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The effect of the molecular weight of ethyl cellulose on the drug release properties of mixed films of ethyl cellulose and hydroxypropyl methylcellulose

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Summary

The effect of the molecular weight of ethyl cellulose on the drug release properties of mixed films of ethyl cellulose and hydroxypropyl methylcellulose has been studied by coating spherical granules with a film and measuring the release of a water-soluble model drug substance. Drug release was found to decrease with increasing molecular weight and on the addition of plasticizer, diethyl phthalate, to the films prepared from the low molecular weight grades. At molecular weights in excess of 35,000 (equivalent to a grade with a nominal viscosity of 20 mPas) the addition of a plasticizer had no effect on drug release. The results have been correlated with the mechanical properties of films prepared from the various molecular weight grades of ethyl cellulose, the rapid release with the low molecular weight grades being caused by the presence of cracks and flaws in the film.

Introduction

Ethyl cellulose in combination with water-soluble polymers, e.g. polyethylene glycols, hydroxypropyl cellulose and hydroxypropyl methylcellulose, is widely used in the preparation of sustained release films (Coletta and Rubin, 1965; Shah and Sheth, 1972; Donbrow and Samuelov, 1980). The ethyl cellulose used in the formulation of coatings invariably has an ethoxyl content of 47.5–49.0% w/w corresponding to a degree of substitution (i.e. the average number of hydroxyl groups substituted per anhydroglucose unit) of 2.42–2.53. It is available in a wide range of grades with various viscosity designations representing the viscosity at 25°C of a 5% w/w solution in a solvent mixture of 80 parts toluene and 20 parts ethanol by weight. Considering that it is well known that the nominal viscosity and hence molecular weight of ethyl cellulose can have an important effect on the mechanical properties of the resultant coatings (Rowe, 1982a) and that the mechanical properties are important in governing the incidence of film cracking (Rowe and Forse, 1980; Rowe, 1981, 1983), little work has been done on the effect of these variables on the drug release properties of such films when applied to an oral dosage form. Recently Bøgelund (1983) showed that the release of chloroquine phosphate from a film coated tablet could be reduced from 90% in 4 h to effectively zero in the same time by simply

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changing the nominal viscosity of the ethyl cellulose in the film coating from 7 to 20 mPas. Rowe (1985) has also reported data on mixed films of ethylcellulose and hydroxypropyl methylcellulose. This work is an extension of that previously reported.

Materials and Methods

Table 1 shows the properties of 5 samples of N-type ethyl cellulose obtained from Hercules (Wilmington, DE, U.S.A.). The viscosities at 25°C of a 5% w/w solution in a solvent mixture of 80 parts toluene and 20 parts ethanol by weight and the ethoxyl contents of each sample were determined using the standard tests (United States National Formulary, XV, 1980). The molecular weight of each sample was calculated using the equation derived by Rowe (1982a). Hydroxypropyl methylcellulose (Pharmacoat 606— Shin-Etsu Chemicals, Tokyo, Japan), used as the hydrophilic component of the film, had a nominal viscosity (the viscosity of 20°C of a 2% w/w aqueous solution) of 5.9 mPas corresponding to a molecular weight of 53,500 (Rowe, 1980). Diethyl phthalate was used as plasticizer.

The oral dosage form chosen for the study was a spherical granule, approximately 1 mm in diameter, consisting of a water-soluble model drug substance (a propanolamine derivative with a pK_a of approximately 9.5) mixed with microcrystalline cellulose in the proportion 65 : 35% by weight. The granules were prepared using a spheronization technique (Reynolds, 1970), the formulation being chosen since previous experience had indicated that the granules were prone to film cracking when coated. The granules were coated with a film formulation consisting of 90% w/w ethyl cellulose, 10% w/w hydroxypropyl methylcellulose with and without diethyl phthalate (10 and 20% w/w based on total cellulose) applied as a 5% w/v solution in dichloromethane–methanol (50 : 50% v/v) in a fluidized bed (WSLD 5, Glatt, Haltingen, F.R.G.). The total charge of granules used was 2 kg and the amount of polymer applied equivalent to a 5% increase in weight. The coated granules were hand filled into size 0 hard gelatin capsules (fill weight 258 mg) and the dissolution of the model drug in simulated gastric juice (pH 1.5) was monitored using the U.S.P. rotating basket method and ultraviolet spectrophotometry.

