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Compression and compaction properties of plasticised high molecular weight hydroxypropylmethylcellulose (HPMC) as a hydrophilic matrix carrier

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Abstract

The compression and compaction properties of plasticised high molecular weight USP2208 HPMC were investigated with the aim of improving tablet formation in HPMC matrices. Experiments were conducted on binary polymer–plasticiser mixtures containing 17 wt.% plasticiser, and on a model hydrophilic matrix formulation. A selection of common plasticisers, propylene glycol (PG) glycerol (GLY), dibutyl sebacate (DBS) and triacetin (TRI), were chosen to provide a range of plasticisation efficiencies. T_g values of binary mixtures determined by Dynamic Mechanical Thermal Analysis (DMTA) were in rank order PG > GLY > DBS > TRI > unplasticised HPMC. Mean yield pressure, strain rate sensitivity (SRS) and plastic compaction energy were measured during the compression process, and matrix properties were monitored by tensile strength and axial expansion post-compression. Compression of HPMC:PG binary mixtures resulted in a marked reduction in mean yield pressure and a significant increase in SRS, suggesting a classical plasticisation of HPMC analogous to that produced by water. The effect of PG was also reflected in matrix properties. At compression pressures below 70 MPa, compacts had greater tensile strength than those from native polymer, and over the range 35 and 70 MPa, lower plastic compaction values showed that less energy was required to produce the compacts. Axial expansion was also reduced. Above 70 MPa tensile strength was limited to 3 MPa. These results suggest a useful improvement of HPMC compaction and matrix properties by PG plasticisation, with lowering of T_g resulting in improved deformation and internal bonding. These effects were also detectable in the model formulation containing a minimal polymer content for an HPMC matrix. Other plasticisers were largely ineffective, matrix strength was poor and axial expansion high. The hydrophobic plasticisers (DBS, TRI) reduced yield pressure substantially, but were poor plasticisers and showed compaction mechanisms that could be attributed to phase separation. The effect of different plasticisers suggests that the deformation characteristics of this HPMC in the solid state is dominated by hydroxyl mediated bonding, rather than by hydrophobic interactions between methoxyl-rich regions.

Keywords: Hydroxypropylmethylcellulose; HPMC; Plasticiser; Matrix; Compaction; Mechanical properties

1. Introduction

Hydroxypropyl methylcellulose (HPMC) is widely used in pharmaceuticals. Low molecular weight HPMC is used predominantly for tablet film coating whilst higher molecular weight materials are utilised as rate controlling polymers in extended release 'hydrophilic' matrices (Melia, 1991). Plasticisation in low molecular weight HPMC has been studied extensively, and the effect on the mechanical properties important in film coating is well understood (Sakellariou and Rowe, 1995; Rowe, 1982; Rowe and Forse, 1981; Sakellariou et al., 1986). The mechanical properties of high molecular weight HPMC are important in the manufacture of hydrophilic matrix dose forms by compression. High molecular weight grades of HPMC are harder, less plastic and require higher pressures to deform than low molecular weight HPMC (Nokhodchi and Rubenstein, 2001). The importance of T_g in the tablet compaction process has been highlighted by Picker (2003, 2004), who studied the relationship between T_g and tableting behaviour for a range of materials including a high viscosity USP 2208 HPMC. She proposed that

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if T_g was reversibly exceeded during compaction, the improved deformation and the resulting increase in particulate bonding surface, would result in a higher strength of compact. It was suggested that HPMC might undergo this transition at high compaction densities, but the relatively high T_g of HPMC meant that compaction properties were poorer at low densities where insufficient heating might occur during compaction. It has been demonstrated that the compression and compaction properties of high molecular weight HPMC can be improved by water, which is a potent plasticiser (Nokhodchi et al., 1996a,b; Malamataris and Karidas, 1994; Malamataris et al., 1994) but it is often inconvenient to use high moisture content HPMC, as high relative humidities are needed during processing and there can be deleterious effects on the stability of other ingredients and the physical properties of the compact if it dries. The investigations in this paper therefore explore the effect of some other plasticisers on HPMC compression, compaction and matrix tablet properties. A compaction simulator was utilised as it allowed the compaction and compression characteristics to be studied under controlled and well-defined conditions (Celik and Marshall, 1989). The properties of a high molecular weight HPMC used as a matrix carrier were studied both in a simple binary mixture, and in a model tablet formulation more representative of a realistic HPMC tablet formulation. The plasticisers utilised, propylene glycol, glycerol, dibutyl sebacate and triacetin, were selected to provide a range of plasticisation efficiencies as confirmed by T_g measurements

