DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 6(2), 105-119 (1980)

THE EFFECT OF DISINTEGRANTS AND PROCESSING ON THE BIOAVAILABILITY OF FRUSEMIDE FROM COMPRESSED TABLETS

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ABSTRACT

Batches of frusemide tablets were produced using Explotab, Polyplasdone XL, Amberlite IRP88, maize starch, and Elcema P100 as disintegrants. Bioavailability studies were carried out on a double blind basis.

The bioavailability differences between formulations was shown to be significant. Explotab rendered the frusemide far more bioavailable than the other four disintegrants.

INTRODUCTION

The influence that a change in formulation can have on the resultant bioavailability of a drug is important to most pharmaceutical companies. Although important, these

bioavailability changes cannot easily be determined in practice and, therefore, it has become necessary to investigate the effect of formulations on the dissolution rate of the drug. Dissolution rate will yield information on the release of the active ingredient from the dosage form under in-vitro conditions, but in the absence of an in-vivo/in-vitro correlation will not predict bioavailability. In addition, dissolution rates will only be useful if it is known that the absorption rate of the drug is dissolution rate limited. Thus, bioavailability of digoxin from tablets can be predicted from dissolution rate measurements, since an in-vivo/in-vitro correlation has been established and it is known that digoxin dissolution is the rate limiting step controlling absorption. However, for most other drugs including frusemide (furosemide), no such correlations have been established.

An aid to formulation is, therefore, necessary to know how common tablet excipients and processing methods influence drug bioavailability directly. The purpose of the present investigation is to report on the effect of various tablet disintegrants and methods of processing on drug bioavailability.

MATERIALS AND METHODS

It was necessary to choose a model drug for use in these studies and it was decided to use frusemide for the following reasons:-

(a) Frusemide has a very short half-life. This means that in 24 hours it is possible to collect urine for at least 9-12 half-lives.

(b) Frusemide is eliminated unchanged in the urine.

(c) Frusemide is relatively easy to assay.

(d) Frusemide is not protein bound.

(e) Frusemide is relatively safe to administer to normal healthy volunteers.

(f) Frusemide is very poorly water soluble and is known to exhibit bioavailability differences.

(g) Frusemide promotes urine flow and, therefore, it is possible to obtain many samples of urine in a 24 hour period.

Bioavailability can be measured in a number of ways. The most common method is to measure the amount of drug reaching the circulation as a function of time. However, there are pitfalls in estimating bioavailability from measurements of unchanged drug in blood. These include:-

(a) The total area under the curve must be estimated which involves a model dependant correction for the period between cessation of sampling and time infinity.

(b) The correction term requires a knowledge of the rate constant for the elimination phase.

(c) Depending upon the model, parameters such as renal clearance, various rate constants and volumes of distribution must be assumed to be constant either inter- or intrasubject.

(d) The assay procedure must be sensitive enough to determine drug levels approximately one twentieth that of the peak level.

(e) In the case of rapidly eliminated drugs like frusemide, peak blood levels are difficult to determine with any degree of precision and invariably they are missed altogether.

Bioavailability can be determined, however, by measuring the amount of intact drug in the urine. This approach offers a number of advantages. The method is model independent provided the drug does not exhibit non linear pharmacokinetics. Samples are much easier and less costly to obtain. The only major assumption in deriving the bioavailability data is that the average fraction of drug reaching the circulation is excreted in the urine for a given panel. This is the same for two or more treatments. Thus, in the present study, bioavailability of frusemide was determined from various tablet formulations by measurement of the amount of frusemide excreted unchanged in the urine.

Methods of Assessing Bioavailability

Two methods for the measurement of bioavailability were used. The first was that of Oser et al (2) (Method 1).

$$\% \text{ AVAILABILITY} = \frac{\left[X_{u\,\infty}\right] \text{ tablet form}}{\left[X_{u\,\infty}\right] \text{ aqueous solution}} \times 100 \qquad (1)$$

where $\left[X_{u\,\infty}\right]$ tablet form is the total amount of frusemide excreted in the urine after tablet administration.

$\left[X_{u\,\infty}\right]$ aqueous solution is the total amount of frusemide excreted after administration of an oral aqueous solution of frusemide.

