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THE EFFECT OF PARTICLE SIZE ON SOME IN-VITRO AND IN-VIVO PROPERTIES OF INDOMETHACIN-POLYETHYLENE GLYCOL 6000 SOLID DISPERSIONS

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ABSTRACT

Drug release from indomethacin-polyethylene glycol solid dispersions has been examined using three different size fractions. Release rates at a stirring rate of 100 rpm were generally higher from the 250-375 micron fraction than from particles in the ranges 125-188 and 500-750 microns. Release rates were highest from dispersions containing 5% indomethacin and showed a 240-fold increase at 100 rpm and a 1200-fold increase at 50 rpm over those at the same stirring rate of indomethacin alone (125-188 microns). As the percentage of indomethacin in the dispersions increased (5 to 40%) the dissolution rates decreased and for dispersions containing ≥15% indomethacin, complete solution of the drug was not achieved within 2 hours. The 500-750 micron fraction of the dispersion containing 10% indomethacin was significantly more gastro-toxic than particles of 125-188 microns.

INTRODUCTION

Polyethylene glycol was first used as a vehicle for poorly water-soluble drugs in 1969 [1] when its dispersions with

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griseofulvin were found to possess higher dissolution rates than the drug alone. Subsequently, many drugs including steroids [2], diuretics [3] and benzodiazepines [4] have been solid-dispersed with polyethylene glycol (PEG). Although PEGs vary in molecular weight from 200 to above 20,000 the most commonly used fraction is PEG 6000 and the indomethacin-PEG 6000 system has been one of the most extensively studied dispersions.

Allen and Kwan [5], using constant surface area discs, showed that the dissolution rates from discs containing 10% indomethacin: 90% PEG 6000 were related to crystallinity of the indomethacin. Hoelgaard and Moller [6] found that dissolution rates from 20% indomethacin dispersions in PEG 6000 were higher than from indomethacin alone. Ford and Rubinstein [7-10] have comprehensively examined the indomethacin-PEG 6000 dispersion. A eutectic existed containing 13% indomethacin [7] and the dissolution rate of the 15% indomethacin melt was 200-times that of pure indomethacin. Solid solutions existed of indomethacin in PEG 6000 and, at high drug content, the fused systems solidified to a glass dispersion [7]. The enhanced dissolution rates were subsequently reduced by storage [8] and were markedly affected by storage temperature and moisture. The system was, at certain compositions, tacky and therefore difficult to formulate into solid dosage forms but formulation into tablets has subsequently been achieved by novel granulation techniques [9,10]. Elliott et al [11], have recently shown that solid dispersions of 10% indomethacin in PEG 6000 were more gastro-irritant than 10% physical mixes in PEG 6000 or lactose and that higher blood levels were achieved following administration of the solid dispersion.

This study describes the effect of particle size on the dissolution rate of indomethacin-PEG 6000 dispersions and the gastro-toxicity in the rat of 10% indomethacin dispersions.

MATERIALS AND METHODS

Indomethacin B.P. and Polyethylene glycol 6000 (B.D.H.) were used as supplied.

Solid dispersion preparation

Solid dispersions were prepared by fusing mixtures of indomethacin and PEG 6000 at 160°C and pouring the melts onto glass surfaces, chilled to 0°C. The resultant dispersions were stored at 4°C for 48 hours before trituration and the powders were mechanically sieved to produce size fractions of 500-750, 250-375 and 125-188 μm.

Dissolution-Rate Determinations

These were determined using the Copley Computerised Dissolution System Series 8000. 1000 ml of distilled water, maintained at 37°C, was used as the dissolution fluid and indomethacin was assayed at 266 nm. PEG 6000 did not interfere with the assay. Weighed samples, equivalent to 10 mg. indomethacin, were used and stirring rates of 50 or 100 rpm were employed. The dissolution from indomethacin (125-188 μm only) was also examined.

Gastro -Irritancy Studies

200 g male Wistar rats, previously deprived of food for 24 hours before drug administration, were used. The 10% indomethacin - 90% PEG dispersion only was studied and rats were dosed with the equivalent of 6 $mg.kg^{-1}$ indomethacin.

