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# THE EFFECT OF FOUR TABLET BINDERS ON THE BIOAVAILABILITY OF FRUSEMIDE FROM 40MG TABLETS

Michael H. Rubinstein and Jayshree M. Rughani,
School of Pharmacy, Liverpool Polytechnic,
Byrom Street, Liverpool L3 3AF., U.K.

## SUMMARY

Tablets containing frusemide 40mg have been prepared using four different binders; polyvinylpyrrolidone, starch mucilage, stearic acid and methylhydroxyethyl cellulose. With the exception of the tablets prepared using stearic acid, all the tablets disintegrated in under 2 minutes and exhibited hardnesses ranging from 12 to 17 s.c.u. The dissolution rate, measured in the B.P. apparatus as the time to achieve 50% solution in distilled water, discriminated more effectively between the tablet batches. Tablets made using polyvinylpyrrolidone and methylhydroxyethyl cellulose had dissolution half lives of 3.65 and 3.30 minutes respectively, whilst tablets incorporating stearic acid and starch mucilage exhibited respective values of greater than 200 minutes and 117 minutes. The bioavailabilities of the four tablet formulations were assessed on a double blind basis in four healthy males

aged 18-30 with reference to an oral frusemide solution. The bioavailability of each formulation was determined by two different methods and it was found that polyvinylpyrrolidone and methylhydroxyethyl cellulose rendered frusemide equally bioavailable (71.7% and 71.6% respectively) whilst the starch mucilage formulation rendered frusemide 25% less bioavailable (54.10%). The poorest binding agent was stearic acid which decreased the bioavailability of frusemide by 50% (35.04%). The results indicate that the choice of binding agent can significantly affect the bioavailability of frusemide from tablets and that these bioavailability differences can best be detected in vitro by dissolution rate measurements.

## MATERIALS AND METHODS

Materials. Frusemide B.P. (Hoechst U.K. Ltd, Milton Keynes). Diluent: Calcium hydrogen orthophosphate (British Drug Houses, Poole). Disintegrant: Maize starch B.P. (British Drug Houses, Poole). Binding agents: Polyvinylpyrrolidone (Povidone, G.A.F. Corp., Manchester), stearic acid (British Drug Houses, Poole), methylhydroxyethyl cellulose ("Tylose", Hoechst U.K. Ltd., London) and maize starch B.P.

Methods. Batches of tablets were prepared according to the following formula: frusemide 40mg/tablet, calcium hydrogen orthophosphate 100mg/tablet, maize starch 14mg/tablet, binding agent 20% w/w solution or mucilage 8.4mg/tablet and magnesium stearate 1.48 mg/tablet. The drug and excipients were wet granulated through a 40 mesh sieve and dried overnight at 55°C. The fraction that passed through a 44 mesh but was retained on a 60 mesh sieve was collected, lubricated with magnesium stearate and compacted between 5/16" punches to a tablet weight of 165 mg.

Uniformity of weight of each of the tablet batches was determined by weighing ten tablets and evaluating the coefficient of variation. Tablet crushing strength was measured using a Schleuniger tester. Disintegration time was assessed using the standard British Pharmacopoeia apparatus. Dissolution rate of single tablets was evaluated in the B.P. apparatus. The basket was revolved at 100 RPM and the dissolution medium used was distilled water. 5ml aliquots of dissolution fluid were withdrawn at specified time intervals, filtered through a 0.8μm membrane and assayed at 229nm.

Bioavailability studies were carried out on a double blind basis in four healthy male subjects, aged 18-30 years. On each day of the experiment each person under observation took the same 40mg frusemide tablet at 10.00 a.m. after having previously emptied his bladder, together with 500mls of orange juice. The orange juice helped to act as a potassium supplement. The volunteers subsequently continued with their normal work. Urine was collected as near as possible to the following time intervals: 30 minutes, 1 hour, 1.5 hours, 2.5 hours, 4 hours, 9 hours, 12 hours and 24 hours. The total volume of each urine sample was recorded together with the exact time of collection and about 100mls was placed in an amber bottle. The urine samples were stored at $4^{\circ}C$ in a refrigerator until analysed.