From the cumulative amount of frusemide excreted with time plots (Fig.1), the amount of frusemide eliminated after 24 hours was estimated. Since at least 9 half-lives had elapsed during this period, the amount eliminated after 24 hours was considered to be the amount eliminated at infinite time and thus bioavailability as a percent was evaluated according the equation (1)

Method 2 was that of Niebergall et al (3)

$$U = U_\infty - \frac{U_\infty k_a}{k_a - k_e} e^{-k_e t} \qquad (2)$$

$$= U_\infty - Pe^{-k_e t}$$

$$\frac{du}{dt} = U = Pk_e e^{-k_e t}$$

$$U = U_\infty - \frac{U}{k_e} \qquad (3)$$

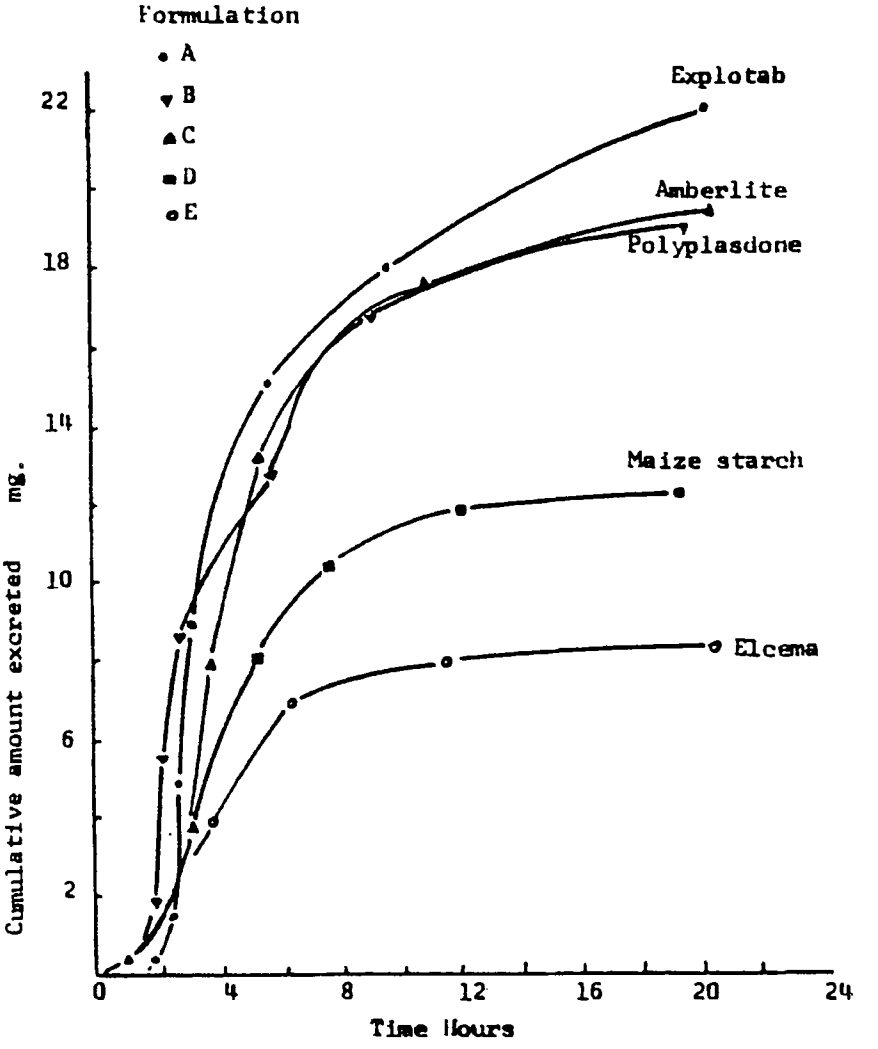

FIG. 1 - Cumulative amount of frusemide exereted with time (Subject 1)

where U = Cumulative amount of drug unchanged in the urine up to the time t

U_∞ = Total amount of drug excreted in the urine

ka = Absorption rate constant

ke = Overall elimination rate constant

From equation (3) U_∞ for each tablet was evaluated and bioavailability determined by substitution in equation (1).

The Effect of Five Disintegrants on the Bioavailability of Frusemide from 40 mg tablets

Identical batches of 40 mg frusemide tablets were produced, compressed at 150 MNm^{-2} to the following formulation: frusemide 40mg/tablet, calcium phosphate 100mg/tablet, protein S solution 20% w/w qs, disintegrant 14mg/tablet and magnesium stearate 1% w/w. The disintegrants used in the five batches were:

(a) Explotab (Edward Mendell Co., Inc.)

(b) Polyplasdone XL (GAF)

(c) Amberlite IRP 88 (Rohme and Haas)

(d) Maize Starch

(e) Elcema P 100 (Degussa Corporation)

The overall tablet weight was 165 mg.

In each case the tablets were consumed by male volunteers aged between 18-30. The bioavailability studies were carried out on a double-blind basis, with each volunteer taking the same tablet at least twice. On each day of the

experiment each subject took the same 40 mg tablet of known code or an oral solution of frusemide. The bladder was emptied prior to the start of the experiment and the time noted. The tablet or solution was given by mouth with 500ml or 400ml of orange juice respectively. Urine samples were collected as near as possible to the following times: 30 mins., 1h., 1.5h., 2.5h., 4h., 9h., 12h. and 24h. The total volume of each urine sample was recorded together with the exact time of collection. The urine samples were analyzed for frusemide content (1).