12 mg of the melt was weighed into a 12 cm. length of Portex tubing (800/100/150/800) and gently compacted to form a plug, approximately 2 cm. from one end of the tube. This end was attached to a syringe containing distilled water. The free end of the tube was inserted through a hole in a piece of perspex (approximately 12 mm x 7 mm in cross section) which was held between the jaws of the rat. The tube was manipulated to pass through the oesophagus into the stomach. The drug was driven into the stomach by the passage of 1 cm^3 of water through the tube from the syringe. The empty tube and perspex bar were then withdrawn. Gastric lesions were counted in the everted stomachs of rats, killed by exposure to ether, 5 hours after drug administration.

Polymorph Analysis

The polymorphic forms of indomethacin were identified by differential scanning calorimetry [7] and infra-red methods [12]. The untreated drug was found to be form I indomethacin [7, 8, 9, 12].

RESULTS AND DISCUSSION

DISSOLUTION DATA

5% Indomethacin Dispersions

Dissolution from these melts was rapid and total solution was achieved within 8 mins. at 50 rpm. and within 5.5 mins. at 100 rpm. At each stirring speed with the 250-375 μm fraction total solution was achieved almost instantaneously (<80 secs.) and more rapidly than the 125-188 and 500-750 μm particles (figure 1). The intermediate fraction was better wetted than the lowest size fraction which floated on the water surface hindering dissolution. Dissolution from the largest size fraction was retarded since, before dissolving, the particles coalesced as an agglomerate directly underneath the paddle.

10% Indomethacin Dispersions

At 100 rpm. the 250-375 μm. fraction dissolved rapidly and within 60 secs. Complete solution at 100 rpm. was achieved within 12 mins. for the other size fractions. However at the lower stirring speed of 50 rpm. complete solution of the indomethacin was not achieved. For instance, only 73% of the drug had dissolved from the 500-750 μm particles after 30 minutes (figure 2). The particles aggregated and coalesced to form a hard compact mass of indomethacin as the form II polymorph [7,12] directly under the paddle and only slowly dissolved. Chiou and Riegelman [13] have postulated that solid dispersions should overcome the problems of aggregation displayed by very small particles but this study confirms that aggregation may present problems in solid dispersed systems. Similar problems [7, 14, 15] were encountered when measuring release rates by

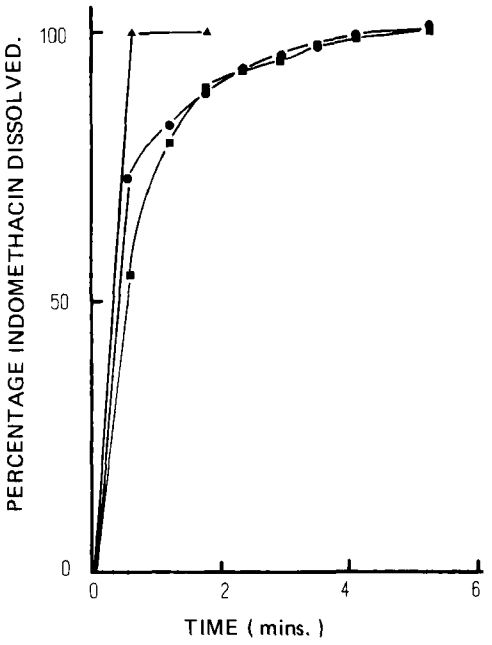

FIGURE 1. DISSOLUTION PROFILES OF THE 5% INDOMETHACIN-95% PEG 6000 DISPERSION AT 100 r.p.m.

PARTICLE SIZE
●: 500-750 microns
▲: 250-375 "
■: 125-188 "

constant surface methods from solid dispersions. The other size fractions did not aggregate at 50 rpm. but complete solution of the indomethacin was not obtained. PEG 6000 dissolved from the particles and left a hard surface layer rich in form II indomethacin from which slower dissolution occurred. These observations support the theory of Simonelli et al[16] that drug rich layers may control the release of drugs from solid dispersions.