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose HPMC USP 2208 (Methocel K4M Batch KD101812N11, methoxyl 23%, hydroxypropoxyl 8.4%) was a kind gift of Colorcon Ltd., Dartford, UK. Excipients used in matrix tablets were spray dried lactose (Borculo, Zwolle, Netherlands), polyvinylpyrrolidone PVP-40 (K29-32) (Sigma–Aldrich, Poole, UK) and magnesium stearate (BDH–Merck, Poole, UK). The plasticisers, propylene glycol, glycerol, dibutyl sebecate and triacetin were supplied by Sigma–Aldrich, Poole, UK. Chlorpheniramine maleate was obtained from Sigma–Aldrich, Poole, UK and ethanol 95% from Fisher Scientific, Loughborough, UK.

2.2. Preparation of binary polymer–plasticiser mixtures

A 63–90 μm particle size sieve fraction of HPMC was used throughout this work. Binary mixtures were prepared by adding 0.75 g plasticiser to 3.75 g HPMC powder, with the mixture stirred vigorously using a spatula and then stored in sealed glass jars at room temperature a minimum of 18 h prior to use. Dynamic mechanical thermal analysis showed that storage up to 56 days under these conditions had no significant effect on the glass transition temperature of these mixtures (ANOVA, $\alpha > 0.05$).

2.3. Glass transition temperature measurements by Dynamic Mechanical Thermal Analysis (DMTA)

The binary polymer–plasticiser mixes were compressed into 17 mm × 5 mm slabs of 2 mm thickness using an IR press operating at a pressure of 110 MPa. The glass transition temperature of these samples was measured over the temperature range 0–220 °C using a Polymer Laboratories DMTA Mark II at 1 Hz, at strain level 2 in bending mode.

2.4. Preparation of granules for the model matrix tablet formulation

Granules for tableting were prepared in batches of 100 g by wet granulation. The formulation comprised of chlorpheniramine maleate (70%, w/w), HPMC (15%, w/w) and spray dried lactose (q.s.) with PVP and magnesium stearate added later as below. The HPMC was used either unplasticised or plasticised with propylene glycol at a 17 wt.% polymer ratio. The drug, HPMC and lactose were dry mixed and then wet granulated in a Kenwood mixer, using 10 mL 1.5% (w/v) PVP K40 in ethanol 95% as the binder solution The granules were dried overnight at room temperature, sieved through a 1 mm mesh and mixed in a Y-cone blender with 1% (w/w) magnesium stearate for 5 min.

2.5. Compaction experiments

Compaction experiments were conducted using an ESH compaction simulator (ESH Testing, Brierly Hill, UK). Ten millimeter diameter flat circular compacts of 240 mg weight were prepared at punch speeds of 3 and 100 mm s^{-1} and using a saw-tooth displacement profile, from each binary polymer–plasticiser mixture, and from model formulations containing plasticised and unplasticised HPMC. Compression pressure was varied by controlling the punch displacement at the point of maximum compression. Five parameters were measured as described below:

(i) Mean yield pressure

The mean yield pressure (the pressure above which the material is irreversibly deformed) was calculated from the reciprocal gradient of a plot of density as a function of compression pressure (Heckel (1961a,b)). Mean yield pressures were determined directly from the compaction data and corrected for elastic deformation of the punches using the ESH data analysis software. Linear regions with a minimum correlation coefficient of $R^2 = 0.994$ were considered acceptable for analysis.

(ii) Strain rate sensitivity (SRS)

The mean yield pressure of a plastically deforming material changes as a function of compression speed and this phenomenon can arise either from the time dependency of plastic flow, or alternatively may represent a change in the compression mechanism (Roberts and Rowe, 1987). Strain rate sensitivity values (SRS) were calculated as the difference in yield pressure at low (3 mm s^{-1}) and high (100 mm s^{-1}) compression speed, normalised with respect

to the mean yield pressure at the highest speed (Roberts and Rowe, 1985).

(iii) Plastic energy of compaction

The plastic energy of compaction is the net energy utilised in the formation of the compact. It was calculated for each compaction event, from the total energy (the area under the curve (AUC) of the force displacement profile) minus the elastic energy determined from the AUC of the recovery curve (Ragnarsson and Sjogren, 1983). All AUC values were measured with the ESH data analysis software.

