J. Pharm. Pharmac., 1977, **29**, 688-694 *Received May* 2, 1977

The effect of composition and ageing on the dissolution rates of chlorpropamide-urea solid dispersions

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Discs of chlorpropamide and urea have been prepared by (a) melting and (b) compression. Intrinsic and relative dissolution rates of the discs have been measured and the dissolution process investigated microscopically. Higher dissolution rates were found from melts than from physical mixes. The optimum dissolution rate composition found was for a melt composed of 30% w/w chlorpropamide which possessed an intrinsic dissolution rate 930 times greater than for the pure drug. Sphere formation, during dissolution rate measurement has been observed and a likely mechanism proposed to account for its occurrence. Dissolution rates generally increased with age for most melt compositions.

Solid dispersions were first proposed by Sekiguchi & Obi (1961) as a novel method for reducing drug particle size. They showed that formation of a eutectic mixture of the poorly water soluble drug, sulphathiazole, and the physiologically inert, water soluble carrier, urea, produced an increased absorption of sulphathiazole. Goldberg, Gibaldi & Kanig (1965) considered solid solutions as a mechanism by which dissolution might be increased. They attempted to show solid-solution formation and increased dissolution rate behaviour for griseofulvin-succinic acid (Goldberg, Gilbaldi & Kanig, 1966a) and chloramphenicol-urea (Goldberg, Gibaldi & others, 1966b). Subsequently these systems have been shown not to contain solid solutions (Chiou, 1971; Chiou & Niazi, 1973) and increased dissolution rates were considered attributable to decreased particle size. Hajratwala (1974) reviewed solid dispersions and summarized the theories of enhancement of dissolution by such systems. These included a solubilizing effect by the carrier (Goldberg, Gibaldi & Kanig, 1966c), a decreased particle size in eutectics (Rastogi & Bassi, 1964), a decrease in aggregation and agglomeration in hydrophobic drugs (Chiou & Riegelman, 1971), an increased wettability (Sekiguchi & Obi, 1961) and solidification of the drug in a metastable form which is readily available for rapid dissolution (Haleblian & McCrone, 1969). It is probable that any of these factors, or any combination might contribute to increased dissolution. Recently the chlorpropamide-urea system has been shown to be capable of formulation as a fast release tablet (Wells, Rubinstein & Walters, 1975) and of forming a eutectic, a solid solution and a glass solid (Ford & Rubinstein, 1977). The present paper reports the variations found in dissolution rate from various chlorpropamide-urea combinations into water and some aqueous urea solutions. The effect of ageing has also been investigated.

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MATERIALS AND METHODS

Materials

Chlorpropamide (Pfizer Ltd) and urea (Analar Reagent) were used without further purification.

Method 1. Compressed physical mixes

Both chlorpropamide and urea were powdered (sub 60 mesh sieve) and mixed thoroughly by trituration in a glass-mortar in the desired proportions. Weighed quantities of various mixes were compressed into discs, 2·54 cm diameter, at a pressure of about 4×10^8 Nm^{-2} in a hydraulic punch and die assembly. The discs were mounted before dissolution, centrally on the lower surface of the top part of the U.S.P. dissolution basket apparatus, using molten hard paraffin such that only the whole of the lower surface was available for dissolution.

Method 2. Uncompressed resolidified melts

Mixes of chlorpropamide, similar to those used for the physical mixes, were prepared. Quantities (about 3 g) were melted in test tubes in an oil bath with occasional stirring at 135–140° for 5 min. Sufficient molten material was then poured into an upturned aluminium vial cover (2 cm internal diameter) so that an excess existed. Immediately before a dissolution rate measurement the excess was sliced away with a razor blade to produce a

smooth uniform surface. The discs were stored over anhydrous copper sulphate at room temperature. Before a dissolution measurement the discs were mounted on the same apparatus as Method 1 using a Perspex ring and sealed in position using molten hard paraffin, such that only the drug disc surface was available for dissolution.