15, 20 and 40% Indomethacin Dispersions

None of the size ranges of these dispersions displayed complete solution within 2 hours at either stirring speed (figs 3 & 4). Initial periods of rapid solubilisation of indomethacin were of short duration and complete within 5 mins at 50 rpm. and within 1 min at 100 rpm. and were followed by slower

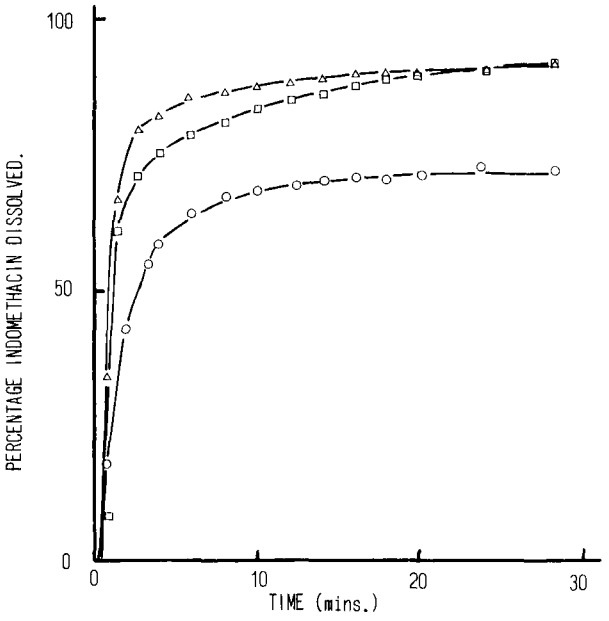

FIGURE 2. DISSOLUTION PROFILES OF THE 10% INDOMETHACIN-90% PEG 6000 DISPERSION AT 50 r.p.m.

PARTICLE SIZE
○ : 500-750 microns
△ : 250-375 "
□ : 125-188 "

dissolution from indomethacin rich surface layers. This initial rapid solubilisation became less apparent as the PEG content of the discs decreased and from particles containing 40% drug the dissolution curves were monophasic (fig. 4).

Dissolution Discussion

Dissolution rates are particle size dependant and smaller particles possess higher rates than larger particles due to the former possessing a greater surface area per unit weight. The observed differences may be explained by the fact that the 125-188 μm sized fractions were the poorest wetted fractions and floated on the water surface and that the larger particles (500-750 μm) sank to the bottom of the flask and aggregated. Such particle-size dependent dissolution can be compared with

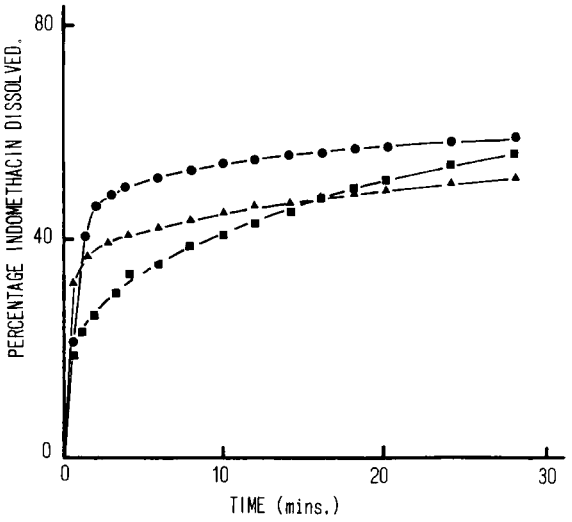

FIGURE 3.
DISSOLUTION PROFILES OF THE 15% INDOMETHACIN- 85% PEG 6000 DISPERSION AT 100 r.p.m.

PARTICLE SIZE
●:500-750 microns
▲:250-375 "
■:125-188 "

other reports on particle size effects of solid dispersions. Chiou and Niazi [17] reported that there were no differences in the dissolution rates of sulphathiazole from its melts (5 or 10% sulphathiazole in urea) between the particle size fractions 840-2000 and 150-250 μm. However the dissolution of the 10% griseofulvin-90% succinic acid dispersion increased as the particle size decreased [18]. Similar results were observed with dissolution of dispersions of phenandione (50-70%) in succinic acid [19]. Sugimoto et al [20] have however, shown that the highest dissolution rates from a 25% dispersion of nifedipine in polyvinylpyrolidone was obtained from particles of 250-300 μm rather than from 710-1410 and <105 μm sizes. It will therefore be apparent that despite solid dispersions offering increased wettability of poorly soluble drugs [13] an optimal size range still exists for maximum dissolution rates.

