydrophilic polymers (XG, SA, and CMC) have been produced using different methods. The drying profiles of the polymeric gels during film formation were investigated and the tensile properties of CMC films characterized by means of a Texture Analyser. The vortex hydration was the method of choice for SA and CMC, and cold hydration for xanthan. Drying rates were affected by glycerol content, temperature, and relative humidity. Low glycerol content, high temperature, and low relative humidity increased drying rates, while the converse was true at high glycerol contents. In addition, the residual water content of the films increased with increasing glycerol content and high relative humidity and decreased at higher temperatures. Temperature was observed to affect the rate of drying to a greater extent than relative humidity. The results indicate that drying of CMC gels at 45°C and 6% RH produced reproducible films at the fastest rate.

From the mechanical characterization, glycerol was required to reduce brittleness and impart flexibility to the CMC films. Increasing glycerol content increased the time to break point, percent strain at break, and the work done to break to a maximum value. However, increasing glycerol content resulted in a decreased tensile strength and the elastic moduli for all the CMC films. Films produced from an equal proportion of CMC and glycerol possessed an ideal balance between rigidity and toughness and are recommended for future drug delivery studies.

Acknowledgments

The authors acknowledge Pfizer (UK) for sponsoring this research work.

Declaration of interest: The authors report no conflicts of interest.

References

1. Dirim SN, Ozden HO, Bayindiril A, Esin A. (2004). Modification of water vapour transfer rate of low density polyethylene films for food packaging. J Food Eng, 63:9–13.
2. Sarbach C, Yagoubi N, Sauzieres J, Renaux C, Ferrier D, Postaire E. (1996). Migration of impurities from a multilayer plastics container into a parenteral infusion fluid. Int J Pharm, 140:169–74.
3. Banker GS. (1966). Film coating theory and practice. J Pharm Sci, 55:81–9.
4. Ofori-Kwakye K, Fell JT. (2003). Biphasic drug release from film coated tablets. Int J Pharm, 250:431–40.
5. Jimenez-Castellanos MR, Zia H, Rhodes CT. (1993). Mucoadhesive drug delivery systems. Drug Dev Ind Pharm, 19:143–94.
6. Ahuja A, Khar RK, Ali J. (1997). Mucoadhsive drug delivery systems. Drug Dev Ind Pharm, 23:489–515.
7. Lin DM, Kalachandra S, Valiyaparambil J, Offenbacher S. (2003). A polymeric device for delivery of anti-microbial and anti-fungal drugs in the oral environment: Effect of temperature and medium on the rate of drug release. Dent Mater, 19:589–96.
8. Perugini P, Genta I, Conti B, Modena T, Pavanetto F. (2003). Periodontal delivery of ipriflavone: New chitosan/PLGA film delivery system for a lipophilic drug. Int J Pharm, 252:1–9.
9. Boateng JS, Matthews KH, Stevens HNE, Eccleston GM. (2008). Wound healing dressings and drug delivery systems: A review. J Pharm Sci, 97(8):2892–923.
10. Schacht E, Van Den B, Delaey B, Jean-Pierre D. (2002). Medicaments based on polymers composed of methacrylamide-modified gelatin, US Patent No. 6,458,386.
11. Cho CY, Lo JS. (1998). Dressing the part. Dermatol Clin, 16:25–47.
12. Lee JW, Park Robinson JH. (2000). Bioadhesive-based dosage forms: The next generation. J Pharm Sci, 89:850–66.
13. Khan AT, Peh KK, Ch'ng AS. (2000). Mechanical, bioadhesive and biological evaluations of chitosan films for wound dressing. J Pharm Pharm Sci, 3:303–11.
14. Wittaya-areekul S, Prahsarn C. (2006). Development and in vitro evaluation of Chitosan-polysaccharides composite wound dressings. Int J Pharm, 313:123–8.
15. Thomas S. (1990). Wounds and wound healing in: Wound management and dressings (Chap. 1). London: Pharmaceutical Press, 1–14.
16. Morgan DA. (2002). Wounds—what should a dressing formulary include?. Hasp Pharma, 9:261–6.
17. Boateng JS, Auffret AD, Humphrey MJAJ, Matthews KH, Eccleston GM, Stevens HNE. (2002a). The mechanical properties of solvent cast films. AAPS PharmSciTech, 4(4):T3186.
18. Nagai T, Obara S, Kokubo H, Hoshi N. (1997). Application of hydroxypropylmethylcellulose and hydroxypropylmethylcellulose acetate succinate to aqueous film coating of pharmaceutical dosage forms. In: McGinity JW, ed. Aqueous polymeric

