DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 3(5), 439-450 (1977)

THE EFFECT OF EXCIPIENT SOLUBILITY ON THE IN-VITRO AND IN-VIVO PROPERTIES OF BENDROFLUAZIDE TABLETS 5 MG.

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SUMMARY

Tablets containing bendrofluazide 5 mg have been prepared at 190, 220 and 290 MNm^{-2} using four different excipients; sorbitol, lactose, calcium orthophosphate and calcium hydrogen orthophosphate. The solubilities in water of the excipients were respectively 70, 17.8, 0.03 and 0.01% W/W. Granules prepared under identical conditions were found to have moisture contents of about 3% W/W. All the four excipients were found to be equally effective in producing minimal tablet to tablet weight variation. Tablet hardness was governed by the intrinsic nature of the excipient and for all diluents an increase in compressional force produced an increase in tablet hardness. However, the size of this hardness increase varied markedly dependent on the excipient. Disintegration time and the nature of the disintegrating process varied greatly with the excipient. Generally, decreasing the solubility of the diluent decreased the disintegration time, but the pattern was complicated by the effect of compaction pressure which produced marked disintegration time differences with some excipients but not with others. No correlation was found between disintegration time and dissolution

rate. However changing the excipient greatly affected the dissolution rates of the tablets in some cases by as much as 600%. Disintegration time was found to be no indicator of dissolution performance. In-vivo assessment of the tablets demonstrated that there was a direct correlation between in-vivo activity, measured as initial micturation rate, with bendrofluazide dissolution. In general the study showed that by changing the diluent, marked differences in the in-vivo and in-vitro properties of the bendrofluazide tablets could be demonstrated and that these differences were more marked using very soluble excipients. The best excipients were found to be calcium orthophosphate and calcium hydrogen orthophosphate. Sorbitol was found to be the least useful as a tablet diluent.

INTRODUCTION

In many tablet formulations the excipient constitute the bulk of the tablet and hence its properties may markedly affect the bioavailiability of the active ingredient. Work done on investigating the effects of changing the tablet excipient has, however, been minimal. Tyrer et al (1) investigated an outbreak of anticonvulsant intoxication in Brisbane and found that it was due to an excipient change in phenytoin capsules directly affecting blood levels of phenytoin. Alkers (2) found various excipient materials markedly altered the absorption of dicoumarol, the effects not always being abolished by lowering the drug - excipient ratio. Since pharmaceutical manufacturers select an excipient often on the basis of availability, price and batch consistency, the present work was conducted in order to ascertain whether the excipient plays an important role in governing the physical and biopharmaceutical properties of bendrofluazide 5 mg tablets.

MATERIALS AND METHODS

Materials. Bendrofluazide B.P. (The Boots Company Ltd., Nottingham). Disintegrant: Cross-linked polyvinylpyrrolidone

(Polyclar A.T., G.A.F. Corp.). Excipients: Sorbitol, lactose, calcium orthophosphate and calcium hydrogen orthophosphate (British Drug Houses). The solubilities in distilled water at 25° of the excipients were respectively 70, 17.8, 0.03 and 0.01% W/W.

Methods. The formulation for the tablets prepared by moist granulation was as follows:- Bendrofluazide 5 mg/tablet, excipient 95 mg/tablet, cross-linked polyvinylpyrrolidone 15 mg/tablet and polyvinylpyrrolidone 10% solution qs.

Four batches of granules were prepared from the above formulation using each of the excipients. The amount of binder solution required to granulate the sorbitol formulation was found and the same amount of binder was used to granulate the other three batches; distilled water being used as necessary to produce the right consistency. In all cases the moist mass was screened through a 16 mesh sieve and the resulting granules dried at 55° for 12 h. and dry sieved through a 30 mesh screen. Granules that were retained on a 44 mesh sieve were used for tablet preparation. After the addition of 1% W/W magnesium stearate the angles of repose by the poured method, Train (3), and moisture contents of each batch were determined. Each granule batch was compressed on an instrumented single punch tabletting machine fitted with 1/4 inch flat faced punches at three different compaction pressures, 190, 220 and 290 MNm^{-2}.

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 Strong-Cobb tester. Disintegration time was assessed using the Standard British Pharmacopoeia apparatus. Dissolution rate was evaluated in the apparatus described by Rubinstein et al (4). The dissolution rate in the apparatus was found by withdrawing 5 ml samples of dissolution fluid (simulated intestinal fluid at pH 6.5) at specified time intervals, filtering through 0.8 µm membrane and assaying at 273 nm.

