THE EFFECT OF LUBRICANT TYPE AND CONCENTRATION ON THE BIOAVAILABILITY OF FRUSEMIDE FROM 40MG TABLETS

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The effect of changing the concentration and type of lubricant on the bioavailability of frusemide from 40mg tablets has been measured. Four tablet batches of frusemide 40mg were prepared. Each batch contained one of the following lubricants: magnesium stearate 2%W/w, magnesium stearate 0.5%W/w, glyceryl tris 12-hydroxy stearate (Thixcin R) 1%W/w or sodium ricinoleate 1%W/w. Tablet dissolution rates were measured in the B.P. apparatus using distilled water as the dissolution medium and bioavailability studies were carried out in 4 healthy volunteers aged 18-30 years on a double blind basis. Urine was collected at fixed time intervals over a period of 24 hours and analysed by the method of Rubinstein & Price (1977). Using the methods of Oser & others (1945) and Niebergall & others (1975) the bioavailability of each tablet formulation was determined with reference to an oral frusemide solution. The in-vivo and in-vitro results are summarised in Table 1.

Table 1. In-vitro and in-vivo data

	Lubricant			
	Magnesium Stearate 2%W/w	Magnesium Stearate 0.5%W/w	Thixcin R 1%W/w	Sodium Ricinoleate 1%W/w
Disintegration time (min)	0.73	0.85	0.89	1.09
Hardness SCU	13.32	12.78	8.31	11.2
Dissolution rate $T_{50\%}$ min	2.65	2.05	1.55	1.85
Mean bioavailability %				
Oser & others	91.37	74.09	62.99	87.63
Niebergall & others	90.89	73.18	59.20	88.31

The disintegration times of all the batches were found to be very good; all the tablets disintegrated in under $1\frac{1}{2}$ minutes. Similarly the dissolution $T_{50\%}$ values were all less than 3 minutes. It would therefore be expected that all the tablets would have correspondingly similar bioavailabilities. This was found not to be the case. There were very significant bioavailability differences between the batches and this was confirmed by a two way analysis of variance. Surprisingly tablets containing 2%W/w magnesium stearate rendered the drug 25% more bioavailable than the formulation containing 0.5% W/w magnesium stearate. A possible explanation is that with 2% magnesium stearate particle slippage can occur more easily during compression to produce a harder and denser tablet. This harder tablet will then disintegrate more efficiently. Tablets containing only 0.5%W/w magnesium stearate were found to be not as hard and therefore are less likely to deaggregate as effectively. The formulation containing the water soluble lubricant sodium ricinoleate rendered the drug as equally bioavailable as 2%W/w magnesium stearate, whilst Thixcin R was the poorest of the four; producing a bioavailability reduction of 30% from that of 2%W/w magnesium stearate.

The results indicate that the choice and concentration of lubricant can significantly affect the bioavailability of frusemide from tablet formulations. These bioavailability differences cannot be detected by simple in-vitro dissolution rate measurements. 2%W/w magnesium stearate rendered frusemide very much more bioavailable than 0.5%W/w, the opposite to what might be expected.

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