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HIGH-VISCOSITY HPMC AS A FILM-COATING AGENT

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ABSTRACT

The possibility of using high viscosity grades of hydroxypropylmethylcellulose (HPMC) as a film forming agent in a conventional coating process has been investigated. Ethanol/water mixtures having different weight ratios (5 to 18) and containing up to 5 % of HPMC revealed to be suitable.

The influence of some formulation additives (talc, PVP and plasticizers) on both the overall coating process and the in-vitro release profiles of ketoprofen containing coated tablets was also investigated and discussed.

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INTRODUCTION

Low viscosity grades of hydroxypropylmethylcellulose (HPMC) are commonly used in film-coating while high viscosity grades of HPMC have not been deeply investigated in this regard. On the other hand, a film-coating made of such a hydrophilic swellable polymer to form a viscous barrier could represent a innovative approach in the design of a delayed-release dosage form. As far as modified release dosage forms are concerned, high viscosity HPMC is generally applied to preparing matrix systems.

Undoubtedly, there are obvious technical problems to be faced in using high viscosity HPMC as a film coating agent. The only example reported in literature is based on a high temperature process to reduce the viscosity of the polymeric dispersion to be sprayed (1).

On the basis of these considerations, the aim of this work was the development of a film-coating technique suitable for applying a layer of high viscosity HPMC onto cores (pellets or tablets) by using a conventional coating equipment, as an alternative to compression coating, which is a method requiring specially developed presses.

Results concerning the influence of the nature of the solvent mixtures, the additives and the process conditions to give a film with a defined range of properties are reported.

Finally, preliminary results of an in-vitro release profile of ketoprofen containing systems are given and discussed.

MATERIALS AND METHODS

The following materials have been used:

-Ketoprofen (U.S.P. grade), M.W. = 254.29, m.p. ≅ 93.9°C,

S.I.M.S., Italy;

-Lactose monohydrate (U.S.P. grade): Lactose Powder D 80, Meggle, West Germany;

-Maize starch (U.S.P. grade): Roquette Frères, France;

-Magnesium stearate (U.S.P. grade): F.A.C.I., Italy;

-Poly(1-vinyl-2-pyrrolidone) (U.S.P. grade): Kollidon K 25 and Kollidon K 90, BASF, West Germany;

-Hydroxypropylmethylcellulose (U.S.P. grade, 2208): Methocel K 4 M and Methocel K 15 M, Dow Chemical, U.S.A.;

-Poyethylene glycol (U.S.P. grade): P.E.G. 400, Hoechst, West Germany;

-Diethylphthalate (analytical grade), Carlo Erba reagent;

-Talc (U.S.P. grade), Società Italiana Talco e Grafite, Italy.

The methods applied were as follows.

Ketoprofen (2.5 Kg), lactose (6.2 Kg) and maize starch (1 Kg) were granulated by wetting with 2 L of a 10 % Kollidon K 90 aqueous solution. The moistened mass was forced through a 1,25 mm screen and dried at 55°C. The granules were lubricated with 0.5 % of Magnesium Stearate and tableted in a rotary tablet press using the following two sets of punches: 2.0 mm in diameter with 2.0 mm of radius of curvature or 4.5 mm in diameter with 4.5 mm of radius of curvature.

Tablets were checked for weight (8 mg or 50 mg), height (1.85 mm or 2.66 mm) and hardness (40 N or90 N).

The coating dispersions were prepared by adding hydroxypropylmethylcellulose and the auxiliary substances to suitable ethanol/water mixtures. The dispersions were allowed to rest at room temperature for at least 12 hours.

The tablets were coated in a rotating pan (35 cm diam., 15 L capacity) and the following coating process variables were evaluated:

-mode of spraying

-spray rate

-inlet air temperature

-nozzle port size

-atomizing air pressure

-nozzle height

-drying time

All coating dispersions were stirred for 30 minutes before spraying and continuously stirred throughout the coating process.

The coated tablets were dried for 20 minutes in the coating pan at the same temperature and air flow, then they were checked for weight.

The release tests were performed in simulated intestinal fluid without enzymes (pH 7.5) using the USP paddle apparatus (900 ml at 37 °C and 50 rpm).

Six tablets were tested simultaneously by means of a Sotax Dissolution Apparatus AT 6 equipped with an automatic sampling device. The drug was assayed spectrophotometrically (Cecil 5500 UV Spectrophotometer) at 260.5 nm.

RESULTS AND DISCUSSION

Formulation of the Coating Dispersions

The use of high viscosity HPMC in an aqueous film-coating process would require very low polymer concentrations in order to achieve acceptable *sprayability* (i.e. feasible spraying conditions) and, in any case, a long processing time would be necessary. In fact, the increase of polymer concentration gives rise to solutions within a no-workable range of viscosity.