Method 3. Compressed resolidified melt

A mixture of 20% chlorpropamide in urea (5 g) was prepared and fused as Method 2. The resultant melt was poured into a petri-dish maintained at 0° to solidify. After storage at room temperature for 1 h the sample was pulverized (sub 60 mesh sieve size) and compressed and mounted for dissolution as for the physical mixture discs.

Dissolution rate measurements

Dissolution studies were carried out in a 1 litre flask (Quickfit FV-1L) at 37° using either 1 litre of freshly distilled water or various aqueous urea solutions. The discs were mounted so that the disc surface was positioned centrally in the flask, 3 cm from the bottom and rotated at 100 rev min^{-1} using a variable speed motor. Directly underneath the disc revolving in a counter direction to the disc, at 200 rev min^{-1} was a 2 cm long magnetic stirrer. At suitable intervals 2 cm^3 samples were withdrawn. Appropriate dilutions were made in distilled water before spectrophotometric determinations of chlorpropamide were made at 232 nm. Urea was found not to interfere with the assay.

Microscopical dissolution studies

Powdered samples of chlorpropamide-urea mixtures were placed on a microscope slide and covered with a cover slip. The slides were heated using a Reichert Kofler micro heating stage; heating until all crystals had melted. The slides were cooled to room temperature until crystallization occurred. One drop of water was placed under the cover slip and drawn by capillary action to the solid-air interface, at which dissolution commenced. Dissolution was followed using a Vickers M.41 photoplan microscope coupled with an Autowind Camera with electromagnetic shutter to produce prints.

Sphere analysis

Spheres produced during dissolution studies were removed after 5 min, 1 h and 24 h after dissolution had commenced. They were dried at 55° for 24 h before analysis. 2–5 mg samples were analysed by differential scanning calorimetry (Ford & Rubinstein, 1977) and samples (300–500 mg) were analysed by the B.P. assay for chlorpropamide (B.P. 1973).

Solubility studies

Chlorpropamide (20 mg) was added to 10 ml of water or various aqueous urea solutions in stoppered tubes and continually shaken in a water bath maintained at 37° for 72 h. The solutions were filtered and diluted appropriately in distilled water before spectrophtometric determinations of chlorpropamide were made at 232 nm.

RESULTS AND DISCUSSION

Dissolution profiles of some compressed physical mixes are shown in Fig. 1. For low chlorpropamide concentrations dissolution is a two-phase phenomenon, whereas at high concentrations it is monophasic. The slower initial rate at high urea concentrations could be due to either a lag time for the whole of the surface to become wetted or more likely to a leaching out of urea from the disc. This leaching leaves porous compressed chlorpropamide from which dissolution proceeds at an increased rate due to an effectively increased surface area. The latter explanation is substantiated by the appearance of the discs on examination after dissolution, when they were found to be pitted, increasingly so at higher urea concentrations. Pitting of discs was similarly shown to increase dissolution of urea-salicylic acid discs (Collett, Flood & Sale, 1976).

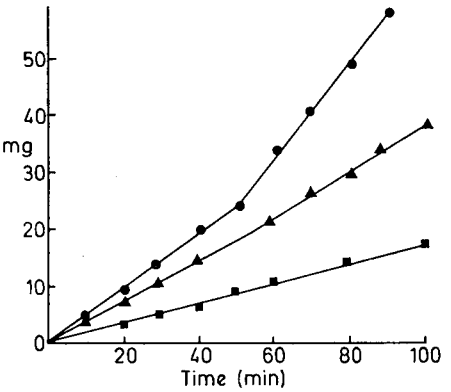

FIG. 1. Dissolution profiles of some urea-chlorpropamide compressed physical mixes into distilled water at 37°. Urea-chlorpropamide mixes:—● 80% 20%: ▲ 40% 60%: ■ 20% 80%. Ordinate—Chlorpropamide released (mg).