(iv) Axial expansion of the compact post-compression

Axial expansion was calculated from tablet thickness, measured 24 h post-compression with a micrometer, using the following equation:

$$\text{axial expansion}\,(\%) = \left(\frac{h - h_c}{h_c}\right) \times 100 \quad (1)$$

where h is the axial thickness 24 h post-compression and h_c is the axial thickness at minimum punch separation in the compression cycle.

(v) Tablet tensile strength

Radial tensile strength was calculated from the tablet-crushing load determined with a diameteral compression tester (CT40 Hollands, Nottingham, UK) using the following equation (Fell and Newton, 1970):

$$\sigma_x = \frac{2F}{\pi Dh} \quad (2)$$

where σ_x is the radial tensile strength, F the tablet crushing load, D the tablet diameter and h is the tablet thickness.

3. Results and discussion

3.1. The effect of plasticisers on the deformation mechanics of HPMC

Table 1 shows mean yield pressure, strain rate sensitivity (SRS) and glass transition temperature (T_g) values for the binary polymer–plasticiser mixtures. The yield value is the pressure above which permanent deformation of the material occurs, and a polymer undergoing a greater plastic deformation will exhibit reduced yield values, accompanied by higher SRS values, reflecting the greater sensitivity of yield pressures to deformation rate. Classical plasticisation also results in a reduction in T_g, and across the range of plasticisers examined it can be seen that changes in yield pressure corresponded in rank order to the reductions in T_g.

The HPMC:propylene glycol binary mixture showed the greatest reduction in yield pressure, and the greatest increase in SRS. Mean yield pressures were reduced to 26–32% of the values obtained for unplasticised HPMC; a highly significant difference (unpaired t-test, $p < 0.01$). A reduction in T_g of 137 °C confirmed this as the most efficient HPMC plasticiser within the group. Considered together, the marked reduction in yield value, the increase in SRS and the large reduction in T_g, strongly suggests that propylene glycol induces a potent plasticisation of HPMC. The effect on these parameters parallels those of water, another significant plasticiser of HPMC (Nokhodchi et al., 1996a). In the HPMC:glycerol binary mixtures, decreases of 30% in yield pressure values were seen, and a 68 °C reduction in T_g was observed. This indicates a substantial degree of plasticisation, but shows glycerol to be less potent than propylene glycol. This was reflected in the SRS value which was statistically indistinguishable from unplasticised HPMC. For HPMC to be effectively plasticised it has been suggested that the plasticiser should possess some structural similarity to HPMC and there should be some mutual solubility (Sakellariou and Rowe, 1995; Rowe et al., 1984; Entwistle and Rowe, 1979; Sakellariou et al., 1986). The similarity of these polyols to the hydroxylated backbone and hydroxypropoxyl substituents of HPMC perhaps explains their ability to act as plasticisers, and their potency suggests that the solid state mechanical properties of this HPMC have a large dependency on hydroxyl mediated interactions (e.g. hydrogen bonding) between polymer chains.

In contrast, the effect of dibutyl sebecate and triacetin on the mechanical properties of HPMC was clearly different (Table 1). Dibutyl sebecate reduced mean yield pressure values as effectively as propylene glycol, but reduced T_g by only 10 °C. Triacetin reduced yield values by 40–50% but with no reduction in T_g and interestingly, in both cases, the polymer–plasticiser mixtures had lower SRS values than HPMC alone. This minimal effect on T_g shows dibutyl sebecate and triacetin to be poor plasticisers of HPMC and the results overall suggest that mechanisms other than plasticisation may be contributing to the observed reductions in yield pressure. It is well known that poorly compatible plasticisers form mixed systems in which phase separated regions of plasticiser, plasticised and unplasticised polymer coexist. In these systems, the compression properties of one component may predominate (Ilkka and Paronen,

Table 1
The effect of plasticisers on mean yield pressure, strain rate sensitivity and glass transition temperature of the binary polymer–plasticiser mixtures