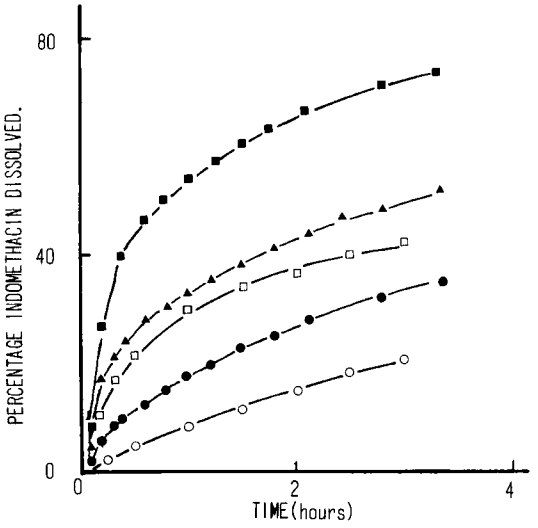

FIGURE 4. DISSOLUTION PROFILES OF THE 40% INDOMETHACIN-60% PEG 6000 DISPERSION AT 100r.p.m. AND INDOMETHACIN (125-188 microns) AT 50 & 100 r.p.m.

KEY

● : 40% INDOMETHACIN DISPERSION 500-750 microns
▲ : " " " 250-375 "
■ : " " " 125-188 "
○ : INDOMETHACIN AT 50 r.p.m.
□ : " AT 100 r.p.m.

From the dissolution profiles (figs. 1-4) estimates of the initial release of indomethacin were made and these are plotted against particle composition for the two stirring rates employed (figs. 5 and 6). At 100 rpm. (fig. 5), when the particles were generally suspended for a longer period of time, the dissolution rates rank as 250-375 μm > 500-750 μm > 125-188 μm due to the wettability previously discussed. At 50 rpm. particle size effects became less predictable since for particles containing 5% indomethacin dissolution rates ranked as 125-188 μm > 250-375 μm > 500-750 μm whereas for particles containing 10% indomethacin the release rates ranked as 500-750 μm > 125-188 μm > 250-375 μm. For comparison the dissolution profiles of indomethacin (125-188μm) at both stirring rates are included in figure 4. It may be noted that the indomethacin alone dissolved faster than the 500-750 μm 40% dispersion.

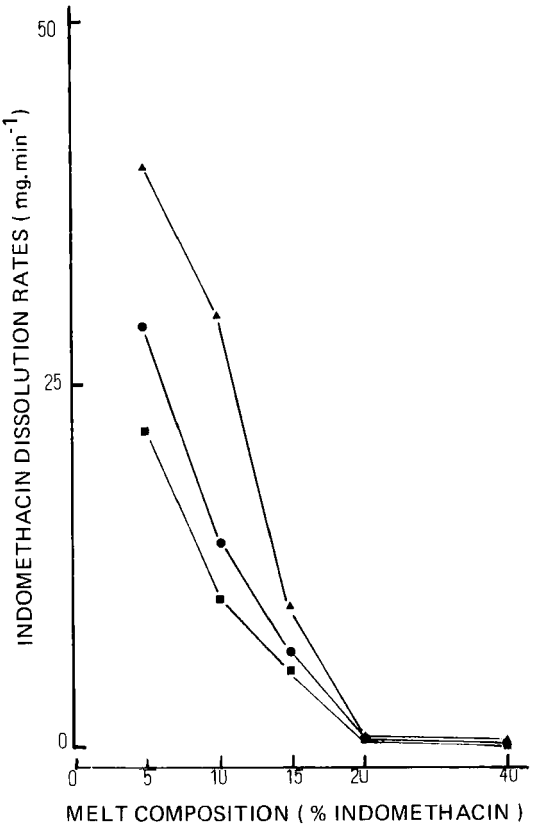

FIGURE 5. THE EFFECTS OF INDOMETHACIN-PEG6000 COMPOSITION AND PARTICLE SIZE ON THE INITIAL DISSOLUTION RATES OF SOLID DISPERSIONS AT 100 r.p.m.

