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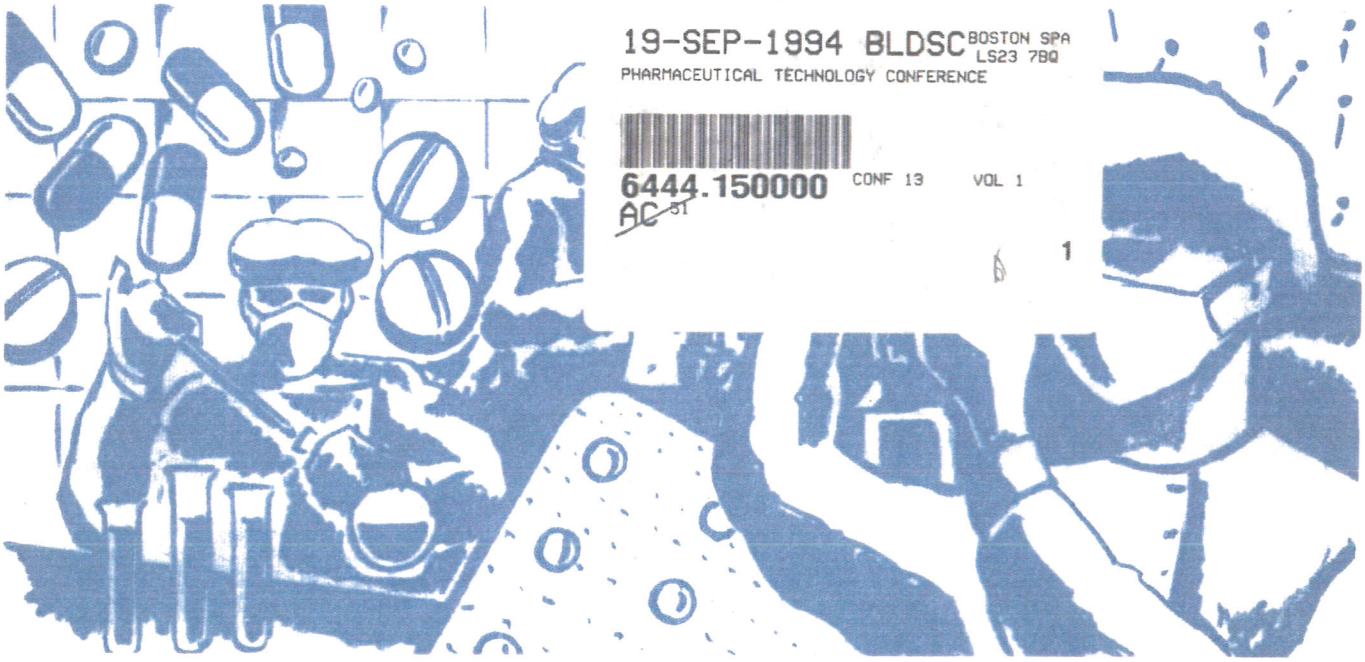

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A CHARACTERIZATION OF THREE HPMC SUBSTITUTION GRADES: RHEOLOGICAL PROPERTIES AND DISSOLUTION BEHAVIOUR

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INTRODUCTION

Hydroxypropylmethylcelluloses (HPMC) represent a wide family of polymers: each of the three subtitution types described in the US Pharmacopeia (2906, 2910 and 2208) is available in a wide variety of molecular weights and under different trademarks.

The extensive and successful use of these polymers in pharmaceutical formulation justifies the efforts still recently made to thoroughly characterize them. Both the choice of the most suitable grade and the assessment of brand to brand variability and lot to lot reproducibility, require in fact the knowledge of the functionally relevant properties of the polymer. In particular, in hydrophilic matrix formulation, the influence of either the substitution type or the viscosity grade of the polymer on the physical properties of the gel layer that is formed around the matrix is worth investigation (1,2).

Alderman described marked differences in drug release control between the three USP grades of HPMC. In his findings, the 2906 grade (Methocel® F) gave the fastest release, followed by the 2910 grade (Methocel® E) while the 2208 grade (Methocel® K) produced the slowest release. These differences were explained by considering the differing proportions of the hydrophobic methoxyl groups and of the hydrophilic hydroxypropyl groups that characterize the three polymer grades. The rate of polymer hydration was pointed out as a critical property towards controlled drug release (3).

More recently, a few studies dealt with the characterization of the three grades of HPMC, with various results. V.S. Georgiannis et al. (4) compared for example the three grades of HPMC in the formulation of floating matrices. The behaviour observed agreed with the assumption of a K>E>F rank order of hydration rates. On the contrary, Mitchell et al. found that the three grades of HPMC performed similarly in hydrophilic matrices containing propranolol hydrochloride. They studied the

influence of substitution type of HPMC by using several techniques. Only cloud point determination was able to differentiate between the three grades, while no evidence of differences could be found when hydration rates were directly measured (2, 5).

Besides the rate of hydration or gelation, other polymer properties have been considered in the literature as possibly relevant to drug release control. Among these are, for example, the viscosity and the gel strength of the matrix outer gel layer. It sounds conceivable that, as already suggested by Alderman (3), the viscosity and gel strength of the outer layer affect its resistance to dilution and erosion; the effect on drug release will depend, of course, whether erosion is a limiting step or not. The relationship between gel strength and erosion has been recently studied by Mitchell et al. They used a penetrometer to investigate differences in gel strength between the three substitution grades of HPMC, which resulted to behave very similarly (2).