The calculated intrinsic rates of the initial and secondary profiles of compressed physical mixes are shown in Table 1. The significance levels of the

Table 1. *Intrinsic dissolution rate constants (mg min^{-1} cm^{-2} of variously prepared chlorpropamide-urea discs into distilled water at 37°.*

Composition %		Intrinsic dissolution rate constants (mg min^{-1} cm^{-2}) method of preparation	
% Urea	Chlorpropamide	Compressed physical mix disc	Uncompressed melt disc
80	20	(a) 0·0915 (b) 0·1678	26·89
60	40	(a) 0·1281 (b) 0·1816	52·03
40	60	(a) 0·0628 (b) 0·0834	48·55
20	80	0·0367	(a) 2·273 (b) 0·284
—	100	0·0429	0·0576

(a) Dissolution rate from primary linear profiles
(b) Dissolution rate from secondary linear profiles.
} where dissolution was biphasic.
All probability levels of regression coefficient <0·001.

correlation coefficients are also indicated and show that two straight lines provide a good intepretation of the experimental results. However, if all points of the dissolution curve of the 60% chlorpropamide disc are interpolated as being one straight line *P* is also <0·001 and a dissolution rate of 0·0739 mg min^{-1} cm^{-2} is obtained. However as dissolution profiles of melts containing 20 and 40% chlorpropamide are obviously biphasic, the transition between the profiles being biphasic and monophasic probably occurs at approximately 60% chlorpropamide.

High drug ratio discs show only a single linear dissolution profile, presumably due to urea leaching only at the surface of the disc to rapidly leave pure chlorpropamide from which dissolution can occur. Dissolution from compressed mixes is therefore a function of the surface area of chlorpropamide remaining at the face of the disc once local urea has dissolved.

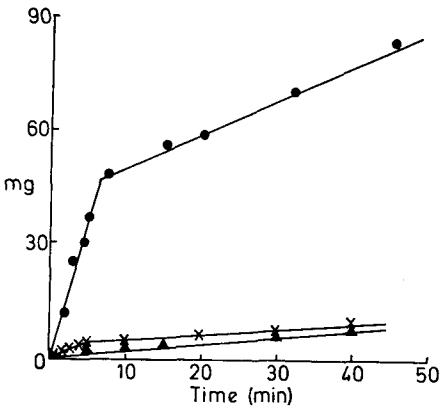

FIG. 2. Dissolution profiles of some 1 h old urea-chlorpropamide uncompressed resolidified melts into distilled water at 37°. Urea-chlorpropamide mixes:— ● 20% 80%: × 10% 90%: ▲ 100% chlorpropamide melt. Ordinate—as for Fig. 1.

Dissolution rate profiles of 1 h old uncompressed resolidified melt discs were linear except from melts containing 80 and 90% chlorpropamide which were biphasically linear and are shown in Fig. 2. All melts exhibit an increased dissolution rate over the pure drug. Fig. 3 shows the corresponding intrinsic

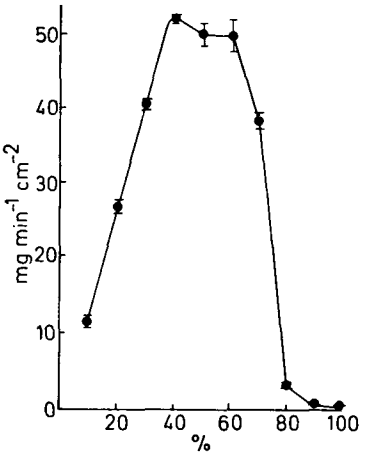

FIG. 3. Effect of chlorpropamide-urea composition on the intrinsic dissolution rates (mg min^{-1} cm^{-2}) of 1 h old uncompressed resolidified melts into distilled water at 37°. For 80 and 90% chlorpropamide melts the intrinsic dissolution rates were calculated from the initial linear portions of the dissolution profiles. The mean and standard deviation of three replicates for each composition are indicated. Abscissa—% chlorpropamide in disc.