In order to solve this problem a reasonable approach would be the use, along with water, of a water-miscible solvent capable of limiting the water-polymer interaction, thus allowing to prepare mixtures having relatively high polymer concentrations without increasing viscosity dramatically.
In these mixtures water, due to its plasticizing properties, has to be present to guarantee film forming capacity.
Among water-miscible solvents ethanol, in which HPMC is not soluble, turned out to be suitable for the preparation of a sprayable dispersion.

With the purpose to prepare at least a 4 % (w/w) Methocel K 4M dispersion to be sprayed, different ethanol/water ratios were investigated.
The results, in terms of *sprayability* - neither clogging of the nozzle nor powdering during spraying - showed that at least 80 % (w/w) of ethanol and not less than 5 % (w/w) of water in the mixture are necessary. As a consequence, the ethanol/water weight ratio can range between 5 and 18: high ratios allowing either to spray more concentrated polymer dispersions up to 10 % (w/w) and/ or to increase the rate of spraying up to 25 g/min.

Formulae of sprayable coating dispersions are given in Table I.

In spite of their *sprayability*, formulae A, B and C couldn't be processed in the film-coating of tablets (4.5 mm diameter) because of the marked tackiness of the coating layer being formed on the tablet surface.
The introduction in the formulation of an antiadherent agent (i.e. Talc) prevented the agglomeration of the tablets making coating operation possible and a uniform, smooth coating was obtained.

TABLE I
Sprayable Coating Dispersions

Composition (% w/w):	A	B	C
METHOCEL K 4 M	4	4	10
ETHANOL	80	88	84
WATER	16	8	6
Ethanol/Water Weight Ratio:	5	11	14
Rate of Spraying (g/min.):	10	25	18

However, in an attempt to shorten processing time, not yet acceptable from an industrial point of view, the introduction of other traditional film-coating additives was evaluated. It was found that, by adding a water soluble binding agent such as polyvinylpyrrolidone and a suitable plasticizer (either hydrophilic or lipophilic), the desired weight gain per tablet could be attained in a shorter time, contemporarely reducing the total amount of solvent mixture employed for coating. Moreover, the presence of these additives allowed to improve significantly the technological properties of the coating layer in terms of appearance and homogeneity due to improved mechanical characteristics of the film (i.e. reduction of the risk of film cracking and better adhesion of the film to the substrate).

The relevant process conditions and coating dispersion compositions based on the use of Methocel K 4 M are given in Table II and Table III, respectively.

From these results the important role played by the plasicizer with respect to processing time is evident.

TABLE II
Coating Conditions

PARAMETER	VALUE
Batch size	0.5 Kg
Mode of spraying	intermittent
Inlet air temperature	50 °C
Outlet air temperature	35 °C
Tablet bed temperature	30 °C
Temperature of the dispersion	R.T.
Nozzle port size	1.6 mm
Atomizing air pressure	2.2 bar
Nozzle height	15 cm
Pan rotating rate	20 r.p.m.

TABLE III
Coating Dispersions With METHOCEL K 4 M

Composition (% w/w):	D	E	F
METHOCEL K 4 M	5	5	5
TALC	3	2.5	2.5
PVP K 25	2	1.5	1.5
PEG 400	-	1	-
DIETHYLPHTHALATE	-	-	1
ETHANOL	83	83	83
WATER	7	7	7
Ethanol/Water Ratio:	11.8	11.8	11.8
Processing Time for 20 % Weight Gain (h):	2.4	1.6	1.0

TABLE IV
Coating Compositions Tested In Vitro

Composition (% w/w):	G	H	I	L
METHOCEL K 4 M	4	5	-	-
METHOCEL k 15 M	-	-	5	5
TALC	2	2	2	2
PVP	2.5	2.5	2.5	2.5
PEG 400	0.2	1	1	-
DIETHYLPHTHALATE	-	-	-	1
ETHANOL	81	84	84	84
WATER	10.3	5.5	5.5	5.5

Particularly, the use of a hydrophilic plasicizer seems to be advantageous.

Analogous results, in terms of processing conditions and technological properties of the coated tablets, were obtained by using Methocel K 15 M and when coating was performed onto tablets of 2 mm in diameter.

In-vitro release

Coated tablets prepared with various film coating compositions containing high viscosity HPMC and selected on the basis of their process feasibility and film quality (Table IV) were evaluated for their in-vitro release characteristics.

