BIOAVAILABILITY OF X-RAY AMORPHOUS AND SEMI-CRYSTALLINE FRUSEMIDE - PVP SOLID DISPERSIONS

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Solid dispersion systems can offer improved drug solubility and in-vitro dissolution by a supersaturation solution phenomenon in X-ray amorphous drug region (Doherty and York, 1986). However, while these effects are readily demonstrated in-vitro, only a few reports examine in-vivo effects in humans (Corrigan et al, 1976). This work tests the clinical significance of reductions in drug crystallinity (Doherty et al, 1985) in a frusemide-PVP (K-25) model solid dispersion system. To achieve these aims, an X-ray amorphous dispersion (40% w/w drug Formulation A)and semi-crystalline dispersion (60% w/w drug, Formulation B) produced by the solvent method (Doherty and York, 1986) were compared to crystalline frusemide (Formulation C)and an oral frusemide solution (Formulation D).

The trial protocol, approved by the University sub-committee on ethics and safety, involved seven healthy male caucasians, aged between 23-40 years (mean 26.6 years) and weighing between 65-85kg (means 71.4kg). Each was given 20mg oral solution (Lasix, Hoechst) or a white opaque capsule containing 20mg frusemide, or equivalent, of each formulation on a single blind basis. Food and fluid intake were controlled.

Each formulation was taken with 200ml water, all urine collected for half an hour preceeding administration, half hourly for three hours then hourly up to 8 hours and analysed for sodium and potassium using a high precision flame photometer (Instrument Lab IL943). Frusemide, a loop diuretic, acts on the ascending loop of Henle preventing the reabsorption of sodium ions leading to a diuresis. Many workers report a linear relationship between sodium ion excretion rate and frusemide urinary excretion rate (e.g. Cutler and Blair, 1979). In the present study sodium excretion rate was used to measure frusemide effect and relate to its absorption.

The average excretion data (Table 1) show that the bioavailability of all the formulations do not differ significantly indicating the extents of absorption are equal, and equivalent to an oral solution.

Table 1. Average sodium and potassium excretion data (± standard deviation) and calculated A.U.C. data by triangulation method.

Formulation	Cum. Urine Volume (mls)	Cum. Na^+ excretion (m.mol)	Cum. K^+ excretion (m.mol)	A.U.C.	T(max) (mins)	% Bioavailability to oral solution
A	1871 ± 584	128.6 ± 19.8	58.1 ± 10.3	5564 ± 772.0	67.0 ± 22.4	95.6
B	1463 ± 591	113.9 ± 52.1	51.03 ± 18.1	5080 ± 2442	94.3 ± 29.4	87.3
C	1842 ± 725	136.6 ± 64.6	50.6 ± 20.1	5977 ± 2650	90.43 ± 26.4	102.7
D	1581 ± 310	126.4 ± 33.0	54.5 ± 17.1	5818 ± 1596	53.67 ± 16.13	-

However, the times for maximum effect (Tmax) reveal that the amorphous dispersion was absorbed significantly faster ($p<0.05$) than either the semi-crystalline or crystalline formulations. This is consistent with a supersasturated solution enhancement mechanism as crystalline frusemide has a very low solubility in acidic or gastric conditions. In addition, the variability in absorption from an amorphous dispersion was significantly better ($p<0.025$) than from the other solid preparations.

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