approach zero and the particle will be invisible. In the case of sugar solutions, many of the particles will be degraded sugar particles or sugar particles which may be crystallizing out. In these cases the refractive index of the particle will be similar to that of the solution and hence they will be invisible when using optical detection methods but countable by electrical conductivity measurements. We believe that these effects rather than differences in particle shape, are the major causes of the discrepancies found in both our results with sugar solutions and those of Dawes et al (1983) using amino acid solutions.

REFERENCES

Bayvel, L. P., Jones, A. R. (1981) Electromagnetic Scattering and its Applications. Applied Science Publishers, London

British Pharmacopoeia (1973 and 1980) HMSO London, p A123 and p A120 respectively

Dawes, V. H., Erawati, J., Eluemuno, J. (1983) J. Pharm. Pharmacol. 35: Suppl. 53P

Groves, M. J., Wana, D. (1977) Powder Technol. 18: 215–233

Jelinek, Z. K. (1970) translated by Bryce, W. A. J. Particle Size Analysis Ellis Henwood, Chichester, pp 35–42

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An in-vivo – in-vitro correlation for the bioavailability of frusemide tablets

The late MICHAEL KINGSFORD, N. J. EGGERS*, GEORGE SOTEROS, T. J. B. MALING†, R. J. SHIRKEY†, *Chemistry Division, Department of Scientific and Industrial Research, P.O. Box 2224, Auckland, New Zealand, †Wellington Clinical School of Medicine, New Zealand*

The dissolution behaviour of four commercial and two experimental formulations of frusemide tablets has been investigated using the USP rotating basket apparatus and pH 5·0 buffer at 37 °C as the test medium. There is a linear relationship between the percentage dissolution in 30 min and the bioavailability relative to an oral solution of frusemide over the bioavailability range 76–97%. Predicted bioavailabilities differed by no more than 2% from the measured values.

We have reported (Eggers et al 1983) a bioavailability trial of four commercial tablet formulations whose performance was assessed by comparing urinary recovery of frusemide and chloride excretion with the values obtained after administration of a frusemide solution. One of the tablets showed significant reduction of frusemide recovery.

This work has been extended by determinations of the bioavailabilities of two further batches of tablets, formulated to have impaired bioavailability, and use of the six tablet batches to develop a dissolution test using the rotating basket system (United States Pharmacopeia 1975).

Dissolution specifications or attempts at in-vivo/in-vitro correlations for tablets commonly involve either the time for a specified proportion of dose content (usually 50%) to dissolve, or the proportion of the dose content that dissolves in a specified time. The former approach suffers from the need to ignore the shape of the dissolution curve subsequent to the selected point and particularly the possibility that a proportion of the dose may dissolve only with great difficulty. The latter approach comes close to the clinicial situation.

If bioavailability problems exist with a drug, this commonly reflects the fact that absorption takes place for a limited time after ingestion. This places a time limit on the dissolution process in the gut, if good bioavailability is to be achieved. Thus the present study was directed towards finding the critical time at which the percentage dissolution should be measured.

Previous studies (Rubinstein & Price 1977; Rubinstein & Eastwood 1978; Rubinstein 1980; Marvola et al 1979; Stuber et al 1982) suggest that pH 5·0 might be suitable for the dissolution medium but cast little light on the critical time for dissolution. To facilitate identification of the critical time, a decision was made to fit our data to the Rosin-Rammler-Sperling-Weibull (RRSW) distribution (Langenbucher 1976; Gurny et al 1976; Goldsmith et al 1978; Christensen et al 1980) and use an iterative procedure to locate the desired time. The RRSW distribution has the following form:

$$W(t)/W(\infty) = 1 - \exp(-((t - T)/\alpha)^{\beta}) \quad (1)$$

Equation (1) expresses the amount dissolved in time t (W(t)) in terms of the dose content (W(∞)), the lag time for dissolution (T), the time for 63·2% dissolution (α) and the parameter, β which controls the curve shape.

Methods

The experimental tablets were prepared by Mr C. J. Budgen of the New Zealand School of Pharmacy. Batch 57 comprised frusemide (40 mg), dicalcium phosphate (100 mg), wheat starch (3·5 mg), magnesium stearate

* Correspondence.

