GAMMA SCINTIGRAPHIC EVALUATION AND SIMULTANEOUS PLASMA ANALYSIS OF RAPID RELEASE KETOPROFEN SEMI-SOLID MATRIX CAPSULES

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The benefits of filling liquids or semi-solids into hard gelatin capsules is now well recognised. These include improved stability, sustained drug release, dust control, dose uniformity and simple processing of solid dispersions (Cole 1989). The latter can be used to achieve rapid drug release and potentially enhance bio-availability. The in-vitro and in-vivo behaviour of a liquid filled vehicle (Gelucire 44/14, Gattefosse), which has been reported to promote faster drug absorption than equivalent PEG 1000 capsules in dogs (Serajuddin et al 1988), has been investigated.

Capsules containing 17%w/w ketoprofen in fused Gelucire 44/14 (a mixture of hydrogenated fatty acid esters with mp. 44°C and HLB value of 14) were filled at 60°C, forming a semi-solid matrix (SSM) on cooling. In-vitro dissolution comparisons were made between the ketoprofen SSM dispersion and powder ketoprofen capsules (Orudis, May & Baker). Dissolution was performed using a BP basket apparatus at 100rpm using 0.01N HCl. In-vivo studies were performed on 6 healthy, informed, male volunteers aged 21-35yrs. Each subject was administered after a light breakfast, one 100mg SSM ketoprofen capsule, containing 0.5% amberlite resin labelled with 3MBq of 99mTc. The stomach was outlined by administering 1MBq of In-DTPA complex dissolved in 200ml of water. Gastric spreading and emptying was followed by gamma scintigraphy, corrected for background interference and decay. Blood samples were withdrawn simultaneously at regular intervals over 8hr and plasma ketoprofen analysis performed by an HPLC method (Upton et al. 1980).

Dissolution results showed very rapid release of ketoprofen from the SSM (T90% < 10 min), faster than Orudis capsules (T60% >30 min). This is achieved by a combination of improved wetability, the molecularly dispersed nature of drug and the favourable co-solvent effect of the vehicle. In-vivo pharmacokinetic properties of the SSM show comparable tmax, Cmax and AUC results to published data for Orudis capsules (Houghton et al 1984). Plasma drug concentration data and scintigraphic measurements (Table 1) indicated that the time for the SSM to disperse correlated with gastric half emptying time ($r=0.989$, $p<0.01$) and tmax ($r=0.975$, $p<0.01$). This suggests a process of capsule dispersion in the stomach, followed by emptying into the small intestine from where drug is rapidly absorbed. In one case (I) time to peak plasma conc. was short (20min), this was related to additional water intake causing rapid matrix dispersion. In a second volunteer (VI), where administration of the capsule after breakfast was delayed, tmax was slow (180min), corresponding to slow gastric dispersion and emptying. This can be explained by an empty stomach in which only mucus is available for SSM spreading.

Gelucire 44/14 can therefore achieve enhanced in-vitro dissolution rates but in-vivo behaviour may be modified by the rate and extent of gastric dispersion, related to fluid or food intake.

Table 1.

IN-VIVO PARAMETERS	I	II	III	IV	V	VI	MEAN (STD.DEV)
Tmax. gastric dispersion (min)	10	20	20	20	30	80	30.0 (25.3)
Max. gastric dispersion (%)	41	37	70	91	45	28	52.0 (23.7)
Gastric half emptying time (min)	13	36	44	50	85	188	69.3 (62.6)
tmax (min)	20	30	50	50	40	180	61.7 (59.1)
Cmax (ug/mL)	15.4	14.5	6.8	9.7	9.2	6.5	10.4 (3.8)
AUC (ug/mL hr)	22.1	24.9	22.6	24.1	22.3	26.3	23.7 (1.7)

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