In order to assess the in-vivo absorption of bendrofluazide volunteers between the ages of 18 and 24 agreed to consume the tablets. The following protocol was adopted: 07.30 standard breakfast, 10.00 micturation, 11.00 drink 500 mls organge juice and take the tablet. The subject was then asked to time the onset of micturation and to measure the volume of urine produced. Placebos consisting of 50 mg ascorbic acid were used in a double blind method.

Results and Discussion. The moisture contents of each batch of granules dried under identical conditions is shown in Table I. All the granulations were found to have values of about 3% W/W indicating that there was no correlation between excipient solubility and granule moisture content. The angles of repose for each granulation and the corresponding coefficients of tablet weight variation are also shown in Table I. Granules produced using sorbitol and calcium hydrogen orthophosphate exhibited the highest moisture values and also the highest angles of repose. This is in line with the findings of Wolf & Hohenleiten (5) who showed that angle of repose increases with increasing moisture content. However, this decreased flowability was not reflected in the corresponding values obtained for coefficient of tablet weight variation. Thus it would appear that all of the excipients are equally effective in producing minimal tablet to tablet weight

TABLE I
Moisture Contents, Angles of Repose and Coefficients of Tablet Weight Variation for Bendrofluazide Tablets 5 mg.

Excipient	Moisture Content % W/W	Angle of Repose °	Coefficient of Tablet Weight Variation %
Sorbitol	3.63	37° 36'	0.148
Lactose	3.12	31° 30'	0.100
$Ca_3(PO_4)_2$	2.91	30° 33'	0.898
$CaHPO_4$	3.33	34° 16'	0.500

variation and that the flow properties of sorbitol and calcium hydrogen orthophosphate containing granules are improved under the vibrating conditions experienced during tabletting.

A graph of mean tablet hardness against diluent solubility is shown in Fig.1. There was no relationship, as expected, between excipient solubility and tablet hardness indicating that tablet hardness was a function of the intrinsic nature of the diluent and the compaction pressure applied. For each batch an increase in compressional force produced an increase in tablet hardness, but the size of this increase varied markedly depending on the excipient. For calcium hydrogen orthophosphate containing tablets a small increase in compaction resulted in a large increase in tablet hardness, whereas a large increase in pressure produced only a relatively small increase in tablet hardness for sorbitol containing tablets.

The disintegration times for each batch are shown in Fig.2. As well as displaying widely varying disintegration times, the appearance of the tablets as they disintegrated also differed. Sorbitol containing tablets did not deaggregate; the tablet gradually decreased in size until it passed through the 10 mesh screen. This was probably due to the high solubility of the diluent which dissolved so rapidly from the tablet surface that the disintegrant could not force the tablet apart by swelling. Thus in this case the disintegrating time was mainly dependent on the diluent solubility. However with the low solubility excipients the tablet did deaggregate suggesting that due to the insolubility of the diluent the disintegrant was able to absorb water, swell and so push the tablet apart. From Fig.2 it can be seen that generally decreasing the solubility of the diluent decreased the disintegration time. The effect of compaction pressure on disintegration time differed for each excipient. Bendrofluazide tablets containing lactose and tricalcium phosphate exhibited an increase in disintegration time with increased compaction pressure, whereas tablets containing sorbitol