Another approach to the characterization of the gelified HPMC is based on rheological measurements. Previous studies have pointed out that the simple quotation of the viscosity grade of the polymer (which is expressed by the viscosity of a 1% or 2% polymer solution) does not provide a sufficient description of its rheological properties (6). Rheological characterization should be able to describe the interactions that take place between polymer chains in the gel network and that are, in turn, responsible for disentanglement and erosion processes. In order to better characterize these interactions, in a recent study viscoelasticity analysis was used. The NaCMC behaviour was investigated and a close relationship was found between a series of viscoelastic parameters and sensitivity to erosion of the polymer. In particular, it was found that an increase in resistance of the polymer to dilution (from hydrated gel-like solutions) and to erosion (from matrices) was accompanied by an increase in creep viscosity and oscillation parameters (storage modulus G' and loss modulus G") of the polymer gels (7).

Aim of the present work was therefore to assess whether this kind of rheological analysis allow to reveal differences between three substitution grades of the same viscosity grade of HPMC. Creep and oscillatory tests were performed on 5% and 7% (w/w) polymer solutions. Erosion rate was moreover evaluated from tablets, and the dissolution rate from already hydrated polymers (dilution) was measured on 5% w/w samples.

In order to assess to what degree the observed differences between the three polymers affected drug release, matrices containing 60% of polymer and either a very soluble drug (diprophylline) or an insoluble one (acetazolamide) were

prepared and tested for drug release. For matrix preparation, the same granulometric fraction of the three HPMC grades was used.

EXPERIMENTAL

MATERIALS

Three grades of HPMC were tested: Methocel® K4M, Methocel® E4M and Methocel® F4M (Colorcon Ltd, Orpington, UK). As model drugs diprophylline (Proter, Milan, I) and acetazolamide (Sigma Chimica, Milan, I) were used. Lactose was USP XXII grade.

METHODS

Cloud point measurement

Cloud point measurements were carried out according to Mitchell et al (8) on 2% w/v solutions in distilled water. Trasmittance % was read at 800 nm by means of a Spectracomp spectrophotometer (Advanced Products, Milan, I).

Rheological studies

Polymer solutions at 5% w/w and 7% w/w were prepared in distilled water, taking into account the content in water of the polymers. The samples were stored overnight in refrigerator to allow complete hydration and were analysed within 24 h from the preparation. Rheological analysis was performed with a Bohlin CS Rheometer (Bohlin Reologi, W. Pabish, Milan, I) equipped with a cone and plate system (CP 4/20). All measurements were conducted at 37 ± 2 °C. Dynamic (oscillatory) tests, at frequencies ranging between 0.1 and 4.0 Hz, and constant stress (creep) tests were carried out in the linear viscoelastic response range. From creep curves residual viscosity was calculated; from oscillation tests G' (storage modulus) and G" (loss modulus) were obtained and tg∂ (G"/G') was calculated.

Erosion studies

Erosion studies were performed by measuring the amount of HPMC dissolved both from gel-like solutions (dilution) and from tablets. All the tests were performed at 37°C.

The same 5% w/w solutions characterized for their rheological behaviour were centrifuged to remove entrapped air bubbles, and poured into cylindrical holders

(41 mm diameter and 12 mm height). These holders were placed in USP XXII vessels containing 500 ml desaerated water; paddle apparatus (at 2.5 cm above the samples) was used at 25 rpm.

300 mg tablets of sieved fractions (105-180 μm) of HPMC were prepared by means of a hydraulic press for KBr discs (Perkin Elmer) equipped with a manometer, at 5 tons for 1 minute; a flat punch of 13 mm diameter was used. The tablets were glued at the bottom of rotating discs. 500 ml of desaerated water in USP XXII vessels were used; rotation speed was 100 rpm. Both in the case of erosion and of dilution tests, 5 ml samples were withdrawn at defined times and replaced with fresh medium. All samples were filtered before analysis. The amount of dissolved polymer was quantified by means of the anthrone method (9).

Anthrone method

The reagent was prepared by dissolving 50 mg of anthrone in a mixture of 28 ml water and 72 ml concentrated sulphuric acid. A mixture of 0.5 ml of sample and 2.5 ml of reagent was heated 15 minutes in boiling water, refrigerated and spectrophotometrically read at 625 nm. Four standard solutions ranging from 0.1 and 0.4 mg/ml were analysed together the samples and used to calculate a calibration line.

Drug release studies

Matrices (200 mg total weight) containing either diprophylline or acetazolamide were prepared by direct compression using an hydraulic press at 3 tons for 1 min, with a 10 mm convex punch. Sieved fractions (105-180 μm) of HPMC were used. The matrices contained 60% of polymer and either 40% of acetazolamide or 30% of diprophylline (10% of USP XXII lactose was used in this case as diluent).

The release profiles were obtained in USP XXII basket apparatus at 100 rpm, in desaerated water (1000 ml for diprophylline; 500 ml for acetazolamide). Automatic sampling was performed and absorbance was spectrophotometrically read at 273 nm for diprophylline and at 265 nm for acetazolamide (Spectracomp spectrophotometer; Advanced Products, Milan, I).

RESULTS

The values of cloud point measured for the three polymers (70 °C for HPMC K4M, 57 °C for F4M and 54 °C for E4M) resulted in good agreement with those obtained

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