INFLUENCE OF pH ON THE DISSOLUTION OF PROMETHAZINE HYDROCHLORIDE FROM HYDROXYPROPYLMETHYLCELLULOSE CONTROLLED RELEASE TABLETS

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Although hydroxypropylmethylcelluloses (HPMC) have been used as hydrophilic matrices to provide controlled-release of freely water soluble drugs, little attention has been given to the performance of these tablets when subjected to changes in pH. Alderman (1984)has stated that HPMC provided a matrix component which is essentially pH independent. Additionally, Ventouras & Buri (1978) included succinic and other acids within the matrix to produce faster drug release at pH 7.5 for a variety of drugs including quinidine. This report examines the influence of pH on the release of promethazine hydrochloride (P.HCl) from HPMC matrices.

Tablets (¼" flat faced) were compressed at 1395MNm^{-2} by direct compression to contain 25mg P.HCl (250-500μm) and 25mg HPMC (viscosity grades K100, K4M, K15M or K100M supplied by Dow Chemicals, U.S.A.) or 120mg HPMC K100M and 0.75% magnesium stearate. Dissolution was studied using a Copley Series 8000 Dissolution Tester into 1 litre buffer, at 37°C using the USP Method 1 at 100rpm, monitoring P.HCl at 250nm. Buffers were used at pH1 (HCl:KCl), pH3 (HCl:glycine), pH5 (NaOH:succinic acid) pH7 (NaOH:KH_2PO_4) and pH9 (NaOH: glycine).

Table 1. Influence of pH on the dissolution rate of promethazine hydrochloride from HPMC matrix tablets

HPMC Grade:	HPMC tablet wt. (mg)	Release rates (%min$^{-½}$)* pH1	pH3	pH5	pH7	pH9
K100	25	10.92	15.88	11.89	10.81	7.70
K4 M	25	7.25	6.75	6.92	4.91	4.64
K15M	25	6.44	8.74	6.74	5.47	2.84
K100M	25	6.87	8.18	7.33	4.74	3.78
K100M	120	4.62	4.52	3.81	2.41	1.19

*mean of 3 determinations.

The dissolution profiles, plotted on a $\sqrt{\text{time}}$ axis were essentially linear although initial non-linear regions were encountered, especially into pH1 and pH9. The linear portions were used to derive the data in Table 1. Tablets containing K100 gave consistantly higher rates than the other three grades, but generally rates into pH1 or pH3 were highest, independent of the HPMC grade, with a gradual decrease in rates above pH3. The data does not therefore substantiate entirely claims that drug release from HPMC matrices is independent of pH. However, the low rates at pH9 were due in part to a predicted decrease in solubility of P.HCl at around its pKa of 9.1 (Green 1967) and to micelle formation (Stevens et al 1973) since the level of dissolved P.HCl decreased following initial release at pH9.

The data in Table 1 cannot be divorced entirely from any effects of ionic strength of the dissolution media which were not studied. However it suggests that although pH may modify the release of drug substances from HPMC matrices by an effect on the matrix itself, the major changes in drug release are a property of the drug: carrier ratio (for instance compare 25 and 120mg HPMC K100M in Table 1) and the chemical nature of the drug itself. Changes in the viscosity grade of HPMC from K4M to K100M did not appear to modify the response of the matrix to Ph changes.

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