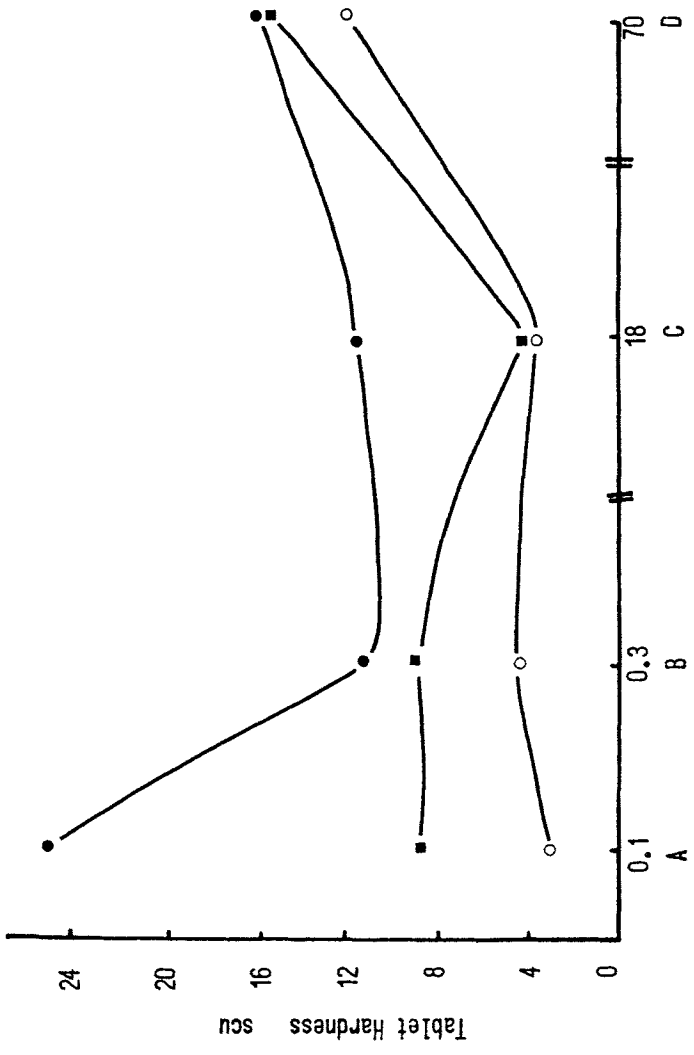

Figure 1

The effect of excipient solubility on tablet hardness. A calcium hydrogen orthophosphate, B calcium orthophosphate, C lactose, D sorbitol.
● 290 MNm^{-2} ■ 220 MNm^{-2} ○ 190 MNm^{-2}

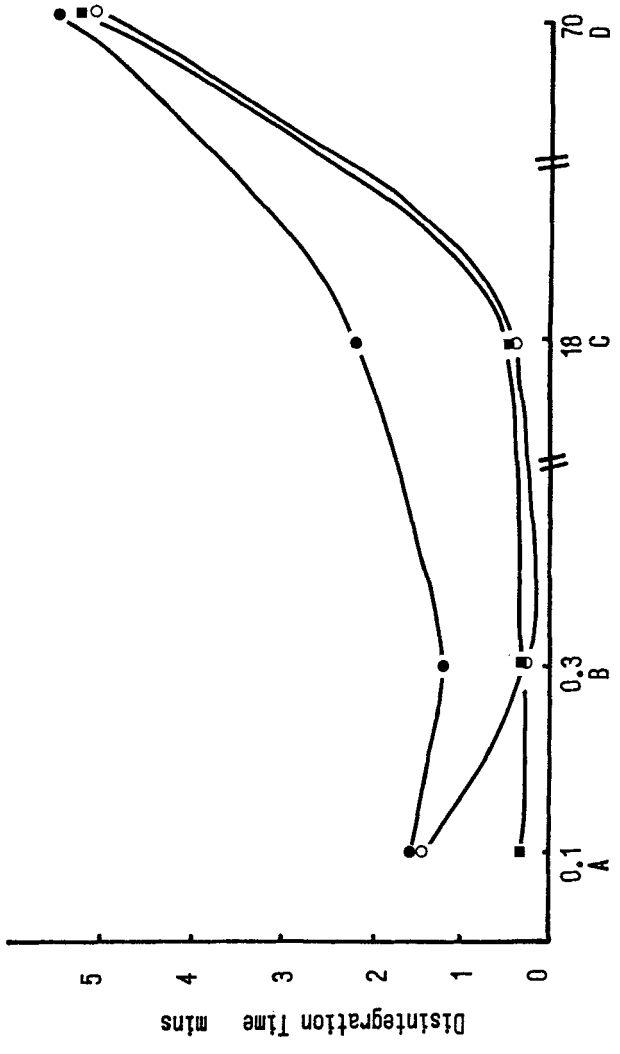

Figure 2

The influence of excipient solubility on tablet disintegration. A calcium hydrogen orthophosphate, B calcium orthophosphate, C lactose, D sorbitol
● 290 MNm^{-2} ■ 220 MNm^{-2} ○ 190 MNm^{-2}

and calcium hydrogen orthophosphate did not. Other workers have also found various results. Higuchi et al (6) showed that the logorithm of the disintegration time varied with compressional force, whereas Sakr et al (7) found that for lactose tablets, disintegration time was not appreciably affected by an increase in the compaction pressure. From the results found here it seems that the relationship varies with the choice of the excipient. Soluble drugs and excipients seem to retard tablet disintegration by forming viscous solutions which inhibit rapid liquid penetration essential for quick tablet disintegration. The best excipient was found to be calcium orthophosphate. This substance exhibited the lowest disintegration times adequate hardness and the minimum increase in disintegration time with compaction pressure. No correlation was found between tablet hardness and disintegration time. Tablets containing calcium hydrogen orthophosphate had very fast disintegration times (less than 2 minutes), but tablet hardness ranged from 3 to 25 s.c.u.