(2·8 mg) and starch mucilage (7·0 mg). The tablets had a hardness of 9 Monsanto units, an assay of 93·7%, and disintegration times of 8–12 min (BP). Batch 58 comprised frusemide (40 mg), dicalcium phosphate (100 mg), wheat starch (7·0 mg), magnesium stearate (1·4 mg) and 5% ethanolic stearic acid (0·050 ml). The tablets had a hardness of 7 Monsanto units, an assay of 105·5% and disintegration times of 3–5 min (BP).

A panel of five normal volunteers was used for in-vivo estimations, the procedures being described elsewhere (Eggers et al 1983). The 24 h urinary excretion of frusemide and chloride was determined for a frusemide solution and the two experimental tablet batches, and the results were normalized to a dose of 80 mg. The members of the panel had ages varying from 35 to 44 years and body surface areas varying from 1·97 to 2·30 m^2.

Dissolution data were obtained at pH 5·0 using the rotating basket apparatus at 150 rev min^{-1} and 900 ml of dissolution medium at 37·0 ± 0·5 °C. The absorbance at 330 nm was monitored continuously spectrophotometrically in 1 cm flow cells. The monitoring line was equipped with a porosity 1 filter packed with glass wool and pumped by a Cole-Parmer Masterflow peristaltic pump at 20 ml min^{-1}. The performance of the rotating basket was satisfactory when checked by the procedures of the United States Pharmacopeia. Six tablets of each batch of frusemide tablets were tested individually, and the mean profiles are shown in Fig. 1.

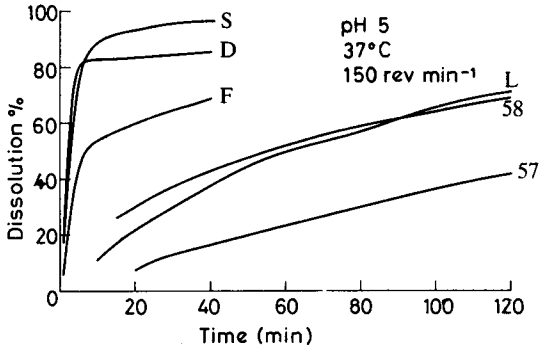

FIG. 1. Dissolution profiles for frusemide tablets in the USP rotating basket apparatus. (D = Diurin, F = Frusid, L = Lasix, S = Selemide, 57, 58 are experimental batches.)

The mean dissolution profiles were calculated for each batch and fitted to the RRSW distribution using an iterative procedure. Where an acceptable fit could not be obtained for the entire dissolution curve, only the region of interest was used.

The start time for iteration was set at 120 min and the percentage dissolution calculated for each tablet, using the RRSW equation. From the resulting data, a linear regression of bioavailability upon time was performed and the residual sum of squares about the regression (RSS) was calculated. The time was reduced by 5 min decrements until the minimum RSS was found, when the corresponding time was taken as the critical time and the regression line as the optimum regression of bioavailability upon percentage dissolution.

Results

The bioavailability results for B57 and B58 are given in Table 1. Both batches have significantly lower frusemide recoveries than the reference solution but there is no difference between the chloride urinary excretions.

The optimum time for a regression of bioavailability (B) upon percentage dissolution (P) is 30 min. The regression line has a correlation coefficient (r) of 0·979 and the equation $B = 0{\cdot}23P + 72{\cdot}6$.

Table 1. Bioavailability results for the experimental formulations. The results are expressed as a percentage of the recovery after administration of the frusemide solution.

	Chloride	Frusemide
B57	104·6	76·2**
B58	101·5	79·9**
Critical difference	17·6	10·8

Results which are significantly less than 100 (Dunnett): **0·01 > α. The critical difference is the reduction below 100% which is significant with α = 0·05 (Dunnet 1955).

Table 2. In-vivo/in-vitro correlation for frusemide tablets. Bioavailabilities are relative to that from a frusemide solution.

Formulation*	Dissolution (%)†	Bioavailability (%) Measured	Calculated
D	86	90	92
F	65	88	88
L	37	80	81
S	96	97	95
B57	12	76	75
B58	31	80	80

* See Fig. 1 for explanation.
† In 30 min in pH 5·0 buffer.

