

# Plasticization of cellulose ethers used in the film coating of tablets

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Plasticizer/polymer interactions have been studied by measuring the intrinsic viscosities of both ethyl cellulose and hydroxypropyl methylcellulose in a series of dialkyl phthalates and in a series of liquid glycols respectively. A correlation was found between the intrinsic viscosity of the polymer/plasticizer solutions and the tensile strength, elongation at rupture and work done in stressing to failure of cast films—the mechanical properties being at a minimum when the intrinsic viscosity was at a maximum. This correlation held only within a homologous series of plasticizers and none was found for plasticizers of different structures. A relationship was found between the lowering of a calculated glass transition temperature of hydroxypropyl methylcellulose in the presence of the plasticizers propylene glycol, polyethylene glycol 200 and glycerol and the intrinsic viscosity of the corresponding solutions—the higher the viscosity the greater the lowering of the transition temperature.

Film formers such as the cellulose ethers, ethyl cellulose and hydroxypropyl methylcellulose are now used extensively in the film coating of solid dosage forms. Plasticizers are often added to these polymers in order to change their physical properties and enhance their film forming characteristics. To be effective a plasticizer must interpose itself between the polymer chains and interact with the forces holding the chains together thereby extending and softening the polymer matrix. A very convenient way of assessing the degree of plasticizer/polymer interaction is to measure the intrinsic viscosity of the polymer dissolved in the plasticizer. In this work these measurements have been made for ethyl cellulose and hydroxypropyl methyl cellulose in a series of liquid plasticizers and correlated with both glass transition temperatures and the mechanical properties of free films.

## MATERIALS AND METHODS

The two polymers used were ethyl cellulose (Grade N50, Hercules Powder Co. Ltd., U.S.A.) and hydroxypropyl methylcellulose U.S.P. (Pharmacoat 606, Shinetsu Chemical Co. Ltd., Japan). Dimethyl phthalate, diethyl phthalate, dibutyl phthalate and dioctyl phthalate were used as plasticizers for the ethyl cellulose; ethylene glycol, diethylene glycol, triethylene glycol, the polyethylene glycols 200, 300, 400, 600, 1000, 4000, 6000, propylene glycol, dipropylene glycol and glycerol were used as plasticizers for the hydroxypropyl methylcellulose.†

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† While it is realised that ethylene glycol, diethylene glycol, triethylene glycol and dipropylene glycol would not normally be used in the film coating of solid dosage forms because of their toxicity, they have been included in this study in order to examine the effect of plasticizer molecular weight.

Intrinsic viscosities of the polymers were determined by measuring the viscosity of the plasticizer (where liquid) and a solution of known concentration of the polymer (usually between 0.1 and 0.5% w/w) using a 'U' tube viscometer and substituting these values in the equations of Rudin & Wagner (1975). All measurements were made at 25 °C.

Cast films were prepared from 5% w/v solutions of the polymers (ethyl cellulose dissolved in toluene/industrial methylated spirits 80:20% v/v mixture, hydroxypropyl methylcellulose dissolved in dichloromethane-methanol 50:50% v/v mixture). Plasticizers were added at a concentration of 1% w/v of the solution to give 20% w/w of the polymer in the dried film. A 5 ml sample of the solution was poured onto cleaned glass substrate bounded by a P.T.F.E. ring (internal diameter 63 mm). The seal between the ring and the glass was ensured by placing a tablet die on top of the ring, the restricted orifice of the die also serving to slow the evaporation of the solvent. After evaporation the film was removed and placed in a vacuum desiccator for at least one week. Strips 40 × 10 mm were cut from the films and stressed to failure at a rate of 0.144 mm s<sup>-1</sup> on a tensile testing apparatus consisting of a constant speed motor and a load transducer (Type UF2, Pye Ether Ltd.) The tensile strength, elongation at rupture and work done in stressing to failure were calculated. The glass transition temperatures of the polymers (8–10 mg sample) were measured using a differential scanning calorimeter (Dupont 990, Dupont Instruments) at a heating rate of 20 °C min<sup>-1</sup>.

