DISSOLUTION OF A POORLY WATER SOLUBLE DRUG, INDOMETHACIN, FROM HYDROXYPROPYLMETHYLCELLULOSE CONTROLLED RELEASE TABLETS

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Hydroxypropylmethylcellulose (HPMC) has been used as the matrix to provide controlled release of freely soluble drugs when drug release follows Higuchi-type kinetics (Salomon et al 1979a). However there are conflicting reports as to the effect of HPMC molecular weight on dissolution rates. Salomon et al (1979b) found that the release rate of potassium chloride was independent of HPMC molecular weight, whereas Harwood and Schwartz (1982) showed that pilocarpine release decreased as the molecular weight increased. Using indomethacin (I) we have examined the influence of HPMC molecular weight, indomethacin:HPMC variation and indomethacin particle size on drug release.

Tablets (¼", flat faced) containing 25mg I (90-125μm), HPMC (Grade K100, K4M, K15M or K100M supplied by Dow Chemicals, U.S.A.) and 0.75% magnesium stearate were prepared by direct compression at 1395MNm^{-2}. Additionally 63-90 and 125-180μm I was used. Dissolution was studied using a Copley Series 8000 dissolution tester into 1 litre water at 37°C using the U.S.P. method 1 at 100rpm, monitoring I at 266nm.

The dissolution profiles when plotted as $\sqrt{time}$ were sigmoidal and a central linear portion (used to determine release rates) followed an intial non-linear region of 2-4 hrs duration, due probably in part to poor wetting of the drug. The release rates from HPMC K100 tablets were independent of the I:HPMC ratio, but for the other grades the rates decreased as the HPMC content increased. At constant I:HPMC ratios the rates decreased as the molecular weight of HPMC increased.

The effect of HPMC grade, I:HPMC ratio and I particle size on dissolution rates (% min$^{-½}$) from tablets containing HPMC

Tablet content of HPMC (mg)	Dissolution Rates*					
	K100	K4M	K15M	K100M	K15M(a)	K15M(b)
25.8	2.42	2.34	2.32	-	-	-
36	2.71	2.25	1.74	1.15	2.02	1.19
61.5	2.87	1.91	1.44	0.92	-	-
200	1.65	1.47	1.21	0.84	2.00	0.84

Key: All release rates to refer to 90-125μm I except a = 63-90 and b = 125-180μm I. *=mean of 3 determinations.

At constant I:HPMC ratio the dissolution rates decreased as the particle size increased. This contrasts with results found previously for freely water soluble drugs (Ford et al 1985) when particle size only affected release rates at low HPMC levels and when rates increased with large size fractions of drugs.

The results confirm that for a poorly water-soluble drug, not only is the drug:HPMC ratio important in controlling release but both the viscosity grade of HPMC and particle size of the drug have far greater contributions than have been recognised for more water soluble drugs. This may be attributed to erosion of the HPMC matrix which is probably the only mechanism by which poorly soluble drugs are released from HPMC matrices.

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