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COMMUNICATION

Effects of Storage Humidity on the Mechanical, Microstructural, and Drug Release Properties of Hydroxypropylmethylcellulose-Based Hydrophilic Matrix Tablets

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ABSTRACT

The effects of storage humidity on the properties of hydroxypropylmethylcellulose (HPMC)-based hydrophilic matrix tablets were investigated. Hydrochlorothiazide tablets prepared with HPMCs of different thickening capacities were stored for 6 months (a) at a relative humidity corresponding to the prestorage equilibrium moisture content of the HPMCs, or (b) at a higher relative humidity. Only tablets stored at the higher humidity showed significant changes in properties, indicating that the observed changes (reduced crushing strength, increased total porosity, and increased mean pore diameter) were due to water uptake. All changes were completed within 1 month of storage. Drug release properties were unaffected, even after 6 months. Effectively identical results were obtained regardless of whether the HPMC variety used had a nominal viscosity of 4,000 cP or 100,000 cP.

The results reported here were first presented as a poster at the First Spanish–Portuguese Conference on Controlled Drug Delivery (Santiago de Compostela, 1995).

INTRODUCTION

Interactions between standard tablet excipients and water are currently attracting considerable research interest. Recent work in this field has included efforts to identify the mechanisms of excipient–water interactions, evaluations of the usefulness of different models of sorption/desorption, and studies of the effects of water uptake and water loss on the properties of tablets or tablet constituents (1–5).

Hydroxypropylmethylcelluloses (HPMCs) are widely used as the principal excipients in hydrophilic matrix tablets for controlled release (6–8). The effects of HPMC moisture content on compression behavior and on properties of HPMC-based tablets have been investigated for several varieties of this polymer (9–11). In the work reported here, we investigated the effects of storage humidity on the mechanical, microstructural, and drug release properties of hydrophilic matrix tablets made with one of two HPMC varieties with different nominal viscosities (4,000 and 100,000 cP). The model drug used was hydrochlorothiazide.

MATERIALS AND METHODS

Excipients and Drug

Methocel K4M (premium quality; batch 88780708; nominal viscosity of a 2% solution at 20°C = 4,000 cP) and Methocel K100M (premium quality; batch 057556-989; nominal viscosity of a 2% solution at 20°C = 100,000 cP) were from Dow Chemical. Initial moisture content of both HPMCs was 5% w/w (as determined by weight loss after drying to constant weight at 105°C (12) in a Shimadzu Libror EB-250 thermobalance). Magnesium stearate BP was from C. Barcia (Spain; batch 482). Hydrochlorothiazide was from J. Escuder (Spain; batch 014).

Preparation of Tablets

Mixtures were made up with HPMC (K4M or K100M) containing 12.5% w/w hydrochlorothiazide (mixed in a Turbula T2C, 30 rpm, 15 min) and 0.5% w/w magnesium stearate (Turbula T2C, 30 rpm, 5 min). Tablets were prepared by direct compression (30 cycles per min; maximum compression pressure 120 MPa) in a Korsch EKO eccentric press fitted with a pressure transducer (13) and flat-headed punches (diameter 9 mm). Tablet weight was in all cases adjusted to 200 mg.

Storage Experiments

Tablets of the two formulations were stored (for 1, 3, or 6 months) at 20°C in air-tight boxes containing reservoirs of sulfuric acid at the dilution required to maintain relative humidity such that the equilibrium moisture content of the HPMC was 5% or 8% (14). Since the initial moisture content of the HPMCs was 5%, this experimental design permits discrimination between alterations in tablet properties due to water uptake and alterations due to other causes.

Characterization of Tablets

Tablets of the two HPMC varieties subjected to each treatment (3 storage durations × 2 storage humidities, plus prestorage controls) were characterized as follows.

a. Weight (10 tablets per treatment/variety, weighed together).
b. Diameter and thickness (and thus volume) (n = 10 tablets), determined with a Carl Mahr digital micrometer (accuracy ± 0.01 mm). Note that weight, diameter, and thickness, unliked the remanaining properties, are determined by nondestructive tests and were thus determined for the same tablets throughout the assay period.
c. Crushing strength (n = 6 tablets), determined in an Erweka TB 2A apparatus.
d. Microporous structure (n = 3 tablets), evaluated by mercury intrusion porosimetry in a Micromeritics Pore Sizer 9305 under pressure over the range 0.6–20,000 psi. This method allows estimation of total porosity (% v/v) and mean pore diameter (16).
e. Dissolution rate (n = 6 tablets), estimated in a Turu Grau apparatus by USP 23 method II (paddle method). Tablets were placed in wire baskets to prevent floating (13). The dissolution medium was 900 ml of 0.1 N HCl, and stirring was at 150 rpm. Hydrochlorothiazide concentrations in the medium were determined every 15 min over the first 2 hr, every 30 min over the subsequent 3 hr, and then every hour up to 8 hr. Determination was by direct spectrophotometry (Shimadzu PR1) at 272 nm, in 0.1 N HCl. The dissolution profile was characterized as 0- to 8-hr dissolution efficiency (17).

Statistical Analyses

For each HPMC variety, each storage humidity, and each tablet parameter (except weight and volume), the

effect of storage duration on that parameter was investigated by one-way analysis of variance. Where a significant effect was detected, pairwise comparisons were performed by the least significant differences (LSD) test (18).