dissolution rates plotted as a function of drug content and reveals an almost linear increase between 10 and 40% chlorpropamide followed by a tailing off most marked between 60 and 80%. The relative dissolution rates (defined as intrinsic dissolution rate divided by drug fraction) are shown in Fig. 4, where high rates were found up to 40% chlorpropamide and thereafter a decrease was observed. Calculated values of intrinsic dissolution rates of some melt systems are given in Table 1. The plateau between 10 and 40% in Fig. 4 indicates that dissolution rate is not proportional to drug concentration and that an optimum chlorpropamide to urea ratio for the system occurs between 20 and 40% chlorpropamide.

During dissolution of the melts it was observed that spherical particles of the drug were generated at the surface of discs containing 50–70% chlorpropamide and these, after detachment from the disc, sank to the bottom of the flask and acted as almost insoluble drug masses; they were unchanged in shape 24 h after dissolution was complete. For

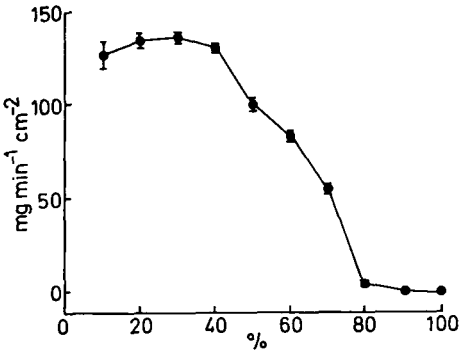

FIG. 4. Effect of chlorpropamide-urea composition on the relative dissolution rates (mg min^{-1} cm^{-2}) of 1 h old uncompressed resolidified melts into distilled water at 37°. For 80 and 90% chlorpropamide melts the relative dissolution rates were calculated from the initial linear portions of the dissolution profiles. The mean and standard deviation of three replicates for each composition are indicated. Abscissa—as for Fig. 3.

50% w/w chlorpropamide the spheres were approximately 0·5 mm in diameter; for 60% melts (Plate 1) 1–4 mm in diameter and for 70% melts, 2–7 mm in diameter, the number of spheres decreasing with increasing drug content.

Analysis of the spheres at various time intervals after dissolution of the disc had commenced showed that after 5 min the spheres contained 90% chlorpropamide and produced a DSC endotherm typical of the eutectic. 1 h after dissolution the spheres contained 98·7% chlorpropamide and after 24 h 100·3% chlorpropamide exhibiting a DSC endotherm typical of the pure drug. The chlorpropamide in the spheres only slowly dissolved since the drug itself is poorly wettable. Dissolution, for instance, of discs containing 70% chlorpropamide and 30% urea produced a concentration of 1500 mg litre^{-1} of chlorpropamide and 900 mg litre^{-1} urea. Saturated solubility studies of chlorpropamide in an equivalent urea solution produced only about one-third of this value indicating that dissolution from the discs produced a supersaturated solution of chlorpropamide, inhibiting further dissolution from the spheres.

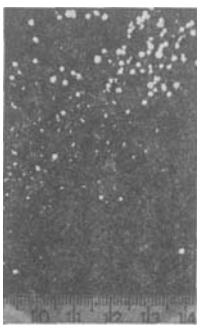

PLATE 1. Spheres produced from the dissolution of a 1 h old 60% chlorpropamide melt disc, showing spheres on the beaker surface. The major divisions are equivalent to 1 cm.