TABLE 1

ETHYL CELLULOSE SAMPLES USED IN STUDY

Sample	Ethoxyl content (% w/w)	Apparent viscosity (mPas)	Molecular weight
N7	48.8	6	18,260
N10	48.4	9	22,920
N14	48.6	13	28,160
N22	48.7	20	35,860
N50	48.5	50	59,870

Results and Discussion

The dissolution profiles of the spherical granules coated with formulations containing the different molecular weight grades of ethyl cellulose are shown in Fig. 1. It can be seen that drug release decreases with increasing molecular weight but at molecular weights in excess of 35,000 — equivalent to the N22 grade — there was no further decrease. This is in direct agreement with the data reported by Bøgelund (1983). On addition of the plasticizer, diethyl phthalate, drug release is decreased with the lower molecular weight grades but with the higher molecular weight grades there is no effect (Figs. 2–6). The relative decrease in dissolution with increasing plasticizer concentra-

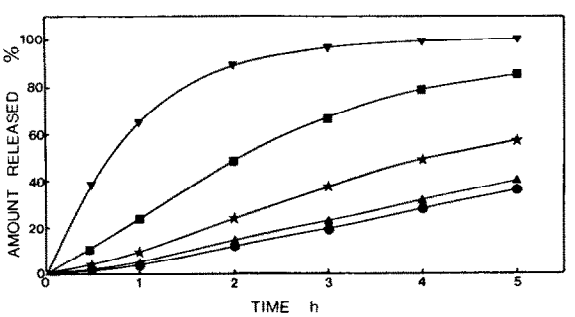

Fig. 1. The effect of the molecular weight of ethyl cellulose on the release of the model drug substance: ▼, Grade N7; ■, Grade N10; ★, Grade N14; ▲, Grade N20; ●, Grade N50.

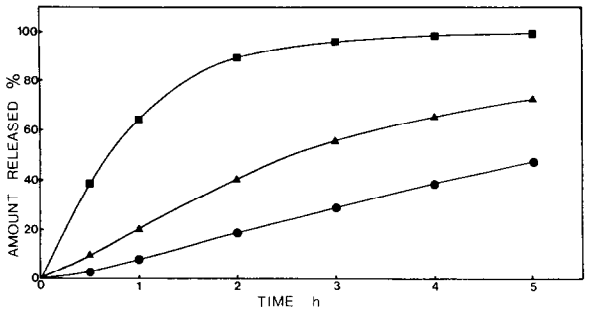

Fig. 2. The effect of plasticizer concentration on the release of the model drug substance through films prepared with ethyl cellulose grade N7: ■, no plasticizer; ▲, 10% diethyl phthalate; ●, 20% diethyl phthalate.

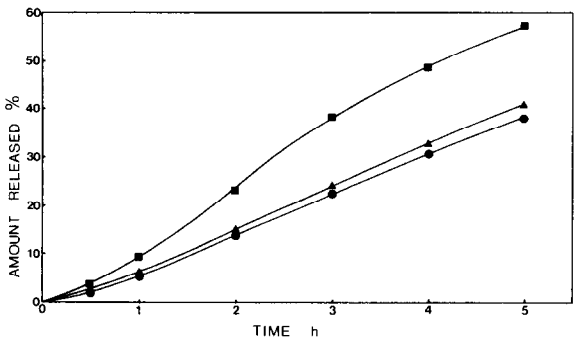

Fig. 4. The effect of plasticizer concentration on the release of the model drug substance through films prepared with ethyl cellulose Grade N14: ■, no plasticizer; ▲, 10% diethyl phthalate; ●, 20% diethyl phthalate.

tion is greatest with the lowest molecular weight grade but gradually decreases with increasing molecular weight.

As a consequence of recent work (Donbrow and Friedman, 1975; Donbrow and Samuelov, 1980) two mechanisms for the release of a drug from such a system have been proposed:

(a) Transport of the drug through a network of capillaries filled with dissolution media — applicable only if the water soluble component of the film is leached out of the matrix.