coating for pharmaceutical dosage forms. New York: Marcel Dekker, 177–225.
19. McGinity JW. (1997). Aqueous polymeric coating for pharmaceutical dosage forms. 2nd ed. New York: Marcel Deckker Inc., 79.
20. Hogan JE. (1982). Aqueous versus organic solvent film coating. Int J Pharm Tech Prod Mfr, 3:17–20.
21. Boateng JS, Stevens HNE, Eccleston GM, Auffret AD, Humphrey MJ. (2002b). Preparation and properties of solvent cast films. J Pharm Pharmacol, 54(Suppl. 074):S–31.
22. Donhowe G, Fennema O. (1993). The effect of solution composition and drying temperature on crystallinity, permeability and mechanical properties of methylcellulose films. J Food Process Preserv, 17:231–46.
23. Kaya S, Kaya M. (2000). Microwave drying effect on properties of whey protein isolate edible films. J Food Eng, 43:91–6.
24. Stading M, Rindlav-Westling A, Gatenholm P. (2001). Humidity induced structural transitions in amylose and amylopectin films. Carbohydr Polym, 45:209–17.
25. Boateng JS, Auffret AD, Humphrey MJ, Matthews KH, Stevens HNE, Eccleston GM. (2003). Mechanical and dissolution properties of freeze-dried and solvent cast films. AAPS PharmSciTech, 5(4):s4101.
26. Wittaya-areekul S, Prahsarn C, Sungthongjeen S. (2006). Development and in vitro evaluation of Chitosan-Eudragit RS 300 composite wound dressings. AAPS PharmSciTech, 7:E30.
27. Whitcomb PJ. (1978). Rheology of xanthan gum. J Rheol, 22:493–505.
28. Matthews KH, Stevens HNE, Auffret AD, Humphrey MJ, Eccleston GM. (2006). Gamma-irradiation of lyophilised wound healing wafers. Int J Pharm, 313:78–86.
29. Matthews KH, Stevens HNE, Auffret AD, Humphrey MJ, Eccleston GM. (2008). Formulation stability and thermal analysis of lyophilised wound healing wafers containing an insoluble MMP-3 inhibitor and a non-ionic surfactant. Int J Pharm, 356:110–20.
30. Park CR, Munday DL. (2004). Evaluation of selected polysaccharide excipients in buccoadhesive tablets for sustained release of nicotine. Drug Dev Ind Pharm, 30:609–17.
31. Singh S, Jain S, Muthu MS, Tilak R. (2008). Preparation and evaluation of buccal bioadhesive tablets containing clotrimazole. Curr Drug Deliv, 5:133–41.
32. Alvarez-Mancenido F, Landin M, Martinez-Pacheco R. (2008a). Konjac glucomannan/xanthan gum enzyme sensitive binary mixtures for colonic drug delivery. Eur J Pharm Biopharm, 69:573–81.
33. Alvarez-Mancenido F, Landin M, Martinez-Pacheco R. (2008b). Konjac glucomannan and konjac glucomannan/xanthan gum mixtures as excipients for controlled drug delivery systems. Diffusion of small drugs. Int J Pharm, 349:11–8.
34. Aulton ME. (1982). Assessment of the mechanical properties of film coating materials. Int J Pharm Tech Prod. Mfr, 3(1):9–16.
35. Cansell F, Henry F, Pichot C. (1990). Study of polymer latex coalescence by dielectric measurements in the microwave domain: Influence of latex characteristics. J Appl Polym Sci, 41:547–63.
36. Vanderhoff JW, Bradford EB, Carrington WK. (1973). The transport of water through latex films. J Polym Sci Polym Symp, 41:155–74.
37. Alcantara CR, Rumsey TR, Krochta JM. (1998). Drying rate effect on the properties of whey protein films. J Food Process Eng, 21:387–405.
