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Influence of ethanol on aspirin release from hypromellose matrices

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Abstract

Release profiles of aspirin from hypromellose matrices in hydro-ethanolic media were studied. Percent aspirin released increased with increasing levels of ethanol in the dissolution media, correlating with the drug's solubility, however, dose dumping of aspirin did not occur. An initial rapid release was observed in media comprising 40% ethanol. Release in these conditions was considered to be both erosion and diffusion-mediated, in contrast to the release in 0, 10, 20 and 30% ethanol media, where erosion-controlled release dominated. Image analysis of matrix swelling indicated a slower initial interaction between ethanol and hypromellose accounting for the initial rapid release. Cloud point studies suggested that ethanol retarded hydration of the polymer.

Keywords: Hypromellose; Hydro-ethanolic media; Controlled release; Aspirin; Matrices

1. Introduction

The potential impact of concomitant alcohol consumption on the *in vivo release* of drugs from modified release oral dosage forms is currently evincing interest. This is a consequence of the finding that co-consumption of significant quantities of alcoholic beverage can result in potentially serious dose dumping of the opioid analgesic hydromorphone from a controlled release capsule dosage form (FDA Alert, July 2005). As studies in human volunteers involving co-administration of drug and significant amounts of alcohol pose ethical and operational challenges it is appropriate to consider in vitro studies to provide insight on release mechanisms in hydro-alcoholic media, thereby guiding formulation programs assessing the potential for alcohol-related dose dumping.

The cellulose ether hypromellose, also known as hydroxypropylmethylcellulose or HPMC, is widely used to form swellable hydrophilic matrices that retard drug release to prolong therapeutic effect (Li et al., 2005). Release from such a matrix is mediated by a combination of polymer hydration, diffusion of drug through the gel layer, which forms as a result of polymer transition from a "glassy" to a "rubbery" state upon hydration, drug dissolution and polymer erosion (Nerukar et al., 2005).

The aim of this investigation was to assess the influence of alcohol on the rate and mechanisms of release of aspirin from hypromellose hydrophilic matrices.

2. Materials and methods

2.1. Materials

Hypromellose (Methocel® K4M, Dow Chemical Co., USA) was a gift from Colorcon Ltd., UK. Aspirin (acetyl salicylic acid, Sigma–Aldrich, UK), sodium acetate anhydrous (Fluka, UK) and glacial acetic acid (BDH Chemicals Ltd., UK) were all used as received. Absolute ethanol was standard reagent grade. Deionised water was produced with a reverse osmosis unit (Select analyst HP, Purite Ltd., UK).

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2.2. Formulation and tablet compaction

Tablets comprising 139.5 mg hypromellose, 139.5 mg aspirin and 1 mg magnesium stearate (hypromellose–aspirin matrices) or 279 mg hypromellose and 1 mg magnesium stearate (hypromellose tablets) were prepared by direct compression on a Manesty F3 single punch tablet press fitted with 8.95 mm diameter, flat punches. Tablets were produced to crushing strengths in the range of 5.5–6 kP (Dr. Schleuniger, 6D tablet tester).

2.3. Dissolution testing

Drug release was monitored using a British Pharmacopoeia (2005) Apparatus 1 (8ST, Caleva Ltd., UK) with rotation speed of 50 rpm, in 500 ml of medium at 37 °C. Media comprised acetate buffer (B.P.) with 0, 10, 20, 30 or 40% (v/v) ethanol. For each medium, six tablets were tested and drug release was monitored spectrophotometrically at 265 nm (Genesys 6, Thermo Electron Corporation, USA).

2.4. Data analysis

Drug release data were analysed using a modified power law equation (Eq. (1)) proposed by Ford et al. (1991).

$$M = k(t - l)^n \quad (1)$$

where M is the percentage of drug release at time t, k a constant incorporating structural and geometric properties of the devices, l the lag time and n is the release exponent, indicative of the drug release mechanism.

2.5. Drug solubility

The solubility of the drug in the different hydro-ethanolic dissolution media was determined spectrophotometrically (265 nm) at ambient temperature, using a solution of known concentration of aspirin in the different media as a standard. To determine the solubility, a saturated solution was prepared by adding an excess of drug to 5 ml of media. This solution was then shaken for 2 h (preliminary tests indicated that 2 h was sufficient time to reach saturation) and a small amount (~1.5 ml) was centrifuged (Z160M, Hermle Laborthechnik, Germany) at 14,000 m^{-1} for 20 s. 0.5 ml of the supernatant was diluted until an absorbance value similar to that of the standard was obtained.

2.6. Compact swelling

The dynamics of the swelling process were investigated using a digital camera (Pixera 120es) and associated image analysis software (Image ProPlus®). Each compact (either hypromellose–aspirin matrix or hypromellose tablet) was placed vertically in a small plastic petri dish, and 10 ml of medium was added at ambient temperature. The petri dish was placed in a plane with a light source (tungsten lamp), and the camera, equipped with macro lens was placed above. The light beam direction was regulated to generate a high contrast image, with the tablet completely black in a bright background. The analysis was performed using the 0 and 40% ethanol media. Images were obtained at 0, 5, 10, 15, 20, 25, 35, 45, 60, 75, 90, 105 and 120 min. Each image was calibrated using a graduated ruler under the same conditions.

2.7. Viscosity

Viscosity measurements were performed on 2% (w/v) hypromellose gels in the different dissolution media. The gels were prepared with 150 ml of each dissolution media and 3 g of hypromellose. Initially, in a pre-weighed beaker, 80 ml of aqueous buffered solution (comprising sufficient buffer salts for 150 ml of media) was heated to 80 °C. Three grams of hypromellose was then added under stirring, until a uniform dispersion was obtained. At this point the heater was switched off, and the beaker was left stirring for 30 min. In this period a viscous gel was obtained and the additional liquid with the requisite amount of ethanol for each medium was added with continuous stirring. The dispersions were left to stir for 1 h and were then stored in a refrigerator (6 °C) for 48 h. Prior to testing, gels were allowed to stand for 1 h at ambient temperature. Additionally, the gels were weighed to determine whether losses due to ethanol evaporation had occurred. The effect of such evaporation resulted

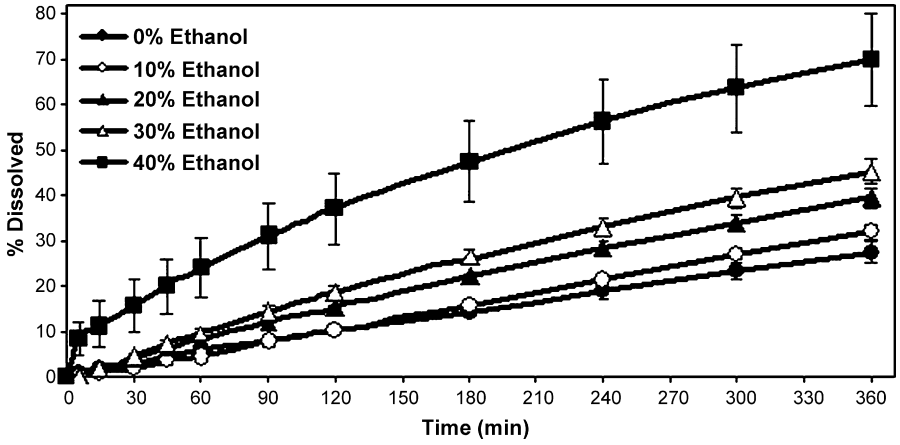

Fig. 1. The effect of ethanol concentration on the release of aspirin from hypromellose matrices in various hydro-ethanolic media ($n = 6 \pm$ S.D. for each data set).