	Mean yield pressure at 3 mm s^{-1} (MPa)	Mean yield pressure at 100 mm s^{-1} (MPa)	Strain rate sensitivity (%)	Glass transition temperature (°C)
HPMC	61.2 ± 1.6	91.1 ± 7.7	32.5 ± 7.2	198 ± 1.2
HPMC + propylene glycol	15.9 ± 0.9	29.0 ± 2.5	46.8 ± 4.4	61 ± 0.7
HPMC + glycerol	19.6 ± 1.1	30.6 ± 1.5	35.7 ± 6.5	130 ± 2.9
HPMC + dibutyl sebacate	17.5 ± 0.2	19.6 ± 0.2	10.7 ± 1.7	180 ± 3.1
HPMC + triacetin	28.7 ± 3.5	34.8 ± 1.0	17.3 ± 1.2	195 ± 0.5

Plasticisers were present at 17% (w/w) in the binary mixture. Yield pressures and SRS values were calculated as described in the text, and glass transition values were measured by DMTA. Mean values ($n = 3$) ± S.D. except DMTA where mean values ($n = 2$) ± range are shown.

1993) or several deformation mechanisms may occur in parallel (Sonnergaard, 1999). There is some evidence for this here: the low SRS values describe a mixture whose response to compression is less strain-dependent than unplasticised HPMC, suggesting a tendency towards a more dilatant material, as would be exemplified by phase separated systems behaving as a surface-lubricated particulate bed. The catastrophic effect of a phase-separated hydrophobic surface film on tablet interparticulate bonding and matrix strength, is exemplified by the well-documented effects of magnesium stearate (Nystrom and Karehill, 1996).

The potency of the more hydrophilic hydroxyl-based polyols, and the ineffectiveness of more hydrophobic plasticisers such as dibutyl sebecate and triacetin, show that the deformation characteristics of this HPMC in the solid state is dominated by hydroxyl mediated interactions such as hydrogen bonding, rather than through hydrophobic interactions between methoxyl-rich regions of the HPMC backbone.

Table 2 shows results from compaction simulator investigations undertaken on model matrix tablet formulations containing plasticised and unplasticised HPMC. Although HPMC comprises only 15% of the total tablet weight, the changes in compression properties appear to correlate well with the effects predicted from the binary mixture.

Fig. 1a shows the plastic energy of compaction of the binary polymer–plasticiser mixtures as a function of the applied compression pressure and plasticiser type. Regardless of plasticiser type, the data shows that above a compression pressure of 35 MPa, significantly less energy (ANOVA, $\alpha < 0.01$) is used in the formation of compacts from plasticised HPMC in comparison with unplasticised HPMC, regardless of the plasticiser used. However, in the absence of plasticiser, increasing the compression pressure results in progressively higher energies of compaction, whilst for the plasticised polymer mixes, above 35 MPa the energy required for compaction remained low. The effect of different plasticisers was indistinguishable in terms of their compaction energy profiles over the range of compression pressures studied.

Fig. 1b shows how a reduction in plastic compaction energy was also apparent in the model tablet formulation. This demonstrates that plasticisation of the HPMC can have a significant effect on the plastic energy of compaction, an effect that is detectable in a formulation that contains only minimal polymer content for a hydrophilic matrix. At an approximate midpoint compression pressure (119 MPa), the observed difference between plasticised and unplasticised formulations was 0.21 J,