Figs 2, 3 and 4 and the formation of spheres can be explained by considering that chlorpropamide is uniformly dispersed throughout the disc as the eutectic. At low drug concentrations (0–40% chlorpropamide) the eutectic is dispersed discretely throughout the urea matrix, and during the dissolution process dissolves unimpeded resulting in a rapid dissolution rate. It is thought that the decrease in dissolution and the increased size of spheres formed during the dissolution of 50–70% drug melts represents a saturation in the diffusion layer adjacent to the disc surface. The liberated eutectic cannot dissolve fast enough into the diffusion layer and this results in the generation of an excess of undissolved eutectic, which, to compensate coheres together to maintain the equilibrium of the system. Obviously at higher chlorpropamide concentrations both the amount of eutectic present and the size of the spheres increase, so reducing the amount of rapidly available chlorpropamide and thereby slowing dissolution. The larger spheres were an agglomerate of smaller spherical aggregates and the basic shape is thought to be due to spheres having a minimum surface area to volume ratio. As 80 and 90% melts contain a large proportion of eutectic dissolution is retarded still further. Only the drug in the initial disc surface is available for solubilization by the urea, and this results in the formation of a barrier of chlorpropamide at the disc surface from which dissolution proceeds slowly, producing the biphasic profiles of Fig. 2. It might be argued that biphasic dissolution is due to polymorphic changes in the melt from a glass to a crystalline state. However, 100% chlorpropamide melts before dissolution existed as supercooled glasses, and during dissolution their surface changed to a crystalline mass but did not produce a biphasic dissolution profile. This indicates that such a profile is not a polymorphic phenomenon in this system.

Sphere formation was also found in the microscopical dissolution experiments. The water solid interface, with melts of less than 20% chlorpropamide migrated quickly; the urea dissolving at the interface and subsequently recrystallizing as large urea crystals as the interface traversed the melt. For melts greater than 20% chlorpropamide the interface moved more slowly but recrystalliza-

tion did occur. The interface migrated only 2 to 4 mm before dissolution ceased. This distance decreased with increase in chlorpropamide concentration until eventually little dissolution appeared to occur with pure chlorpropamide and the interface remained stationary. With high chlorpropamide-containing melts crystallization occurred at the liquid-solid interface and acted as a barrier preventing further dissolution. This observation supported the biphasic dissolution theory proposed for high chlorpropamide containing melts.

Microscopically sphere formation was observed with 10 and 20% chlorpropamide melts. Rapid dissolution occurred initially with the liberation of small spheres at the interface (as shown in Plate 2). These spheres gradually coalesced to form larger spheres of chlorpropamide which eventually crystallized. This sphere formation was considered to be analogous to that found from the rotating disc studies. The lower chlorpropamide concentration at which this occurred was due to the higher melt to water ratio used.

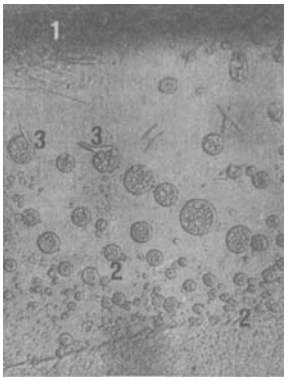

Plate 2. Photomicrograph of the dissolution process in a 10% chlorpropamide melt, 180 s after dissolution had commenced, showing (1) air - water interface, (2) sphere formation and coalescence, (3) crystal formation from spheres. Magnification ×200.

The intrinsic dissolution rates of uncompressed melts and compressed physical mixes are shown in Table 1. A melt of 40% chlorpropamide has an intrinsic dissolution rate 930 times greater than the intrinsic rate of pure drug. This finding is similar to that found by Chiou & Niazi (1971) who reported a 700 fold increase with similarly prepared sulphathiazole-urea discs. In order to eliminate this being due to a compressional artifact, Method 3 was used to prepare 20% chlorpropamide compressed melt discs. The relative and intrinsic dissolution rates of these discs were found to be unchanged from similar prepared uncompressed discs indicating that the increased dissolution rate was solely attributable to the intimate presence of the urea in the disc formulation. This assumption is supported by the fact that a 60% chlorpropamide melt possessed a dissolution rate 600 times greater than a 60% compressed physical mix disc.