## RESULTS AND DISCUSSION

### *Polymer/plasticizer interactions*

The results of the intrinsic viscosity measurements of ethyl cellulose in a series of dialkyl phthalates and

hydroxypropyl methylcellulose in a series of glycols are shown in Figs 1 and 2 respectively. Both systems exhibit a maximum in the intrinsic viscosity corresponding to diethyl phthalate for ethyl cellulose and polyethylene glycol 200 for hydroxypropyl methyl cellulose. Similar results have been reported for polyvinyl chloride in a series of dialkyl phthalates where the maximum intrinsic viscosity occurred with dibutyl phthalate (Wurstlin & Klein 1952). Results for hydroxypropyl methyl cellulose in other plasti-

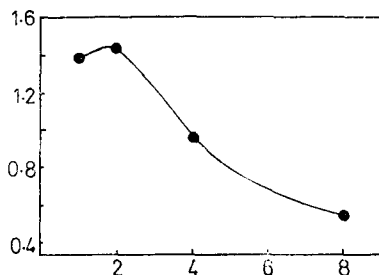


FIG. 1. The intrinsic viscosity ( $[\eta]$  dl g<sup>-1</sup>: ordinate) of ethyl cellulose (Grade N50) in a series of dialkyl phthalates. Abscissa: number of carbon atoms in alkyl group.

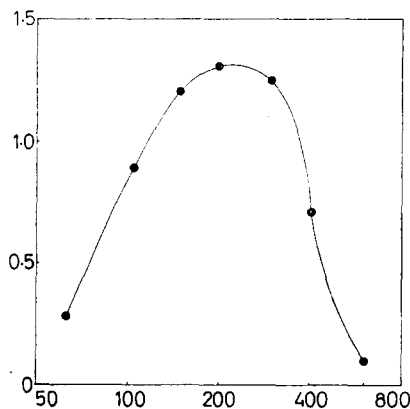


FIG. 2. The intrinsic viscosity ( $[\eta]$  dl g<sup>-1</sup>: ordinate) of hydroxypropyl methylcellulose (Pharmacoat 606) in a series of ethylene glycol derivatives. Abscissa: molecular weight of plasticizer).

cizers are shown in Table 1. The polymer has higher intrinsic viscosities in both propylene glycol and dipropylene glycol, but for glycerol no intrinsic viscosity could be measured since the polymer is only partially soluble in this plasticizer even at its boiling point. Unfortunately hydroxypropyl methylcellulose and the polyethylene glycols are not perfectly uniform chemical compounds but have wide molecular weight distributions as shown by the batchwise variation in the intrinsic viscosity results (Table 2). For both batches of polymer, the intrinsic

viscosities recorded in the polyethylene glycols of molecular weight 200 and 400 are consistently higher than those in the 600 molecular weight grade.

Table 1. Intrinsic viscosities of hydroxypropyl methyl cellulose (Pharmacoat 606) in various plasticizers.

Plasticizer	Intrinsic viscosity dl g <sup>-1</sup>
Propylene glycol	1.73
Dipropylene glycol	2.27
Glycerol	Could not be measured
Polyethylene glycol 200	1.32

Table 2. The effect of batch variation of polyethylene glycol and polymer on the intrinsic viscosity of hydroxypropyl methyl cellulose (Pharmacoat 606).

Sample	Intrinsic viscosity dl g <sup>-1</sup>					
	PEG 200		PEG 400		PEG 600	
Batch 1	1.46	1.29	0.71	1.29	0.10	0.48
Batch 2	1.66	1.44	1.78	0.95	0.81	0.73

Solubility parameter values can also be used to predict optimum interaction since from the theory of Hildebrand & Scott (1950) interaction will be at a maximum when the solubility parameter of both the polymer and plasticizer are the same. Unfortunately no solubility parameter figures for hydroxypropyl methylcellulose are available in the literature but ethyl cellulose has been well researched and found to have a solubility parameter of 21.1 MPa<sup>½</sup> (Burrell 1975). On comparing this with the literature figures for dimethyl (21.9 MPa<sup>½</sup>), diethyl (20.5 MPa<sup>½</sup>), dibutyl (19.0 MPa<sup>½</sup>) and dioctyl phthalate (16.2 MPa<sup>½</sup>) it can be seen that maximum interaction will occur with both the lower members of the series, marginally higher with the diethyl phthalate.