The measured and calculated bioavailabilities are given in Table 2 together with the percentage dissolutions. Fig. 2 shows the regression line together with the lower probability bound for readout from the line (Acton 1959), while Fig. 3 shows the regression of bioavailability upon the logarithm of the half-time for dissolution (r = 0·943), the line being: $B = 96{\cdot}8 - 4{\cdot}15 \ln T_{50}$.

For the six tablet formulations studied, the percentage dissolution in 30 min in pH 5·0 buffer provides a satisfactory estimate of bioavailability. However, it is clear that the regression is linear only over the bioavailability range studied (76–97% relative to the solution) since the 'y-intercept' corresponds to a bioavailability of 73%. Predictions of bioavailability from the half-time for dissolution are less satisfactory.

The confidence limits for readout from the regression on percentage dissolution provide an opportunity for suggesting a tentative standard. If the tablets release at

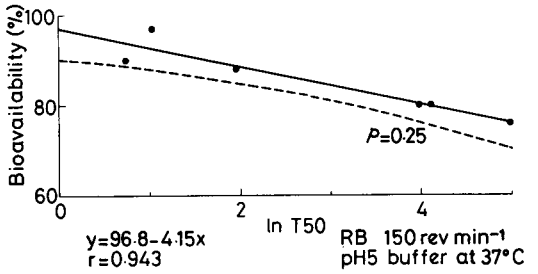

FIG. 2. Correlation between percentage dissolution in 30 min and bioavailability of frusemide tablets. There is 97·5% probability that the 'true' bioavailability associated with a given percentage dissolution lies above the dotted line.

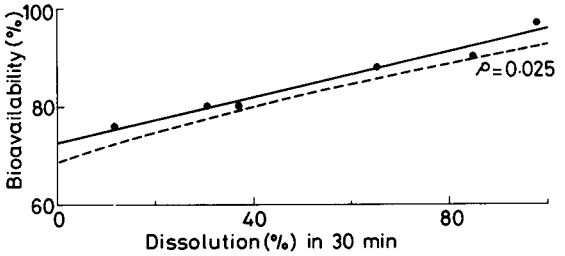

FIG. 3. Correlation between the time for 50% dissolution and the bioavailability of the frusemide tablets.

least 60% of their frusemide in 30 min, there is 97·5% confidence that their bioavailability exceeds 85% of that for a solution. While the regression line applies only to the six formulations tested, it is unlikely that a formulation meeting the requirement would have significantly impaired bioavailability. Accordingly we consider that the specification for frusemide tablets should be augmented to include a requirement for 60% dissolution in 30 min when tested in 900 ml of pH 5·0 buffer at 37·0 ± 0·5 °C using the USP rotating basket apparatus at a rotation rate of 150 rev min^{-1}.

We thank Mr C. J. Budgen for the formulation of the experimental tablets.

REFERENCES

Acton, F. S. (1959) Analysis of Straight-line Data. Wiley, New York.

Christensen, F. N., Hansen, F. Y., Bechgaard, H. (1980) J. Pharm. Pharmacol. 32: 580–582

Dunnett, C. W. (1955) J. Am. Stat. Assoc. 50: 1096–1121

Eggers, N. J., Kingsford, M., Saint Joly, C. M. J., Jellett, L. B., Maling, T. J. B., Shirkey, R. J. (1983) N.Z. Med. J.: 96: 963–967

Goldsmith, J. A., Randall, N., Ross, S. D. (1978) J. Pharm. Pharmacol. 30: 347–349

Gurny, R., Revillard, C., Doelker, E. (1976) Pharm. Ind. 38: 913–914

Langenbucher, F. (1976) ibid. 38: 472–477

Marvola, M., Jokila, P., Eriksson, M., Hietula, M. (1979) Acta Pharm. Fenn. 88: 87–95

Rubinstein, M. H. (1980) Drug Dev. Ind. Pharm. 6: 105–119

Rubinstein, M. H., Eastwood, B. A. (1978) J. Pharm. Pharmacol. 30; (Suppl) 12P

Rubinstein, M. H., Price, E. J. (1977) Ibid. 29: (Suppl) 5P

Stuber, W., Mutschler, E., Steinbach, D. (1982) Arzneim.-Forsch./Drug Res. 32: 693–697

United States Pharmacopeia (1975) 19th Edition, United States Pharmacopeial Convention, Inc., Rockville, Md.