Chiou & Niazi (1971) have shown that increased dissolution rate could also be due to a reduction in surface tension and a better wetting of the drug by the dissolved urea in the dissolution fluid. Similarly Collett & Flood (1976) found that dissolution rates of salicylic acid in urea solutions increased with increasing urea concentrations due to solubilization by urea. Table 1 shows that dissolution of chlorpropamide is enhanced by the intimate presence of urea both in the melt and physical mix systems. Table 2 shows that dissolution of pure chlorpropamide is enhanced in the presence of solutions

Table 2. *Effect of urea concentration on the intrinsic dissolution rate (mg min^{-1} cm^{-2}) and saturated solubility of chlorpropamide (mg litre^{-1}).*

% Urea	Intrinsic dissolution rate (mg min^{-1} cm^{-2})	Saturated solubility of chlorpropamide in urea solutions
0	0·0576	480
5	0·0852	812
10	0·1262	1174
15	0·1676	1630

of up to 15% urea and that urea increases the solubility of chlorpropamide. The increases in dissolution rate, due to the solubilizing effect of urea however, were considered small compared to the 930 fold increase in intrinsic dissolution rate and 2320 fold increase in relative dissolution rate for the 40% melt system over the pure drug, and it is hypothesized that the increase in dissolution rate exhibited by the melts is primarily a surface area phenomenon.

The variation of dissolution rates with ageing over the 0 to 100% concentration range of chlorpropamide presented an extremely complex situation. The effect of ageing for some chlorpropamide-urea melts are shown in Fig. 5. Up to around 40% chlorpropamide there was no change in dissolution rate with ageing, the experimental values differing by less than ±5% after 28 days storage. Melts containing 50–60% chlorpropamide showed an initial decrease in dissolution rate with age followed by an increase as exemplified by discs containing 60% chlorpropamide, Fig. 5. Melts

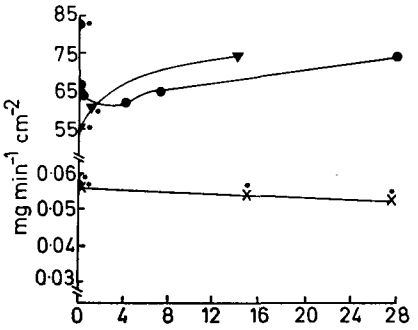

FIG. 5. The effect of ageing on the intrinsic dissolution rates (mg min^{-1} cm^{-2}) of chlorpropamide-urea uncompressed resolidified melts into distilled water at 37°. Chlorpropamide-urea mixes:—● 60% 40%: ▼ 70% 30%: × 100% chlorpropamide. Asterisks indicate that the system appeared as a glass solid before dissolution. Abscissa—Age of melt before dissolution (days).

containing greater than 60% chlorpropamide have been shown to exist as metastable glass solids (Ford & Rubinstein, 1977), and this initial dissolution rate decrease for the 60% melt is therefore probably due to crystallization which was visable after 2 h storage. Total crystallization did not seem to occur, the very high viscosity of the glass appeared to inhibit it. However this partial crystallization was considered sufficient to reduce the free energy of the system which was manifested by the production of smaller spheres during dissolution rate measurement. The subsequent increase in dissolution rate after 4 days was considered to be due to diffusion of drug molecules in the melt. This drug diffusion theory is probably similar to that observed by Komatsu & Grant (1964) with copper matrices of silicon dioxide. They found that silicon dioxide particles could diffuse in the metal matrix and deposit themselves on existing silicon dioxide particles causing particle coarsening. It is proposed that a similar effect is exhibited with chlorpropamide-urea melts.