#### Glass transition temperatures

The effect of plasticizers on the glass transition temperature ( $T_g$ ) of a polymer is a specific measure of plasticizer efficiency since the glass transition temperature is a function of chain mobility and the purpose of a plasticizer is to increase chain mobility. Although the glass transitions of ethyl cellulose and hydroxypropyl methylcellulose could easily be identified using differential scanning calorimetry as being  $129 \pm 1^\circ\text{C}$  and  $177 \pm 1^\circ\text{C}$  respectively, the traces produced by the plasticized films were very complex and the glass transitions were not distinct. However it is possible to construct graphs showing the theoretical decrease in the glass transition temperatures of polymers using the formula derived by Kelley & Bueche (1961).

$$T_g = \frac{(\alpha_p V_p T_{gp} + \alpha_d (1 - V_p) T_{gd})}{\alpha_p V_p + \alpha_d (1 - V_p)}$$

where,  $\alpha_p$  and  $\alpha_d$  are the coefficients of volumetric expansion of the polymer and plasticizer respectively,  $V_p$  is the volume fraction of the polymer and  $T_{gp}$  and  $T_{gd}$  are the glass transition temperatures of the polymer and plasticizer respectively.  $\alpha_p$  is usually taken as  $4.8 \times 10^{-4}$  per  $^{\circ}\text{C}$  but unfortunately the glass transition temperatures and coefficients of expansion of only a few plasticizers are known (Table 3). Since the curves (Fig. 3) represent prediction from theory, the values are only approximate but the data presented by Kelley & Bueche (1961) would seem to suggest that these are good approximations. In the case of the hydroxypropyl methyl cellulose the plasticizer efficiency which corresponds to the lowering of glass transition temperature is ranked propylene glycol > polyethylene glycol 200 > glycerol i.e. in decreasing intrinsic viscosity (Table 1).

#### Mechanical properties of free films

In mechanical testing the most efficient plasticizer is usually defined as the one that gives the best balance of end use properties for the amount incorporated. However, this definition does not lend itself to precise measurement unless the end use properties are well defined. In this study the concentration of the plasticizer has been kept constant and the properties tensile strength, elongation at rupture and work done in stressing to failure measured. For all these properties (Figs 4 and 5) there is a minimum as the molecular weight of a series of plasticizers is increased. The minima, corresponding to polyethylene glycol 200 for the hydroxypropyl methylcellulose and diethyl phthalate for the ethyl cellulose, correlate with the maxima in the intrinsic viscosity curves (Figs 1 and 2). A similar trend has been reported for polyvinyl chloride where the intrinsic viscosity was highest in dibutyl phthalate which has

Table 3. Values for the glass transition temperature of the plasticizer ( $T_{gd}$ ) and the coefficient of cubical expansion ( $\alpha_d$ ) used by Kelley & Bueche (1961).

Plasticizer	$T_{gd}$ $^{\circ}\text{C}$		$\alpha_d$ per $^{\circ}\text{C}$	
	Value	Ref.	Value	Ref.
Glycerol	-86	Williams et al (1955)	$4.4 \times 10^{-4}$	Schulz (1954)
Propylene glycol	-113	Williams et al (1955)	$5.0 \times 10^{-4}$	Parks & Huffman (1927)
Polyethylene glycerol 200	-56	Manufacturers literature (ICI Ltd)	$7.3 \times 10^{-4}$	Manufacturers literature (Hoechst A.G.)
Diethyl phthalate	-65	Kelley & Bueche (1961)	$1 \times 10^{-3}$	Kelley & Bueche (1961)

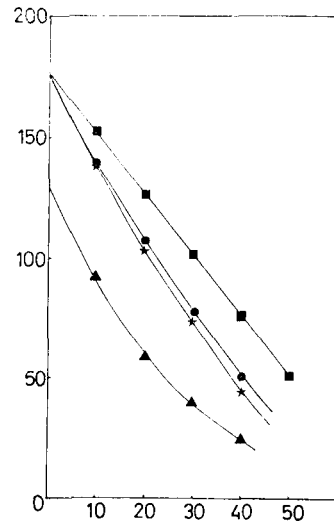


Fig. 3. The effect of glycerol (■) polyethylene glycol 200 (●) and propylene glycol (★) on the glass transition temperature (ordinate:  $^{\circ}\text{C}$ ) of hydroxypropyl methylcellulose. The effect of diethyl phthalate (▲) on the glass transition temperature of ethyl cellulose. All values calculated using the equation of Kelley & Bueche (1961). Abscissa: % w/w plasticizer concentration.

been shown to be the most efficient plasticizer in lowering the torsional modulus of elasticity (Lawrence & McIntyre 1949). A similar correlation between intrinsic viscosity and mechanical properties can be seen for the propylene glycol and dipropylene glycol (Table 4 and Table 1) but no correlation could be found on comparing different plasticizers e.g. glycerol and propylene glycol (Table 4 and Table 1). This may well be due to the differences in the size and shape of the plasticizer molecules since it is well known that long cylindrical plasticizer molecules are more efficient than spherical molecules of the same molecular weight. However, if Brinell hardness numbers from microindentation measurements are used to compare the films (Rowe 1976), there is a direct correlation between the hardness number and intrinsic viscosity, the higher the latter the lower the former, i.e. the softer the film. On testing a series of polyethylene glycols, Rowe (1976) also found a minimum in the Brinell hardness number corresponding to polyethylene glycol 400.