Figure 1 shows the cumulative amounts of frusemide excreted with time for one of the subjects.

It can be seen that after 24 hours only approximately 8mg of frusemide had been eliminated from the Elcema formulation, whereas with the Explotab formulation over 22mg had been excreted.

The Effect of Method of Processing on the Bioavailability of Frusemide from 40 mg tablets

In this study two proprietary frusemide products were compared with two experimental formulations: a direct compression formulation containing Emcompress and a wet granulation containing Explotab.

Dissolution rates and disintegration times were measured and the results are shown in Table II. It can be seen that the proprietory A has a short disintegration time but a very long dissolution half-life (t50%), whilst the

TABLE 1: Comparison of Methods 1 and 2 for Determining Bioavailability

	Formulation A (Explotab)		Formulation B (Polyplasdone)		Formulation C (Amberlite)		Formulation D (Maize Starch)		Formulation E (Elcema)	
	Method		Method		Method		Method		Method	
	1	2	1	2	1	2	1	2	1	2
Subject 1	73.1% 67.6%	71.57% 68.16%	63.5%	67.29%	65.22%	65.28%	41.29%	42.34%	28.02%	28.19%
Subject 2	67.03% 68.24%	65.66% 66.45%	60.83% 56.01%	60.54% 55.07%	52.52% 49.45%	50.27% 47.36%	35.12% 40.57%	32.91% 37.16%	32.02%	38.44%
Subject 3	63.35%	64.19%	55.69% 57.28%	57.11% 57.57%	51.48%	53.03%	46.31%	41.79%	27.9%	28.69%
Subject 4	72.8%	74.63%	72.03%	71.77%	63.29%	62.78%	35.11%	35.19%	30.95%	29.75%
Subject 5			65.14%	75.56%	67.33%	65.59%	50.01%	51.86%	44.3%	44.77%
Mean	68.68%	68.44%	61.49%	63.55%	58.22%	57.38%	41.4%	40.21%	32.64%	33.96%

TABLE II: Comparisons of Disintegration and Dissolution Properties of Test Tablets

PRODUCT	DISINTEGRATION TIME Mins.	DISSOLUTION HALF-LIFE t50% Mins.
Proprietary A	0.65	86.2
Proprietary B	1.41	16.6
Wet Granulation Formulation	6.75	10.5
Direct Compression Formulation	8.50	23.6

direct compression formulation has a fast dissolution rate but a relatively long disintegration time. The in-vitro properties, therefore, indicate that large differences should exist between the bioavailability of the various products.

Bioavailability studies were similarly performed as in the previous work. The cumulative amounts of frusemide excreted with time plots for one of the subjects is shown in Fig. 2. Since with this series frusemide was still being eliminated after 24 hours, equation 2 was fitted to the urinary excretion data. Equation (2) assumes a one compartment open pharmacokinetic model. k_e from previous work was found to be 0.25 hr^{-1} and thus for each administration including a solution, a straight line should result from a plot of U against $e^{-0.25t}$. The regression coefficients for this fit were found to be better than 0.9200 in all cases, indicating a goodness of fit at a probability level of better than 99.9%. Thus a one compartment open model fits very well indeed all the data from the urinary analysis. From the best fit, straight line U_∞ was calculated and the various values of U_∞ are shown in table III. Larger intrasubject variability was found with this series and smaller differences between formulations were apparent. Analysis of variance indicated that inter-subject variability was not significant in relation to the significant differences between formulations. In order to assess