(b) Transport of the drug through a hydrated swollen film — applicable if the water-soluble component is retained within the matrix.

Although no experimental evidence has been offered to distinguish between the two mechanisms when hydroxypropyl methylcellulose is used as the water-soluble component, it would appear that if polyethylene glycols are used, transport is by the first mechanism while if hydroxypropyl cellulose is used, transport is by the second mechanism (Donbrow and Samuelov, 1980). However, neither mechanism can explain the dissolution results obtained with the low molecular weight grades of ethyl cellulose. In order to explain these deviations it is first necessary to consider the validity of the assumptions made in the proposition of the mechanisms, i.e. the film is coherent with no flaws or cracks.

Recent work with both spray coated tablets and granules would suggest that flaws and cracks in film coatings are commonplace especially coatings prepared from low molecular weight grades of polymers (Rowe and Forse, 1980; Row, 1981, 1982b). If this is the case then a third mechanism

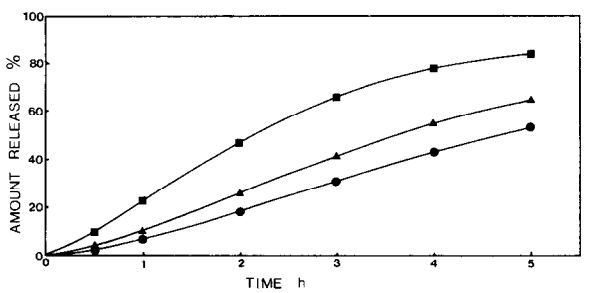

Fig. 3. The effect of plasticizer concentration on the release of the model drug substance through films prepared with ethyl cellulose Grade N10: ■, no plasticizer; ▲, 10% diethyl phthalate; ●, 20% diethyl phthalate.

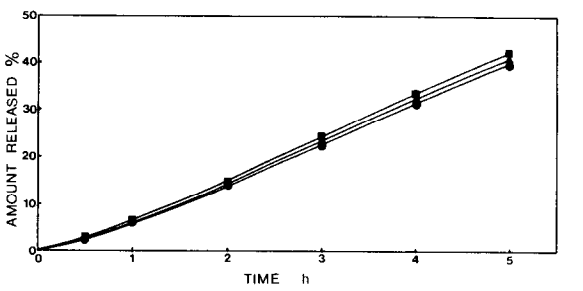

Fig. 5. The effect of plasticizer concentration on the release of the model drug substance through films prepared with ethyl cellulose Grade N22: ■, no plasticizer; ▲, 10% diethyl phthalate; ●, 20% diethyl phthalate.

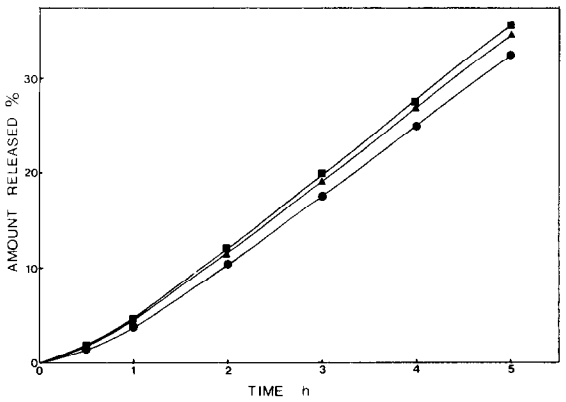

Fig. 6. The effect of plasticizer concentration on the release of the model drug substance through films prepared with ethyl cellulose Grade N50: ■, no plasticizer; ▲, 10% diethyl phthalate; ●, 20% diethyl phthalate.

must also be considered, i.e.:

(c) Transport of the drug through flaws, cracks and imperfections within the matrix.

Drug release via this mechanism will be much faster than that by either the first of second mechanisms and hence the results in Figs. 1–6 can be explained on the basis of the predominance of each mechanism for each formulation.