PARTICLE SIZE
● : 500-750 microns
▲ : 250-375 microns
■ : 125-188 microns

Nonetheless it is clear from figures 5 and 6 that the ranking of dissolution rates in terms of composition was 5% > 10% > 15% > 20% > 40%. The 5% dispersion showed a 240-fold increase at 100 rpm. and a 1200-fold increase at 50 rpm. compared with 125-188 μm indomethacin. These differ from the increases in dissolution rates of indomethacin-PEG 6000 dispersions measured by constant surface area methodology (7). The 15% system possessed the highest dissolution rate showing a 200-fold increase over the rate of indomethacin alone, and a linear relationship existed between

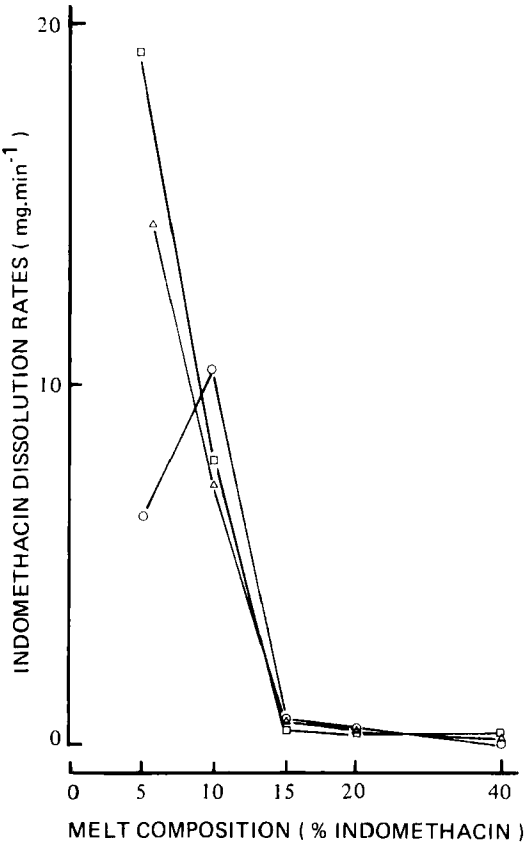

FIGURE 6. THE EFFECTS OF INDOMETHACIN-PEG 6000 COMPOSITION AND PARTICLE SIZE ON THE INITIAL DISSOLUTION RATES OF SOLID DISPERSIONS AT 50 r.p.m.

PARTICLE SIZE
○ : 500–750 microns
△ : 250–375 microns
□ : 125–188 microns

dissolution rate and disc composition for melts containing 2.5 to 15% indomethacin. At higher indomethacin concentrations the release rate dropped markedly due to the formation of poorly soluble indomethacin form II layers at the disc surface and such a phenomenom caused the decreases in release from the particulate system reported here.

GASTRO-TOXICITY DATA

Since the dispersion containing 10% indomethacin was the lowest drug content that showed aggregation at 50 rpm. this

TABLE 1

The effect of particle size on the gastro-irritancy of 10% indomethacin:90% PEG 6000 solid dispersions, 5 hours following administration of the equivalent to 6 mg/kg indomethacin.

Size fraction (microns)	Number of lesions (mean ± S.D.)	Number of rats
500-750	20.8 ± 17.1	20
250-375	14.1 ± 12.3	20
125-188	7.9 ± 5.8	30

composition was chosen for a limited study on the effects of particle size on gastrotoxicity. Elliott et al [11] have demonstrated that there are differences in the gastrotoxicity of solid-dispersed and physically dispersed indomethacin in PEG 6000. The effect of particle size on gastrotoxicity is shown in Table 1. The larger sized particles produced more gastric damage than the smaller particles. The difference in lesion score between the 500-750 μm and 125-188 μm particles was statistically significant ($p < 0.01$) but the differences between the 250-375 μm range and the other size ranges were not significant ($p < 0.25$). Cioli et al [21] demonstrated two mechanisms of indomethacin-induced gastrointestinal toxicity. These were a systemic effect due to the drug being present in the circulation and a local effect exerted by direct contact with the gastric mucosa. The increased gastric damage observed in rats treated with the 500-750 μm fraction may be due to the local irritant action of large aggregates. *In vitro*, the largest particles aggregated at 50 rpm. to form drug rich masses. Such an occurrence *in vivo* could considerably damage the gastric mucosa by direct irritation. Conversely the 125-188 μm fraction, which floated on the water surface during dissolution, may not come in contact as readily with the gastric mucosa resulting in less local irritancy than would otherwise be expected.

CONCLUSIONS

In conclusion great attention should be paid to the measurement of dissolution rates from solid dispersions. Although constant surface urea methodology provides information about the theories of drug release from solid dispersions, the influence of particle size on release is critical to both *in vitro* and *in vivo* quantification of drug release. For drugs which are gastro-irritant, e.g. indomethacin, particle-size related toxicity may be pronounced.

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