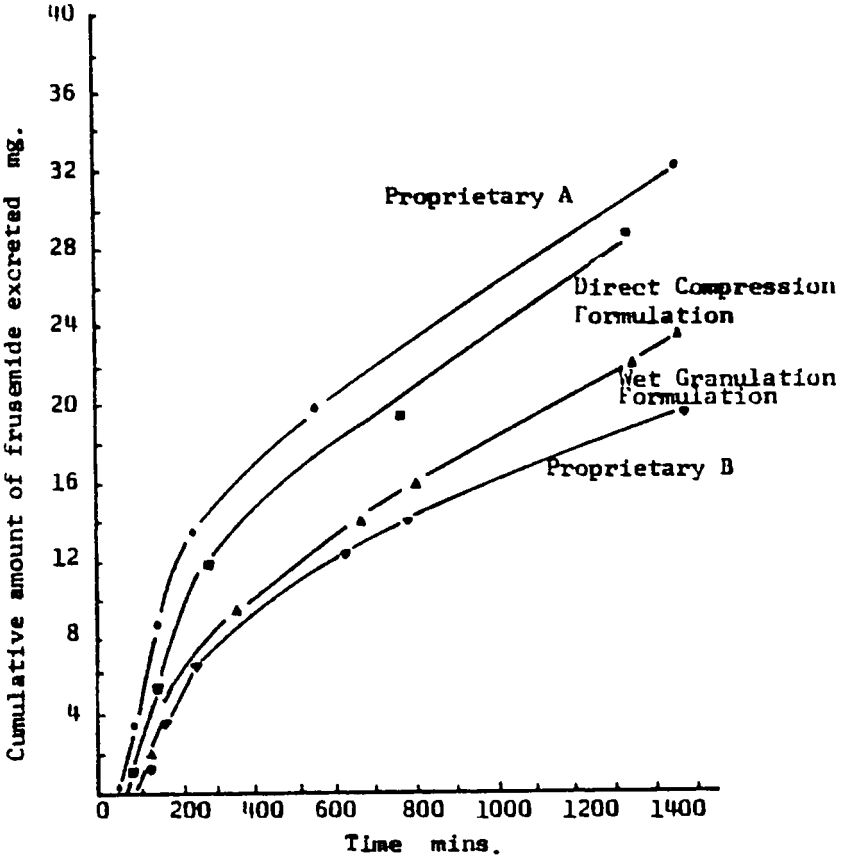

FIG. 2 - Cumulative amount of frusemide excreted with time (Subject MUR)

whether the formulations were individually significantly different, various multiple comparison tests were employed. These included the Tukey, Scheffe and Duncan multiple range tests. All the tests indicated that a solution was significantly different from the other four formulations and that proprietary B was significantly different from proprietary A, the wet granulation and the direct compression

TABLE III: Fitted U_∞ Values for the Various Frusemide Formulations

SUBJECT	PROPRIETARY A (mg)	PROPRIETARY B (mg)	WET GRANULATION (mg)	DIRECT COMPRESSION (mg)	SOLUTION (mg)
M.H.R.	26.4		21.5	18.8	21.4
	17.1	15.6	24.6	7.2	28.5
	21.4			19.9	25.5
R.C.	19.7	-	26.3	19.6	26.1
	23.2		24.2	27.2	25.1
	26.4		30.4	23.6	29.3
P.McC.	26.1	19.4	19.0	19.0	20.5
	29.7		24.5	27.8	21.1
J.D.	15.7	14.3	9.0	12.4	26.6
	19.9		21.2	15.2	37.7
	18.9		28.0		
D.B.	27.5	12.6	29.0	15.1	27.6
	23.9		31.2	29.3	15.5
				20.4	21.1
	22.76±4.34	15.47±2.89	24.08±6.06	19.65±6.34	25.08±5.45

formulation. Thus it can be concluded that a solution is the most bioavailable dosage form and that proprietary B is inferior to the other three tablet formulations. Proprietary A, the wet granulation and direct compression formulations all appear to render frusemide equally bioavailable. This processing, by the direct compression method would seem not to impair the release and absorption of frusemide.

RESULTS

Table 1 depicts the results obtained for the various tablet formulations. It can be seen that measurement of bioavailability by both methods yields similar results, within experimental error. Thus in the case of frusemide, measurement of the amount excreted after 24 hours is a satisfactory procedure for estimating bioavailability. It can also be seen from Table 1 that large availability differences exist between the formulations. By a two way analysis of variance the differences between and within subjects was shown to be insignificant whilst the differences between formulations was shown to be very significant. Thus Explotab renders the drug far more bioavailable than the other four disintegrants. In the case of Elcema the bioavailability is reduced by more than 50% over a similar tablet containing Explotab, whilst tablets containing Amerlite reduced the bioavailability by 15%. The results clearly show that in this series Explotab is the best dis-

integrant to use as far as the bioavailability of frusemide is concerned.

CONCLUSIONS

The bioavailability of frusemide from tablets has been shown to be influenced by the choice of disintegrant included in the formulation. In a comparative study Explotab produced the best release followed in rank order by Polyplasdone XL, Amerlite IRP88, Maize Starch and Elcema P100. In another study two proprietary 40mg tablets were compared and it was found that proprietary B rendered frusemide less bioavailable than proprietary A. A wet granulation formulation and a direct compression formulation containing Emcompress were further shown to be bioequivalent to proprietary A indicating that direct compression formulations do not adversely affect bioavailability. Dissolution rate measurements would seem not to correlate with drug bioavailability. Thus, proprietary A had a slow dissolution rate but exhibited good bioavailability, whilst with proprietary B the converse was true.

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