The origins and causes of flaws and cracks in film coatings applied to solid dosage forms are only just beginning to be understood. One theory that has received prominence involves the presence of residual internal stresses within the film coating (Rowe, 1981, 1983). These are created by the shrinkage of the film on evaporation of the solvent and by differences in the thermal expansions of the coating and the substrate. If these stresses exceed the cohesive strength of the film, cracking will occur and film integrity will be lost. It follows that, if this is the mechanism, then the incidence of such a defect will be dependent on the mechanical properties the polymer and its molecular weight, these two factors being interrelated, the relationship being qualitatively the same for all polymers. Films prepared from low molecular weight polymers with short chains are relatively weak but as the chain length and hence molecular weight is increased the mechanical properties of the films also improve until at some critical molecular weight there is no further improvement (Alfrey, 1965).

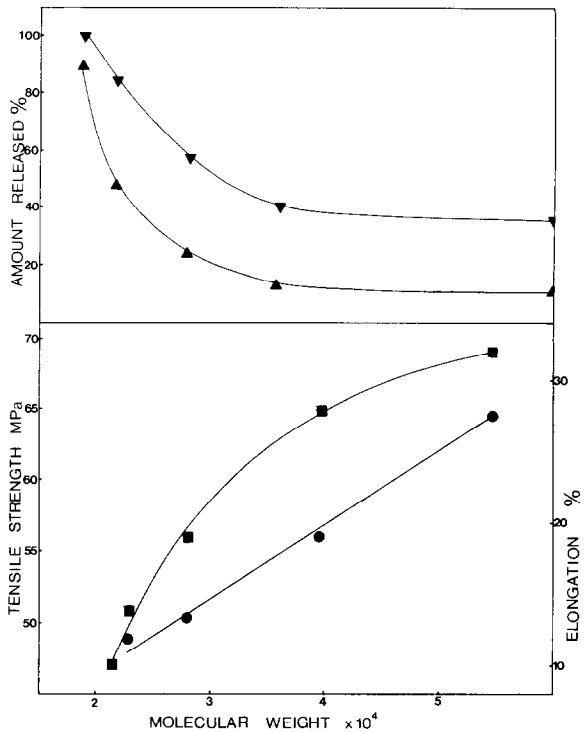

Fig. 7. The interrelationships between the molecular weight of ethyl cellulose, the amount of the model drug substance release after 2 h (▼) and 5 h (▲), the tensile strength of free films (●) and the elongation to break of free films (■). The values for the mechanical properties were obtained from manufacturer's literature.

Data showing the interrelationships between the dissolution of the model drug substance, the mechanical properties (tensile strength and elongation to break) of ethylcellulose and the molecular weight of the ethyl cellulose (Fig. 7) support the concept that cracking is occurring with the low molecular weight grades of the polymers resulting in a rapid release of the model drug and that the incidence of this defect decreases with increasing molecular weight until, at molecular weights of ethyl cellulose of over 35,000, the films are coherent.

Further evidence that imperfections and cracks are important factors in determining drug release though the films prepared from the low molecular weight grades of ethyl cellulose can be obtained by considering the results showing the effect of the addition diethyl phthalate (Figs. 2–6). Diethyl phthalate is a good plasticizer for ethyl cellulose

showing good compatibility and efficiency (Entwistle and Rowe, 1979; Rowe et al., 1984). It is a poor plasticizer for hydroxypropyl methylcellulose and recent work (Sakellariou, 1982) has shown that, when added to mixed films of ethyl cellulose and hydroxypropyl methylcellulose, it partitions itself into the ethyl cellulose lowering its glass transition temperature proportional to the amount added. This will result in a lowering of the residual internal stress (Rowe, 1981, 1983) within the coating and hence the formation of a more coherent film. Therefore, in the case of films prepared from the lower molecular weight grades of ethyl cellulose where drug release is primarily through flaws and cracks the addition of diethyl phthalate will be beneficial resulting in a slower release. However, in the case of films prepared from the higher molecular weight grades of ethyl cellulose where drug release is primarily due to transport through the intact film, the addition of diethyl phthalate will have no effect.

While it must be realized that the effects seen are likely to be exaggerated due to the granule formulation being prone to film cracking when film coated, the results do correlate well with the standard theories of polymer behaviour. Such data as molecular weight and mechanical properties of polymers, polymer/plasticizer compatibility and plasticizer efficiency are invaluable to the formulator in understanding the behaviour of polymers when applied to solid dosage forms and in being able to rectify film defects and optimize film formulations.

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