A similar procedure was adopted for the subsequent tablet formulations with at least two days between successive administrations of the drug. Each subject took each tablet formulation twice. An oral frusemide solution was also administered in duplicate as part of the protocol. This solution contained 40mg of frusemide in 100mls of buffer

at pH 6.5. Each urine sample was analysed for total frusemide content by the method of Rubinstein and Price (1).

Results and Discussion. The disintegration times, hardnesses, dissolution rates and uniformity of weight results are shown in Table I. With the exception of tablets made using stearic acid the disintegration times were all less than 2 minutes, indicating that the tablets disintegrated very well indeed. All the tablets were hard, showing little significant differences so that it can be concluded that varying the tablet binding agent does not significantly affect tablet hardness. All the batches were found to be well within the B.P. weight limits and again no significant variation in weight due to the change of binder was evident.

Table 2 shows the mean cumulative amount of frusemide excreted unchanged in the urine after twenty four hours for each tablet formulation and the oral solution, in each subject. A two way analysis of variance of the cumulative amount of frusemide excreted unchanged after 24 hours was conducted to ascertain whether there was any significant variance between subjects. From F distribution tables the analysis indicated that variability between tablet formulations was highly significant but, that there was no significant variability between subjects. Fig.I summarises the results from the urinary excretion study of the four formulations for one of the subjects.

From the urinary excretion data the biological half life for each formulation and the oral frusemide solution was found by plotting the fraction of drug not excreted against time on semi log paper. This produced a "sigma-minus" plot. By linear regression the best fit straight

TABLE 1

In-Vitro Properties of the Four Formulations of 40mg Frusemide Tablets

| Binder | Disintegration Time Mins. | Hardness S.C.U. | Dissolution Rate $T_{50\%}$ Mins. | Coefficient of Variation of Tablet Weight % |
|---|---|---|---|---|
| Polyvinylpyrrolidone | 0.75 | 16 | 3.65 | 0.98 |
| Stearic Acid | >160 | 16 | > 200 | 3.00 |
| Starch Mucilage | 1.83 | 17 | 117 | 1.03 |
| Methylhydroxyethyl Cellulose | 0.92 | 12 | 3.30 | 2.70 |

TABLE 2

Mean Cumulative Amount of Frusemide Excreted Unchanged After 24 Hours in mg.

| | Solution | Polyvinyl-pyrrolidone | Stearic Acid | Starch Mucilage | Methylhydroxy-ethyl Cellulose |
|---|---|---|---|---|---|
| Subject 1 | 32.92 | 23.83 | 10.57 | 18.70 | 22.68 |
| Subject 2 | 30.30 | 21.98 | 8.80 | 17.73 | 22.11 |
| Subject 3 | 29.42 | 20.32 | 10.23 | 15.49 | 21.30 |
| Subject 4 | 30.10 | 22.70 | 9.94 | 16.36 | 21.32 |
| Mean | 30.68 | 22.20 | 9.88 | 17.16 | 21.74 |