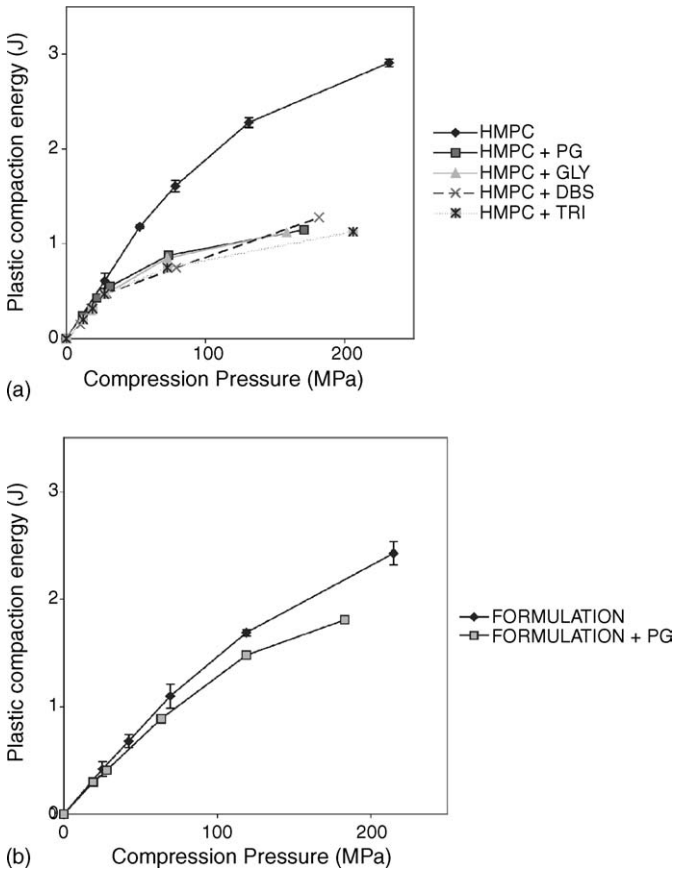

Fig. 1. Plastic compaction energy as a function of applied compression pressure during compression for (a) the HPMC plasticiser binary mixtures and (b) the model HPMC matrix formulation. Compression speed 3 mm s^{-1}. Mean values ($n = 3$) ± S.D. Binary mixtures contained HPMC with or without 17% (w/w) propylene glycol (PG), glycerol (GLY) dibutyl sebecate (DBS) or triacetin (TRI). The model formulation is described in the text and contained 15% HPMC with or without 3% (w/w) propylene glycol. Standard deviations for the plasticised model formulation are smaller than the symbol size.

whilst at the same pressure, the difference between unplasticised HPMC and the HPMC:propylene glycol binary mixtures was 1.11 J. The reduction in the plastic energy of compaction in model formulation was therefore 19% of that observed for the binary mix, sufficiently close to the polymer content of the tablet (15%) to tentatively suggest a proportional effect.

It is important to point out that changes in plastic compaction energy cannot identify the compaction mechanism, as this parameter encompasses all energy-requiring processes contributing to the compaction process. The proportionality with the

Table 2
The effect of propylene glycol on the mean yield pressure and strain rate sensitivity of the model formulation

	Mean yield pressure at 3 mm s^{-1} (MPa)	Mean yield pressure at 100 mm s^{-1} (MPa)	Strain rate sensitivity (%)
Model formulation	54.7 ± 2.62	82.1 ± 5.38	20.7 ± 8.7
Model formulation + propylene glycol	46.6 ± 3.40	77.7 ± 7.13	36.2 ± 10.3

Propylene glycol present at 3% (w/w) of total formulation. This is the same polymer weight ratio as in the binary mixtures. Yield pressures and SRS values were calculated as described in the text. Mean values ($n = 3$) ± S.D. except DMTA where mean values ($n = 2$) ± range are shown.

binary mixtures implies that plasticising HPMC probably alters the deformation characteristics of the polymer in the model formulation in a similar manner. However the model formulation is a complex mixture, and the observed reductions in energy may also have arisen through alternative mechanisms. Examples might include plasticiser lubrication of inter-particle slippage, reduced die-wall friction, or a decrease in the extent of inter-particle bonding.

An interesting aside is the glass transition value determined for HPMC alone (Table 1). T_g values from DSC measurements of a 15,000 cps USP2208 HPMC have been previously reported as 65 and 67 °C (Picker, 2003). Our DMTA measurements clearly suggest a higher value of 198 °C. This disparity may have arisen from the detection by DSC of the thermal gelation transition, which in solution, is around 70 °C, or more pragmatically, from differences in equilibrium moisture content between samples in the solid state.

3.2. The effect of plasticisers on matrix tensile strength and axial expansion 24 h post-compression

The two principal factors believed to influence tablet strength are the predominating bonding mechanism (e.g. solid bridges, Van der Waals forces) and the surface area over which they operate (Nystrom et al., 1993; Nystrom and Karehill, 1996; Eriksson and Alderborn, 1995). Compressed tablets commonly expand axially post-compression, and the extent of this expansion is related to the dissipation of elastic stress which can result in weakening of the inter-particle bonding within the tablet microstructure (Van-der-Voort-Maarschalk et al., 1997, 1998; Nokhodchi et al., 1996b; Doelker, 1993). Unplasticised HPMC has a considerable capacity for elastic storage. This is demonstrated by the extensive uniaxial expansion in the direction of compression, for example when high polymer content matrices are hydrated (Rajabi-Siahboomi et al., 1994).