38. Srinivasa PC, Ramesh MN, Kumar KR, Tharanathan RN. (2004). Properties of chitosan films prepared under different drying conditions. J Food Eng, 63:79–85.
39. Lourdin D, Coignard L, Bizot H, Colonna P. (1997). Influence of equilibrium relative humidity and plasticiser concentration on the water content and glass transition of starch materials. Polymer, 38:5401–6.
40. Chainey M, Wilkinson MC, Hearn J. (1985). Permeation through polymer latex film. J Appl Polym Sci, 30:4273–85.
41. Radebaugh GW, Murtha JL, Julian TN, Bondi JN. (1988). Method for evaluating the puncture and shear properties of pharmaceutical polymeric films. Int J Pharm, 45:39–46.
42. Nielsen LE. (1974). Mechanical properties of polymers and composites. New York: Reinhold.
43. Young RJ, Lovell PA. (1991). Introduction to polymers. 2nd ed. London: Chapman and Hall, 356–69.
44. White GW, Cakebread SH. (1966). The glassy state in certain sugarcontaining food products. J Food Technol, 1:73–82.
45. Kalichevsky MT, Jaroszkiewicz EM, Ablett S, Blanshard JMV, Lillford PJ. (1992). The glass transition of amylopectin measured by DSC, DMTA and NMR. Carbohydr Polym, 18:77–88.
46. Selivansky D. (1989). DSC studies of thermal events at the glass transition temperature region of partially oriented polyester fibers. Thermochim Acta, 148(4):381–6.
47. Wunderlich B. (1981). The basis of thermal analysis. Turi EA. Thermal characterisation of polymeric materials. New York: Academic Press Inc., 91–234.
48. Cocero AM, Kokini JL. (1991). The study of the glass transition of glutenin using small amplitude oscillatory rheological measurements and differential scanning calorimetry. J Rheol, 35:257–70.
49. Gutierrez-Rocca JC, McGinity JW. (1994). Influence of water soluble and insoluble plasticizers on the physical and mechanical properties of acrylic resin copolymers. Int J Pharm, 103:293–301.
50. Tarvainen M, Sutinen R, Somppi M, Paronen P, Poso A. (2001). Predicting plasticisation efficiency from three-dimensional molecular structure of a polymer plasticiser. Pharm Res, 18:1760–6.
51. Bodmeier R, Paeratakul O. (1994). Distribution of plasticizers between aqueous and polymer phases in aqueous colloidal dispersions. Int J Pharm, 103:47.
52. Shang-Yang L, Shao-Ko C, Run-Chu L. (2000). Organic esters of plasticizers affecting the water absorption, adhesive property, glass transition temperature and plasticizer performance of Eudragit acrylic films. J Control Release, 68:343–50.
53. Aulton ME, Abdul-Razak MH, Hogan JE. (1980). The mechanical properties of hydroxypropylmethylcellulose films derived from aqueous systems (2nd proceedings). Int Pharm Tech Conference, Paris, pp. 16–25.
54. Wu C, McGinity JW. (1999). Non-traditional plasticisation of polymeric films. Int J Pharm, 177:15–27.
55. Amidon GL, Leesman GD. (1993). Pulsatile drug delivery system. US Patent No. 5,229,131.
56. Rowe RC, Roberts RJ. (1992). The effect of some formulation variables on crack propagation in pigmented tablet film coatings using computer simulation. Int J Pharm, 86:49–58.