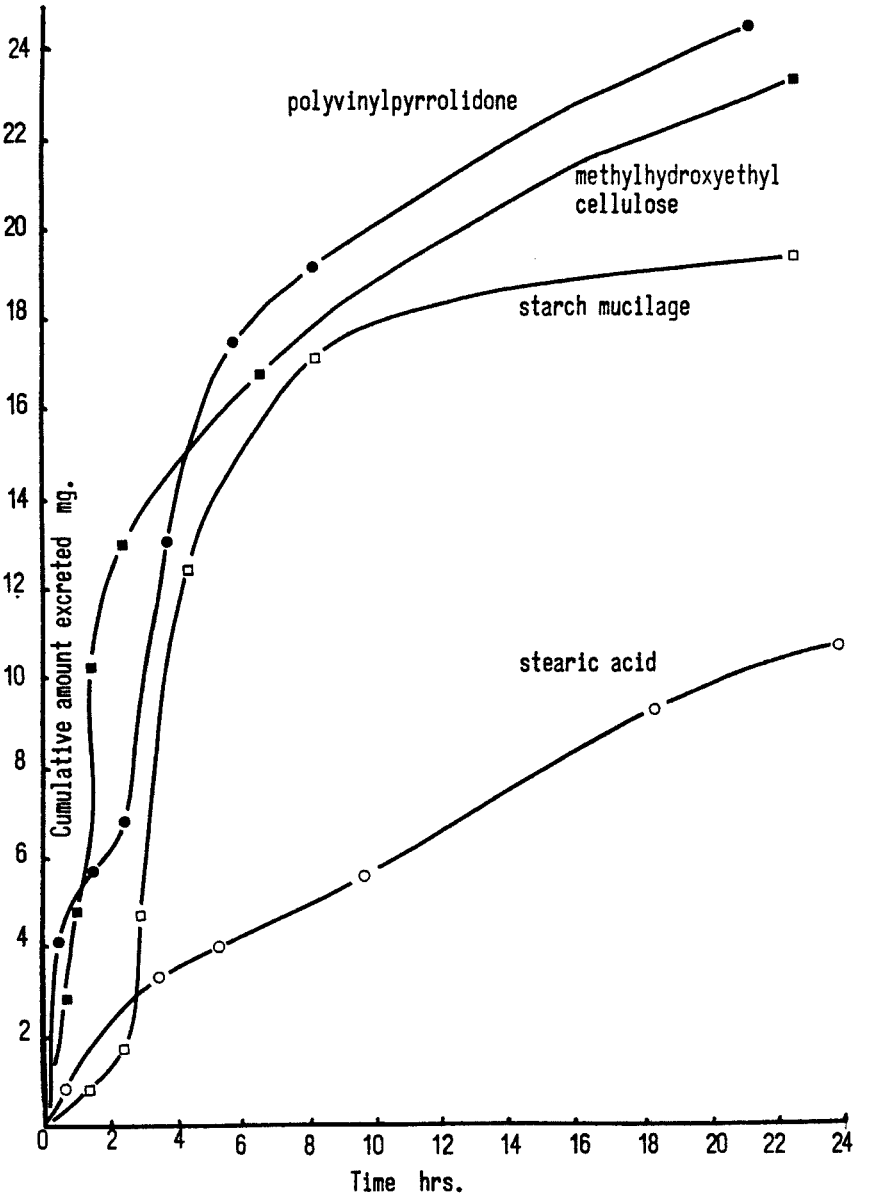


Fig. 1. Cumulative amount of frusemide excreted with time for each formulation (subject 1).

line was evaluated and hence the biological half life determined. Table 3 shows the values of the biological half lives obtained. These values indicate that the biological half life is independent of formulation and is a property of the drug itself and does vary from subject to subject. The biological half life of frusemide from tablets was found to be 4 - 6 hours. Lower values were however obtained from an oral frusemide solution (about 2 hours).

Estimation of Bioavailability. The bioavailability of the oral dose of 40mg frusemide in the various tablet formulations was estimated by two different methods:

(a) By comparing the total amount of frusemide excreted in the urine following administration of the tablet formulation with the total amount of frusemide excreted in the urine following administration of an oral aqueous solution, to give the per cent availability of the dose in the tablet form.

(b) Using the method of Niebergall, Sugita and Schnaare (2).

Based on 24 hour urinary excretion data method (a) was used to evaluate bioavailability from the following equation:-

$$\% \text{ Availability} = \frac{(Xu)_{\infty} \text{ tablet form}}{(Xu)_{\infty} \text{ aqueous form}} \times 100$$

where $(Xu)_{\infty}$ tablet form, is the total amount of frusemide excreted in the urine after administration of the tablet formulation, and $(Xu)_{\infty}$ aqueous solution is the total amount of frusemide excreted after administration of an oral aqueous solution of frusemide. Table 4 summarises the results obtained.

