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Effects of hydroxymethylpropylcellulose (HPMC) moisture content on hydrochlorothiazide release from HPMC-based tablets

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Abstract

The effects of hydroxypropylmethylcellulose (HPMC) moisture content on the properties of tablets made with HPMC as base excipient were investigated. Two varieties of HPMC, with nominal viscosities of 4000 and 100 000 cP, were evaluated. The drug model used was hydrochlorothiazide, present in tablets at 1% w/w. The results for both HPMC varieties indicate that variation in HPMC moisture content over the range 2.25–10.85% has no significant effects on drug release profile, despite the fact that HPMC moisture content is positively correlated with the tensile strength of tablets.

Keywords: Hydroxypropylmethylcellulose; Moisture content; Hydrophilic matrix tablets; Hydrochlorothiazide; Dissolution rate

1. Introduction

In two recent articles, Malamataris et al. (1994) and Malamataris and Karidas (1994) reported an in-depth characterization of the effects of moisture content on the compression properties of hydroxypropylmethylcellulose (HPMC) and on the mechanical properties of tablets prepared with HPMC as base excipient. These authors interpreted the observed effects in terms of the characteristics of distribution of moisture within HPMC particles. In the present study, in view of the extensive use of HPMC as base excipient in hydrophilic-matrix tablets for controlled release (Vázquez et al., 1992), we investigated the effects of HPMC moisture content on drug release from HPMC-based tablets. Two HPMC varieties were used (Methocel K4M, nominal viscosity 4000 cP; Dow Chemical, Premium quality, batch 88760708 and Methocel K100M, nominal viscosity 100,000 cP; Dow Chemical, Premium quality, batch 0257556-989). The drug model used was the poorly hydrosoluble diuretic hydrochlorothiazide (J. Escuder, batch 014). Magnesium stearate (used

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Table 1
Effects of HPMC moisture content on HPMC properties and tablet properties. Values in brackets are standard deviations

HPMC variety	Moisture content, %	Mean yield pressure, MPa	Tensile strength, MPa	Dissolution rate constant, % $h^{-1/2}$
K4M	2.25	62.3 (0.8)	0.65 (0.06)	0.244 (0.009)
	5.10	36.5 (0.1)	1.25 (0.09)	0.242 (0.006)
	10.85	30.2 (0.2)	2.13 (0.17)	0.245 (0.008)
K100M	2.25	77.2 (0.9)	0.77 (0.11)	0.228 (0.004)
	5.10	54.7 (3.5)	1.46 (0.09)	0.238 (0.004)
	10.85	42.7 (3.2)	1.94 (0.14)	0.233 (0.003)

as glidant) was from C. Barcia S.A., Spain, batch 482.

2. Methods

Assays were carried out with HPMCs with moisture content of 2.25%, 5.10% or 10.85%. To obtain the required moisture content, the HPMC was stored in airtight containers containing reservoirs of appropriate mixtures of sulphuric acid and water. That the moisture content obtained was as required was confirmed by drying to constant weight at 105°C (Handbook of Pharmaceutical Excipients, 1994).

Mean yield pressures of the HPMCs of different moisture contents were determined (in triplicate for each sample) in a Korsch EKO eccentric press equiped with flat-faced 9-mm punches and a data acquisition system (Martínez-Pacheco et al., 1985).

A total of six tablet formulations were tested (two HPMC varieties × three HPMC moisture contents); all contained 1% w/w hydrochlorothiazide and 0.5% w/w magnesium stearate. After mixing (Turbula T2C, 30 rpm, 15 min), tablets were prepared in the above-mentioned press (compression pressure 30 MPa). Tablet dimensions were measured with a Carl Mahr digital micrometer (accuracy $\pm$ 0.01 mm). Tensile strength was determined for six tablets of each formulation, as per Fell and Newton (1970), in an Erweka TB-2A apparatus. Dissolution assays were likewise carried out for six tablets of each formulation, in a Turu-Grau apparatus meeting USP 23 Method II (paddle) specifications, with 900 ml of 0.1 N HCl as dissolution medium and with stirring at 150 rev./min. Drug content in the dissolution medium at different times after the start of the assay (see Fig. 1) was determined by direct spectrophotometry at 272 nm, with sample dilution in 0.1 N HCl.

3. Results and discussion

The results of the various assays are summarized in Table 1. For both HPMC varieties, moisture content was negatively correlated with the mean yield pressure of the HPMC and positively correlated with the tensile strength of tablets made with that HPMC. The magnitudes of these effects are similar to those reported by Malamataris et al. (1994) and Malamataris and Karidas (1994).

Dissolution profiles for the various tablet formulations are shown in Fig. 1. All profiles were well-fitted by the Higuchi model; this may appear surprising given the poor solubility of hydrochlorothiazide in water (Vázquez et al., 1992), but is in fact as expected given the small amount of drug present in the tablet. Comparison of the mean values of the dissolution rate constant calculated on the Higuchi model (K_H; Table 1) suggests that HPMC moisture content did not affect dissolution rate. Since K_H is an estimated parameter, we used a Kruskal-Wallis test (Siegel and Castellan, 1988) to confirm this hypothesis: the results show that HPMC moisture content had no significant effect (at $\alpha < 0.01$ level) on K_H, either for HMPC K4M ($H = 0.50$, 2 d.f.) or for HPMC K100M ($H = 8.92$, 2 d.f.). It thus seems likely that

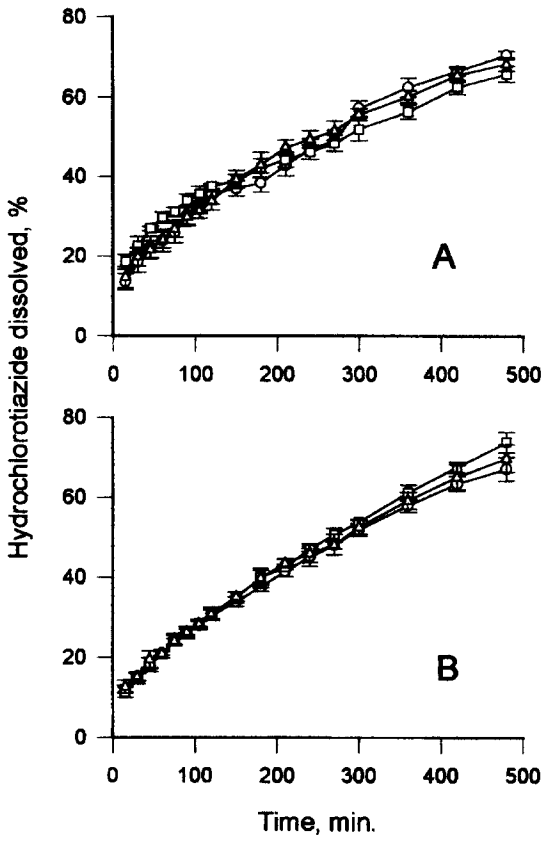

Fig. 1. Cumulative percentage release of hydrochlorothiazide from tablets made with HPMC K4M (A) or HPMC K100 M (B) as base excipient. Moisture content of the HPMC was 2.25% (○), 5.10% (□) or 10.85% (△). Each point is the mean of six determinations.

the individual effects of HPMC moisture content and tablet tensile strength on dissolution rate, if such effects exist, cancel each other out.

In conclusion, the present results indicate that variations in the moisture content of HPMCs, while affecting both the compression behaviour of the HPMC itself and the mechanical properties of tablets made with that HPMC, have no significant effects on the dissolution rate of a poorly hydrosoluble drug like hydrochlorothiazide from tablets made with that HPMC.

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