No relationship was found between dissolution rate measured as t_{40} and excipient solubility (Fig.3), nor between disintegration time and dissolution rate (Figs.2 and 3). It was evident however that changing the excipient greatly affected the dissolution rates of the tablets. A change of excipient from lactose to sorbitol could produce a six fold decrease in dissolution rate for tablets compacted at the same pressure. This change in dissolution rate could not always be detected by disintegration time measurements since calcium orthophosphate tablets with a disintegration time of only 1.2 mins possessed a t_{40} of 66 mins, whereas lactose tablets with a disintegration time of 2.16 mins had a t_{40} of 15.5 mins. The best excipient as far as dissolution rate was concerned was calcium hydrogen orthophosphate, provided the tablets were compressed to at least 8 s.c.u. Dissolution rates of less than 10 mins could then be produced. The worst excipient was sorbitol which gave rise to t_{40} values of up to 55 minutes.

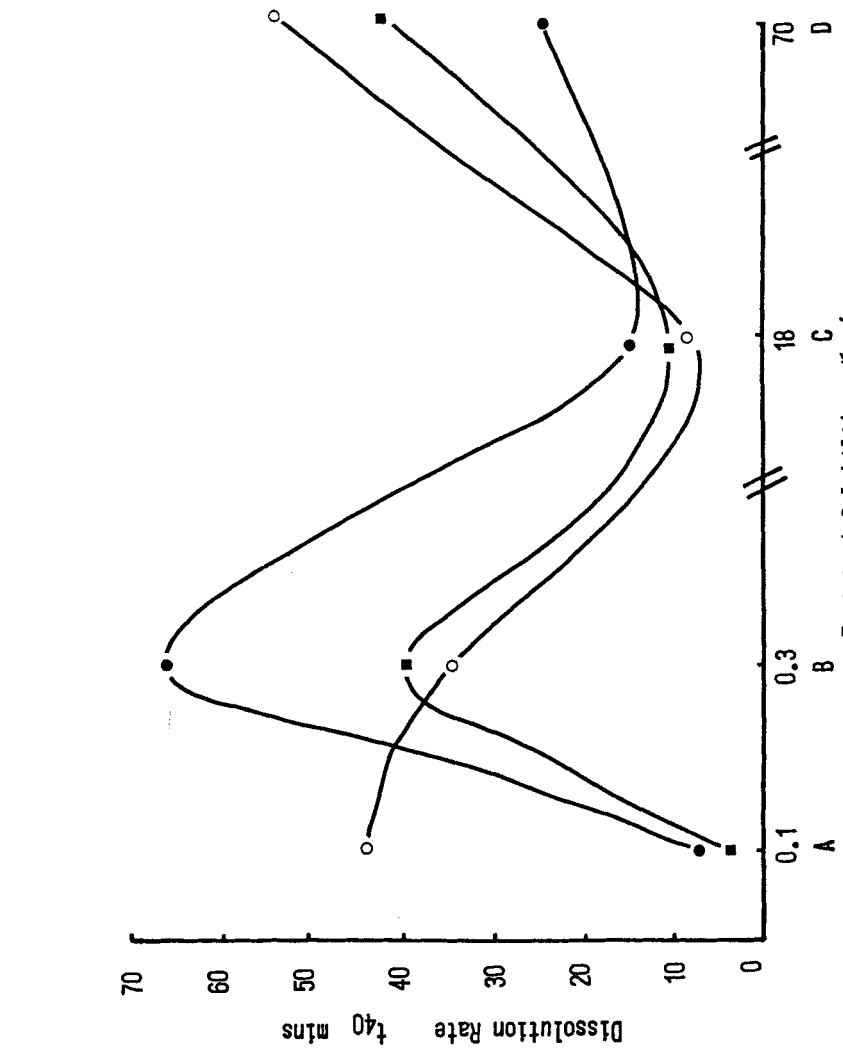

Figure 3

The effect of tablet excipient on dissolution rate. A calcium hydrogen orthophosphate, B calcium orthophosphate, C lactose, D sorbitol.
● 290 MNm^{-2} ■ 220 MNm^{-2} ○ 190 MNm^{-2}