RESULTS AND DISCUSSION

In general, the changes over time undergone by K4M (Fig. 1) were very similar to those undergone by K100M (Fig. 2). Furthermore, and for both HPMCs, analyses of variance indicated that storage at the lower relative humidity had no significant effect on any of the tablet parameters (results not shown); by contrast, storage at the higher humidity led to significant reductions in crushing strength and significant increases in total porosity and mean pore diameter (Table 1). This indicates that the observed effects were due to uptake of water from air. In what follows we restrict our discussion to the results obtained after storage at the higher humidity.

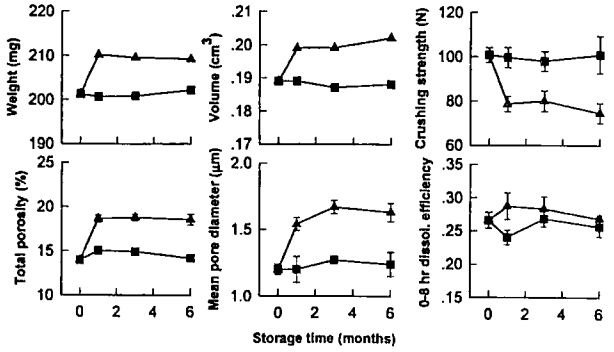

Figure 1. Changes occurring over 6 months of storage in various properties of K4M-based hydrochlorothiazide tablets. Storage was at a relative humidity corresponding to HPMC equilibrium moisture contents of 5% (■) or 8% (▲). Vertical bars show standard deviations (except for weight and volume).

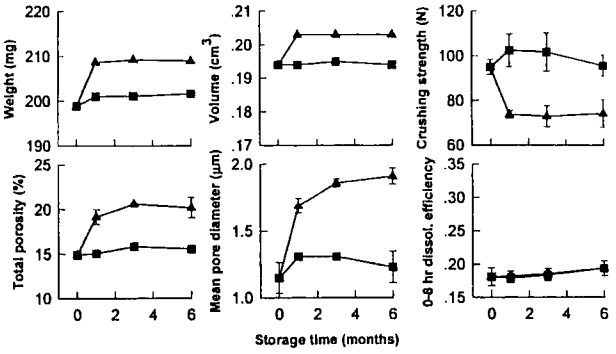

Figure 2. Changes occurring over 6 months of storage in various properties of K100M-based hydrochlorothiazide tablets. Storage was at a relative humidity corresponding to HPMC equilibrium moisture contents of 5% (■) or 8% (▲). Vertical bars show standard deviations (except for weight and volume).

As is apparent from Figs. 1 and 2, most changes occurred within 1 month of storage. This is supported by the results of analysis of variance and subsequent LSD testing (Table 1): only in one case (mean pore

Table 1

Results of Analyses of Variance and Subsequent Least Significant Difference (LSD) Tests to Investigate the Effects of Storage (at a Relative Humidity Corresponding to a HPMC Equilibrium Moisture Content of 8%) on Various Properties of Tablets Made with K4M or K100M

Parameter	*F*	*df*	α	LSD Tests Results
K4M				
Crushing strength (N)	51.05	3 and 20	<0.01	6 1 3 0
Total porosity (%)	95.93	3 and 8	<0.01	0 6 1 3
Mean pore diameter (μm)	45.55	3 and 8	<0.01	0 1 6 3
0- to 8-hr dissolution efficiency	2.87	3 and 20	NS	
K100M				
Crushing strength (N)	36.65	3 and 20	<0.01	3 1 6 0
Total porosity (%)	40.04	3 and 8	<0.01	0 1 6 3
Mean pore diameter (μm)	70.89	3 and 8	<0.01	0 1 3 6
0- to 8-hr dissolution efficiency	2.03	3 and 20	NS	

Note. NS = not significant at 0.05 level. In the LSD test results column, means for groups (i.e., storage times) underlined with the same line do not differ significantly at the 0.05 level.

diameter, K100M) was there a significant change after the first month.

Hydrochlorothiazide release kinetics (characterized as 0- to 8-hr dissolution efficiency) were in no case significantly affected by storage. This is in accordance with previous results which have shown that drug release from tablets of this type is unaffected by the initial moisture content of the HPMC used (11).

The observed increases in tablet weight (about 5% for both K4M tablets and K100M tablets) indicate that the moisture content of stored tablets was about 10%, slightly higher than the equilibrium moisture content for the HPMC alone. This is probably attributable to capillary condensation of water vapor in the micropores of the matrix. In addition, tablet volume increased with storage, presumably because of swelling of the HPMCs. It thus seems reasonable to suppose that absorbed water initially locates in interparticle spaces (where it breaks hydrogen bonds between adjacent HPMC particles) and subsequently diffuses into particles, leading to swelling (19). This hypothesis would explain the observed reductions in crushing strength, together with the observed increases in total porosity and mean pore diameter.

In conclusion, the results of the present study indicate that storage of HPMC-based tablets for 6 months at 20°C has no significant effect on mechanical and microstructural properties unless storage humidity is such that the tablets absorb water. Absorption of water has significant effects on mechanical and microstructural properties within a month, though drug release properties are not affected.

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