TABLE 3

Biological Half Lives (Hours)

| | Solution | Polyvinyl-pyrrolidone | Stearic Acid | Starch Mucilage | Methylhydroxy-ethyl Cellulose |
|---|---|---|---|---|---|
| Subject 1 | 1.61 | 3.68 | 6.0 | 3.62 | 1.6 |
| Subject 2 | 1.65 | 3.6 | 4.2 | 3.1 | 2.0 |
| Subject 3 | 2.1 | 2.0 | 4.7 | 3.5 | 3.9 |
| Subject 4 | 2.1 | 4.4 | 6.0 | 4.8 | 4.8 |

TABLE 4

Bioavailability Values Obtained by Method (a) %

| | A Polyvinyl-pyrrolidone | B Stearic Acid | C Starch Mucilage | D Methylhydroxyethyl Cellulose |
|---|---|---|---|---|
| Subject 1 | 72.38 | 43.00 | 56.81 | 68.90 |
| Subject 2 | 69.51 | 29.00 | 56.96 | 72.90 |
| Subject 3 | 69.07 | 34.77 | 52.65 | 72.41 |
| Subject 4 | 75.41 | 33.03 | 54.36 | 70.82 |
| Mean | 71.59 ±3.81 | 34.95 ±5.10 | 55.55 ±2.28 | 71.44 ±1.47 |

Method (b) was used to predict the total amount of frusemide excreted at infinite time. The method is based on the one compartment open model.

$$U = U_{\infty} - \frac{U_{\infty} K_a e^{-K_e t}}{K_a - K_e}$$

Letting $P = \frac{U_{\infty} K_a}{K_a - K_e}$ then,

$$U = U_{\infty} - Pe^{-K_e t}$$

where U is the cumulative amount of drug excreted unchanged in the urine up to time t, $U_{\infty}$ is the total amount of drug excreted in the urine, $K_a$ is the absorption rate constant and $K_e$ is the overall elimination rate constant. Differentiating the above equation with respect to time gives:

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

Therefore,

$$U = U_{\infty} - \frac{\dot{U}}{K_e}$$

A plot of U versus $\dot{U}$ should therefore be linear with the intercept equal to $U_{\infty}$ which is a reasonable estimate of bioavailability. By means of this approach, using linear regression analysis to find the best fit straight line, values of $U_{\infty}$ were obtained in each case. In order that these values of U can be compared with the values of % availability obtained from method (a), each $U_{\infty}$ value for each tablet formulation is expressed in Table 5 as a percentage of the $U_{\infty}$ value obtained for the oral solution.

TABLE 5

Bioavailability Values Obtained by Method (b) %

| | A Polyvinyl-pyrrolidone | B Stearic | C Starch | D Methylhydroxyethyl Cellulose |
|---|---|---|---|---|
| Subject 1 | 71.70 | 42.00 | 55.00 | 70.10 |
| Subject 2 | 70.56 | 30.00 | 55.91 | 71.95 |
| Subject 3 | 69.16 | 35.50 | 51.72 | 71.07 |
| Subject 4 | 75.29 | 32.69 | 52.53 | 72.70 |
| Mean | 71.67 ±4.12 | 35.04 ±5.01 | 54.10 ±2.31 | 71.60 ±1.52 |

The results obtained from the two different methods of estimating bioavailability show reasonable correlation. From method (a) it appears that physiological availability increases significantly in the order B, C, D and A in subjects 2 and 3 whereas in subjects 1 and 4 the order of increase in bioavailability is B, C, D and A. However, generally tablets made using polyvinylpyrrolidone and methylhydroxyethyl cellulose exhibited equivalent bioavailability whilst there was a very significant decrease in frusemide bioavailability from tablets made with starch mucilage and stearic acid. Thus in the manufacture of frusemide tablets starch mucilage and stearic acid should not be selected as being suitable binding agents. The water soluble binders appear to be better. From the dissolution rate results the bioavailability trend can be predicted, since tablets made with polyvinylpyrrolidone and methylhydroxyethyl cellulose had fast dissolution rates whilst the dissolution rates of the other two formulations were very much poorer. Disintegration times were of no use in this respect and could even be misleading since tablets made using starch mucilage had a good disintegration time of 1.83 minutes but exhibited very poor availability.

## REFERENCES

1. M.H. Rubinstein and E.J. Price, J. Pharm. Pharmacol., 29, Suppl. P5 (1977).

2. P.J. Niebergall, E.T. Sugita and R.L. Schnaare, J. Pharm. Sci., 64, 1721 (1975).