In *figure 1* the release profiles of uncoated and coated tablets are reported. The release profile curves of coated tablets show a characteristic lag-time: when in contact with the dissolution medium the polymeric coating layer swells and a trasparent gel layer around the tablets is obtained. As

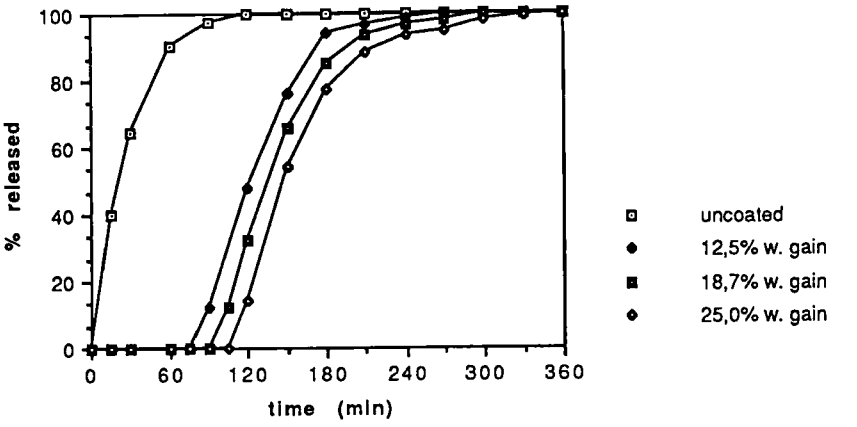

FIGURE 1

Release curves of uncoated and coated tables (composition G)

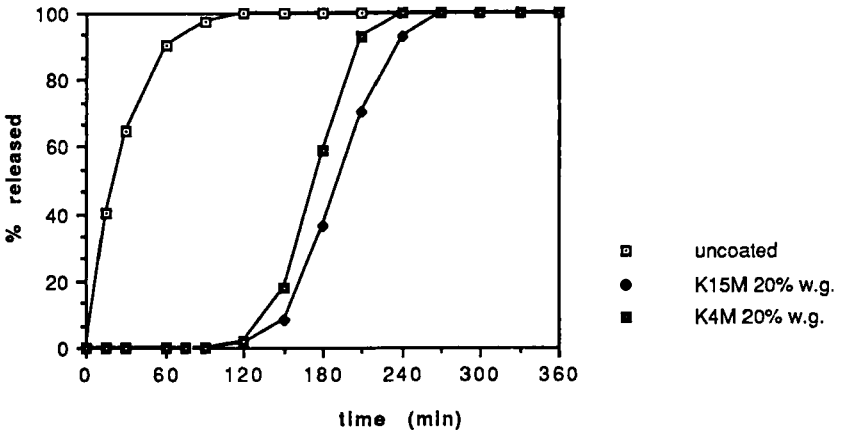

FIGURE 2

Effect of hydroxypropylmethylcellulose grades on release profiles of coated tables (composition H and I)

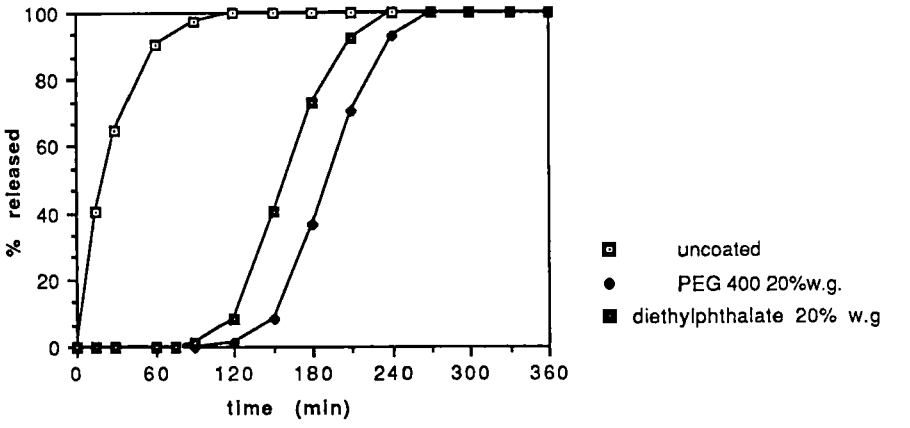

FIGURE 3

Effect of different plasticizers on release profiles of coated tables (composition I and L)

expected, lag-time increases as a function of the amount of the coating layer.

Then the effect of the type of Methocel K on the release profile was evaluated. The results reported in *figure 2* show that a slight change in the slope of the curve can be obtained without affecting the lag-time significantly.

It can also be observed in *figure 3* that the chemical nature of the plasticizer has an influence on the release profile curves: a hydrophilic plasticizer allows to obtain a slight longer lag-time with respect to the use of the lipophilic one. The hydrophilic plasticizer seems to give rise to a more homogeneous and resistent gel layer.

The results prove the feasibility of coating operation with high-viscosity HPMC containing dispersions that are suitable for processing in a conventional coating equipment. The technical problems encountered in terms of poor sprayability and time consuming operation can be solved by using

ethanol/water mixtures, in which HPMC is dispersed, as well as suitable additives such as Talc, PVP and plasticizers.

Such an approach allows to obtain a continuous polymeric layer of high viscosity HPMC at a desired thickness, as an alternative to compression coating technique; it can be exploited for the design of delayed-release dosage forms and was successfully applied to a novel time-based oral site-specific drug delivery system (2).

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