Fig. 2a shows the effect of different plasticisers on the tensile strength of tablet matrices prepared from HPMC:plasticiser binary mixtures. In the case of unplasticised HPMC, tablet strength increased with compression pressure over the whole range examined. However, plasticised HPMC mixtures behaved very differently. Below 70 MPa, the HPMC:propylene glycol mixture produced stronger tablets than HPMC alone, whilst at higher pressures, the compact tensile strength reached a limiting value around 3 MPa. The combination of glycerol, dibutyl sebacate and triacetin in binary mixtures with HPMC resulted in compacts with very little tensile strength.

The increase in tablet tensile strength below 70 MPa exhibited by propylene glycol plasticised HPMC, may be a direct consequence of the lowering of the polymer yield pressure. Table 1 shows how, on plasticisation, the mean yield pressure of HPMC was reduced from 62 to 29 MPa. At compression forces between these values, the plasticised material can therefore undergo considerably more plastic deformation than unplasticised HPMC, and as a result, compression is likely to result in both (i) a greater surface area of contact between particles and (ii) a reduced susceptibility to elastic energy storage as a greater proportion of particle deformation will be irreversable.

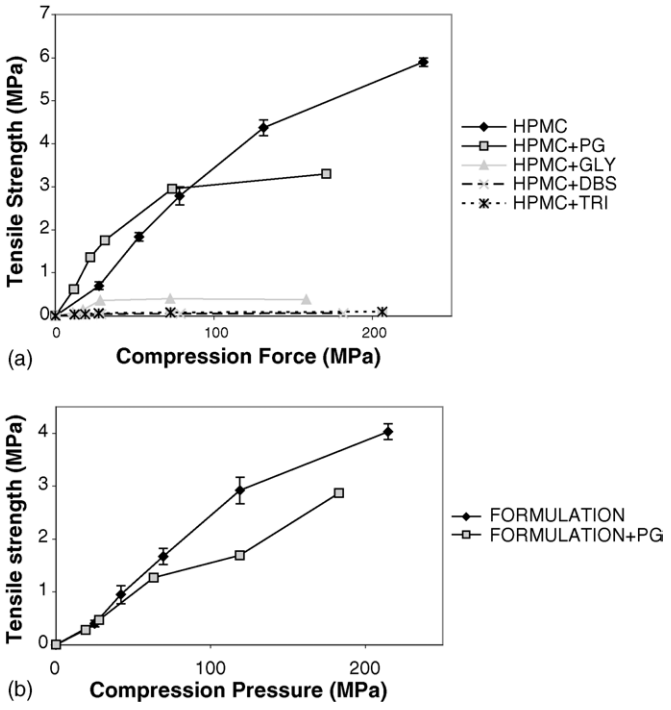

Fig. 2. The effect of plasticisation on the tensile strength of HPMC matrices prepared from (a) the HPMC plasticiser binary mixtures and (b) the model HPMC matrix formulation. Mean values ($n = 3$) ± S.D. Compositions as described in Fig. 1.

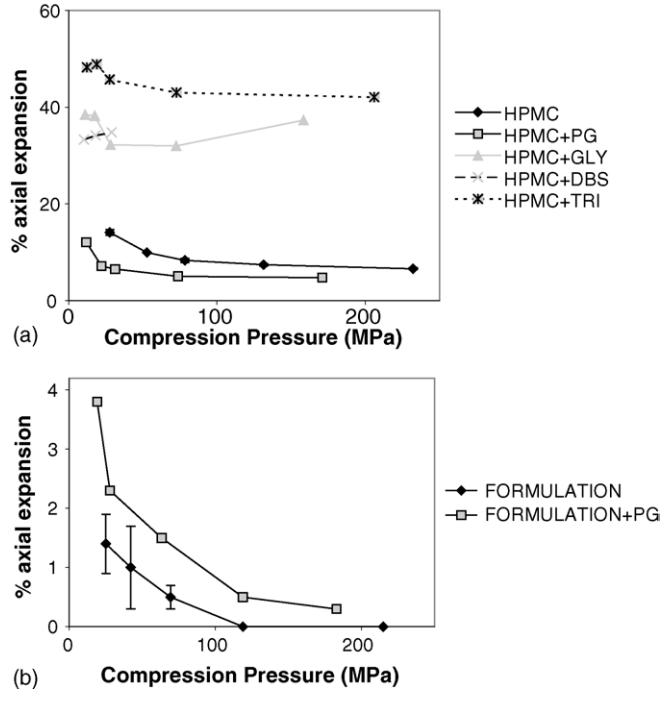

Fig. 3. The effect of plasticisation on the axial expansion 24 h post-compression of HPMC matrices prepared from (a) the HPMC plasticiser binary mixtures and (b) the model HPMC matrix formulation. Mean values ($n = 3$) ± S.D. Compositions as described in Fig. 1.