#### Implications in film formulation

Whilst it must be realized that any simple empirical relationship between intrinsic viscosity measurements and plasticizer activity in films can only really be expected to hold within a series of plasticizers whose structures are similar, the results illustrate the

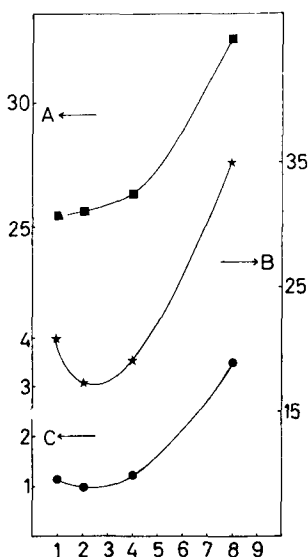


FIG. 4. The effect of chain length in a series of dialkyl phthalates on A, the tensile strength (■), B, elongation at rupture (★) and C, the work done in stressing to failure (●) of films prepared from ethyl cellulose (Grade N50). Plasticizer concentration 20% w/w. Ordinates: A (MPa); B (%); C (mJ). Abscissa: number of carbon atoms in alkyl groups.

potential capability of such a relatively simple technique as intrinsic viscosity measurements in the screening of plasticizers.

The main disadvantage of the technique is that the plasticizer must be a liquid although there is no

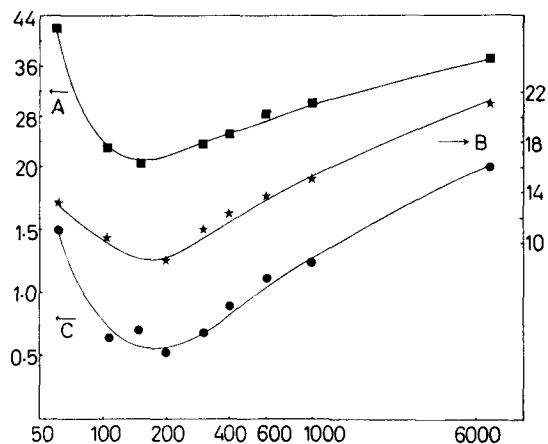


FIG. 5. The effect of the molecular weight of a series of ethylene glycol derivatives on the A, tensile strength (■), B, elongation at rupture (★) and C, the work done in stressing to failure (●) of films prepared from hydroxypropyl methylcellulose (Pharmacoat 606). Plasticizer concentration 20% w/w. Ordinates: A (MPa); B (%); C (mJ). Abscissa: molecular weight of plasticizer.

Table 4. Data on films not shown in Figs 4 and 5 (plasticizer concentration 20% w/w).

Film sample	Tensile strength MPa	Elongation at rupture %	Work done in stressing to failure mJ
Ethylcellulose (unplasticized)	41.5	13.2	1.4
Pharmacoat 606 (unplasticized)	55.6	9.1	1.1
Pharmacoat 606 + propylene glycol	38.0	16.8	1.7
Pharmacoat 606 + dipropylene glycol	23.6	12.0	0.8
Pharmacoat 606 + glycerol	27.3	16.4	1.3

reason why measurements should not be made at higher temperatures e.g. 60–80 °C to accommodate waxes. Good plasticizer/polymer interaction will also affect other properties of the system. One such effect of importance in the film coating of tablets is the change in the thermal gelation temperature (i.e. the temperature above which a polymer will precipitate or gel) of aqueous solutions of hydroxypropyl methylcellulose. Plasticizers which have a strong interaction with this polymer, e.g. propylene glycol and polyethylene glycol 400, increase this temperature while plasticizers which have little or no interaction, e.g. glycerol, lower this temperature. Care must therefore be taken in the choice of plasticizer since if the surface temperature of the tablets is above the thermal gelation temperature of the polymer/plasticizer system precipitation will occur and a rough non-continuous film will result.

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