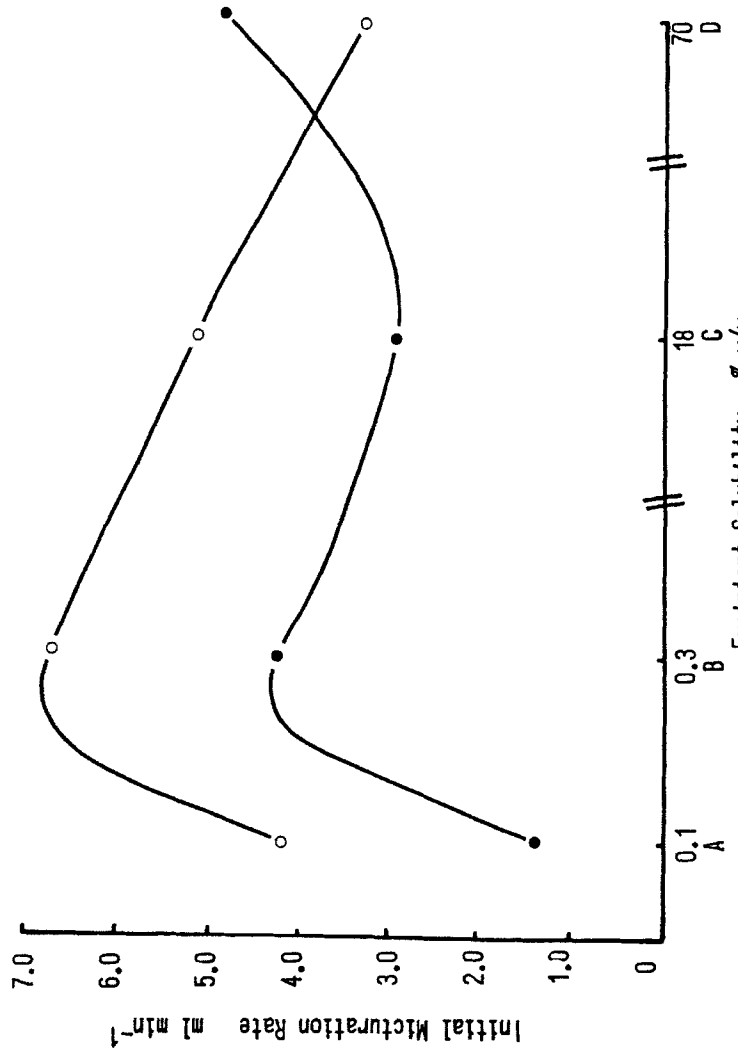

Figure 4

The relationship between excipient solubility and in-Vivo micturation rate.
A calcium hydrogen orthophosphate, B calcium orthophosphate, C lactose,
D sorbitol. • 290 MNm⁻² ○ 190 MNm⁻²

The micturation rate measured as the volume of urine collected after tablet administration divided by the time of onset of micturation was estimated for each volunteer. Repeat determinations for the same tablets administered to two different volunteers (all in the age group 18 - 26) indicated that the range of measured micturation rates was not more than 22% of the mean. Mean rates over the range 1.34 to 6.66 ml/min were recorded. It was considered that the micturation rate was a reasonable indicator of in-vivo activity for bendrofluazide tablets, and that the greater the rate of absorption of the tablets the higher was this initial micturation rate. Because of inconvenience to the volunteers, only eight batches of tablets were used and plots of micturation rate of these tablets are shown in Fig.4. As found from the dissolution rate measurements, the micturation rate values varied widely for each excipient. A comparison of the t_{40} values and the micturation rate (M) values showed that a reasonable correlation existed between the two parameters ignoring one spurious result, the equation being:

$$t_{40} = 80.05 - 7.56M$$

$r = 0.6014$ $(r > 0.5822$ for $\rho < 0.1)$

Thus, at the 90% probability level there appeared to be a direct relationship between in-vitro dissolution rate and in-vivo performance.

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