Elastic energy storage often manifests as tablet expansion post-compaction resulting from internal stress-relaxation. This can play a significant role in reducing tablet strength, as it reduces the internal surface area involved in inter-particle bonding (Nystrom and Karehill, 1996). Fig. 3a shows how propylene glycol plasticised compacts show a clear reduction in axial expansion which suggests that elastic storage is indeed reduced. If a greater bonding area results from enhanced plastic deformation, then both effects would contribute to an increase in tablet strength.

At compression forces of 70 MPa and above, the reason for the limited tablet strength of the propylene glycol plasticised material is unclear. Nokhodchi et al. (1996b) and Nokhodchi and Rubinstein (1998) have shown how HPMC plasticised with water is capable of increased tablet strength regardless of compression pressure and have suggested that a strong hydrogen bond network is formed between adsorbed moisture layers on the surface of adjacent particles, propylene glycol may not be capable of influencing tablet tensile strength in this manner as a result of its increased molecular weight and reduced polarity and, as a result, compact strength may reach a limiting value.

The tablet-forming properties of the other HPMC:plasticiser binary mixtures were extremely poor. There are several mechanisms by which this marked deterioration may have arisen. As these materials are less effective plasticisers than propylene glycol, they are likely to show poorer miscibility with the polymer, resulting in a degree of phase separation. The presence of phase-separated plasticiser on the surface of adjacent HPMC particles may consequently allow (i) the dissipation of compression forces by particle slippage through surface lubrication and (ii) a weakening of inter-particle bonding, both in terms of the bonded surface area and the increased distance over which certain long range inter-particle bonds may be formed. If phase separation is extensive, then interparticulate bonding could be severely reduced, and the compression characteristics of the mixture may then become dominated by the properties of the plasticisers, which are highly deformable. In these cases, we might also expect a high degree of axial expansion as (i) HPMC particles will be poorly plasticised and have a greater propensity to undergo elastic rather than plastic deformation and (ii) in the absence of the restraining effect imposed by interparticulate bonds, they will have greater opportunity to release elastic energy by relaxation. Evidence for this effect is seen in Fig. 3a, which shows how axial expansion post-compression of these compacts was some three to five times greater than compacts of unplasticised HPMC. A weakening of the inter-particle bonds within the tablet microstructure is the most plausible explanation for this phenomenon.

Figs. 2b and 3b show the effect of propylene glycol on the tensile strength and axial expansion of the matrices prepared from the model formulation. It can be seen that the plasticiser had little effect on tablet strength up to 70 MPa, but there was some reduction in strength thereafter, which perhaps reflects the behaviour of the polymer in the binary mixtures (Fig. 2a). Axial expansion of the matrix made with propylene glycol plasticised HPMC also remained minimal, paralleling the behaviour of the unplasticised formulation.

4. Conclusion

This work has examined a range of plasticisers as potential compaction enhancers for high molecular weight HPMC. Plasticisers differed considerably in their effects on compactability and tablet properties. Of the plasticisers studied, only propylene glycol had a beneficial effect in improving compression of HPMC without causing a significant deterioration in tablet properties. In a binary polymer–plasticiser mixture, this was evidenced by a significant reduction in the mean yield pressure of HPMC (i.e. a reduction in the minimum pressure required to form a compact), a reduction in the energy consumed by the compaction process (the plastic energy of compaction) and a reduced axial expansion of the tablet post-compression. Interestingly, these benefits were also detected in a model formulation containing a minimal polymer content of HPMC. These properties suggest the ability of propylene glycol to induce a classical plasticisation of HPMC. Hydrophobic plasticisers caused apparent reductions in yield pressure, but were accompanied by loss of matrix strength and significant stress relaxation post-compression, suggesting interference with interparticulate bonding, and possibly surface lubrication, from a phase separated surface layer.

The use of water to plasticise HPMC and improve compaction properties has been reported previously. Propylene glycol and perhaps other low molecular weight hydroxylated plasticisers, may offer a more convenient viable alternative for improving and controlling the compressibility and compactability of HPMC, without the need for environmental humidity during processing.

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