Melts containing 70 and 80% chlorpropamide showed a rapid increase in dissolution rate with time, exemplified by the 70% melt in Fig. 5. Dissolution of melts prepared from the pure drug showed a decrease in dissolution rate with time as crystallization in the glassy chlorpropamide occurred (Ford & Rubinstein, 1977). Variation in dissolution rates with ageing over the 0 to 100% concentration range of chlorpropamide therefore involved three transitions, i.e. from (a) no ageing effect to (b) decrease in dissolution rate with age followed by an increase to (c) rapid increase in dissolution rates followed by a slower increase to (d) decrease in dissolution rate to a minimum.

Previous work has shown that ageing can effect dissolution rates. Chiou & Riegelman (1969) showed that for a 10% griseofulvin-polyethylene glycol system there was little change in dissolution rate. However, Chiou & Niazi (1971) showed that a sample of sulphathiazole-urea exhibited a decrease in dissolution rate after ageing for 1 h at 105°. This decrease could be attributable to the degree of crystallization, as increased crystallinity was found to decrease dissolution rates for sulphathiazole-urea and indomethacin-polyethylene glycol (Allen & Kwan, 1969). These observations are analogous to the decrease found in the 60% chlorpropamide melt when visible crystallization occurred. It has not previously been reported, however, that ageing can increase the dissolution rate.

Taking the ageing process into consideration it would appear that the optimum concentration for *in vitro* dissolution of the chlorpropamide system corresponds to a melt composed of 30% chlorpropamide which approximates to the granular system used by Wells & others (1975).

Acknowledgement

The authors wish to thank the Science Research Council for financial support of J. L. F. which enabled this work to be undertaken.

REFERENCES

ALLEN, D. J. & KWAN, K. C. (1969). *J. pharm. Sci.*, **58**, 1190–1193.
British Pharmacopoeia (1973). London: H.M.S.O., 108–109.
CHIOU, W. L. (1971). *J. pharm. Sci.*, **60**, 1406–1408.
CHIOU, W. L. & NIAZI, S. (1971). *Ibid.*, **60**, 1333–1337.
CHIOU, W. L. & NIAZI, S. (1973). *Ibid.*, **62**, 498–501.
CHIOU, W. L. & RIEGELMAN, S. (1969). *Ibid.*, **58**, 1505–1509.
CHIOU, W. L. & RIEGELMAN, S. (1971). *Ibid.*, **60**, 1281–1302.
COLLETT, J. H. & FLOOD, B. L. (1976). *J. Pharm. Pharmac.*, **28**, 206–209.
COLLETT, J. H., FLOOD, B. L. & SALE, F. R. (1976). *Ibid.*, **28**, 305–308.
FORD, J. L. & RUBINSTEIN, M. H. (1977). *Ibid.*, **29**, 209–211.

GOLDBERG, A. H., GIBALDI, M. & KANIG, J. L. (1965). *J. pharm. Sci.*, **54**, 1145–1148.
GOLDBERG, A. H., GIBALDI, M. & KANIG, J. L. (1966a). *Ibid.*, **55**, 487–492.
GOLDBERG, A. H., GIBALDI, M., KANIG, J. L. & MAYERSOHN, M. (1966b). *Ibid.*, **55**, 581–583.
GOLDBERG, A. H., GIBALDI, M. & KANIG, J. L. (1966c). *Ibid.*, **55**, 482–487.
HAJRATWALA, B. R. (1974). *Aust. J. pharm. Sci.*, **NS3**, 101–109.
HALEBLIAN, J. & MCCRONE, W. (1969). *J. pharm. Sci.*, **58**, 911–929.
KOMATSU, N. & GRANT, J. N. (1964). *Trans. metall. Soc. A.M.I.E.*, **230**, 1090–1096.
RASTOGI, R. P. & BASSI, P. S. (1964). *J. phys. Chem.*, **68**, 2398–2406.
SEKIGUCHI, K. & OBI, N. (1961). *Chem. Pharm. Bull.*, **9**, 866–872.
WELLS, J. I., RUBINSTEIN, M. H. & WALTERS, V. (1975). *J. Pharm. Pharmac.*, **27**, *Suppl.*, 56P.