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EFFECT OF PARTICLE SIZE ON THE DISSOLUTION RATE OF MONOPHENYLBUTAZONE SOLID DISPERSION IN PRESENCE OF CERTAIN ADDITIVES

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ABSTRACT

Monophenylbutazone is a very sparingly soluble drug. The effect of particle size on the dissolution characteristics of monophenylbutazone in a dissolution medium of 0.1 N hydrochloric acid and 0.1 N hydrochloric acid to which was added 0.005% Tween 80, was carried out. The enhancement of the dissolution rate of the medicament was attained by formulating the drug in both solid dispersion and physical mixture using urea and polyethylene glycol 4000 as carriers. A comparative dissolution behaviour of the medicament in different solid dispersion and physical mixture ratios were investigated at particle size of $< 63\ \mu$. Drug-urea solid dispersion of a ratio 5:95% produced the highest dissolution rate.

INTRODUCTION

There is extensive literature to show that a decrease in particle size of sparingly soluble drugs results in increased dissolution rates owing to the increased surface area of the drug exposed to the solvent. However, control of particle size of the drug substance is very

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important to control the dissolution rate of the drug from solid dispersion if particle bonding or crushing of the drug occurs during the preparation process. The effect of the particle size of drugs on their dissolution rates and biological availability was reviewed comprehensively by Fincher (1). For drugs whose GI absorption is rate limited by dissolution, reduction of the particle size generally increases the rate of absorption and/or total bioavailability. This commonly occurs for drugs with poor water solubility. For example, the therapeutic dose of griseofulvin was reduced to 50% by micronization (2) and it also produced a more constant and reliable blood level. The commercial dose of spironolactone was also decreased to half by just a slight reduction of particle size (3). Such enhancement of drug absorption could further be increased several fold if a micronized product was used (3,4). Although the reduction of particle size can be easily and directly accomplished, the resultant fine particles may not produce the exact faster dissolution and absorption. This primarily results from the possible aggregation and agglomeration of the fine particles due to their increased surface energy and the subsequent stronger van der Waals' attraction between nonpolar molecules.

In 1961, a unique approach of solid dispersion to reduce the particle size and increase rate of dissolution and absorption was first demonstrated (5). They proposed the formation of an eutectic mixture of a poorly soluble drug such as sulfathiazole with a physiologically inert, easily soluble carrier such as urea.

Chiou and Riegelman (6) recently advocated the application of glass solutions to increase dissolution rates. The significance of the solid dispersion technique was strengthened by the demonstration of chiou and Riegelman

(7,8) of the fast and almost complete absorption of the insoluble griseofulivin in man and dogs while the commercial micronized griseofulvin was incompletely absorbed (30-60%). They used polyethylene glycol 6000 as a dispersion carrier. The main advantages of using water-soluble polymers as carriers are their nontoxicity and general applicability to most drugs.

The purpose of this work is the study of the effect of particle size in the dissolution rate of monophenylbutazone from its solid dispersion and physical mixture using urea and polyethylene glycol 4000 as water soluble carriers. The relative change in the particle size of the drug, the preparation of solid dispersion and physical mixture processes was assessed by comparing the dissolution rates of the drug particles before and after preparation of the systems, since a change in the particle size of the drug will be reflected by a change in the dissolution rate.

EXPERIMENTAL

Materials

The following materials were used :
Monophenylbutazone was obtained from El-Nile pharmaceutical Co., Cairo, A.R.E. Tween 80, from Atlas chemical Ind. Delaware, USA. Polyethylene glycol 4000, from Hoechst Co. Urea (analar), from El-Nasr Co. A.R.E.

METHODS

Preparation of Solid Dispersion

The melting procedures were used as follows :
PEG 4000 or urea, were accurately weighed, powdered and melted in a suitable porcelain dish. The calculated amount of the powdered drug was then accurately weighed and added to the melted carrier with constant stirring.

The melted mixture was cooled and solidified rapidly in an ice bath. The product was placed in a dissicator over silica gel. The final solid was crushed and separated into different size fractions by dry sieving. Four different sieve fractions were considered. These were : more than 400 μ, 200-400 μ, 63-200 μ and less than 63 μ mesh diameter. This process was done with the medicament powder, solid dispersion systems and physical mixtures.

The mean particle size was obtained by using a double image shearing microscope when 200 particles were sized. The drug carrier ratio was calculated according to the eutectic composition and at different ratios of drug-carrier (5:95; 50:50 and 80:20). The physical mixture was prepared by gently triturating appropriate quantities of drug and carrier in a glass mortar.

Dissolution studies :

Dissolution rates of solid dispersions and physical mixtures were studied in 250 ml 0.1 N hydrochloric acid and 35^{O}, while the dissolution rate of the pure drug was studied in both 0.1 N hydrochloric acid and the same medium to which was added 0.005% Tween 80. The USP dissolution rate apparatus was used for the dissolution rate studies.

The calculated amount of the powdered drug solid dispersions or physical mixtures of different particle size was rapidly introduced. The absorption of monophenylbutazone was read at 258 nm. 2 ml samples were removed as a function of time and analysed for drug content. Two ml of the dissolution medium was added back to the beaker after each sampling. All smaples were carried out in triplicate, from which the mean values were calculated.

RESULTS AND DISCUSSION

The dissolution profiles, shown in Figure 1 representing the effect of particle size on the dissolution rate of monophenylbutazone-urea or polyethylene glycol 4000 solid dispersion in 250 ml solution of 0.1 N hydrochloric acid, in comparison with that of the drug in both the dissolution medium and the dissolution medium containing 0.005% Tween 80. Results illustrated in figure 1 indicate that the dissolution tendency of the medicament increases as the particle size decreases. This was noticed in case of the drug alone with 63-200 and 200-400 μ particles. While a decrease in the dissolution rate began to occur with 63 μ particles which run opposite to the expected enhancement of dissolution rate of the medicament as the specific surface area increases. This contradiction may be due to either one or both of the following postulations. The first, as the particle size of the powder decreases, the powder exhibits more cohesive tendencies resulting in dispersion defficulties due to aggregation in aqueous media under the slow rate of stirring in the dissolution procedures. The second, as the particle size of the powder decreases, the surface energy of the particles greatly increases which results in adsorption of a surface film of air, thus rendering the surface of the particles more hydrophobic, not easily wetted and floating on the air/Liquid interface of the dissolution media. Thus, although the specific surface area of the medicament is increased in more fine powders, the effective surface area is reduced with a resultant reduction in the dissolution behaviour of the smaller size of the medicament used in this investigation. To verify these assumptions, the dissolution behaviour of the different sieve fractions of monophenylbutazone powder was determined in the dissolution medium to which

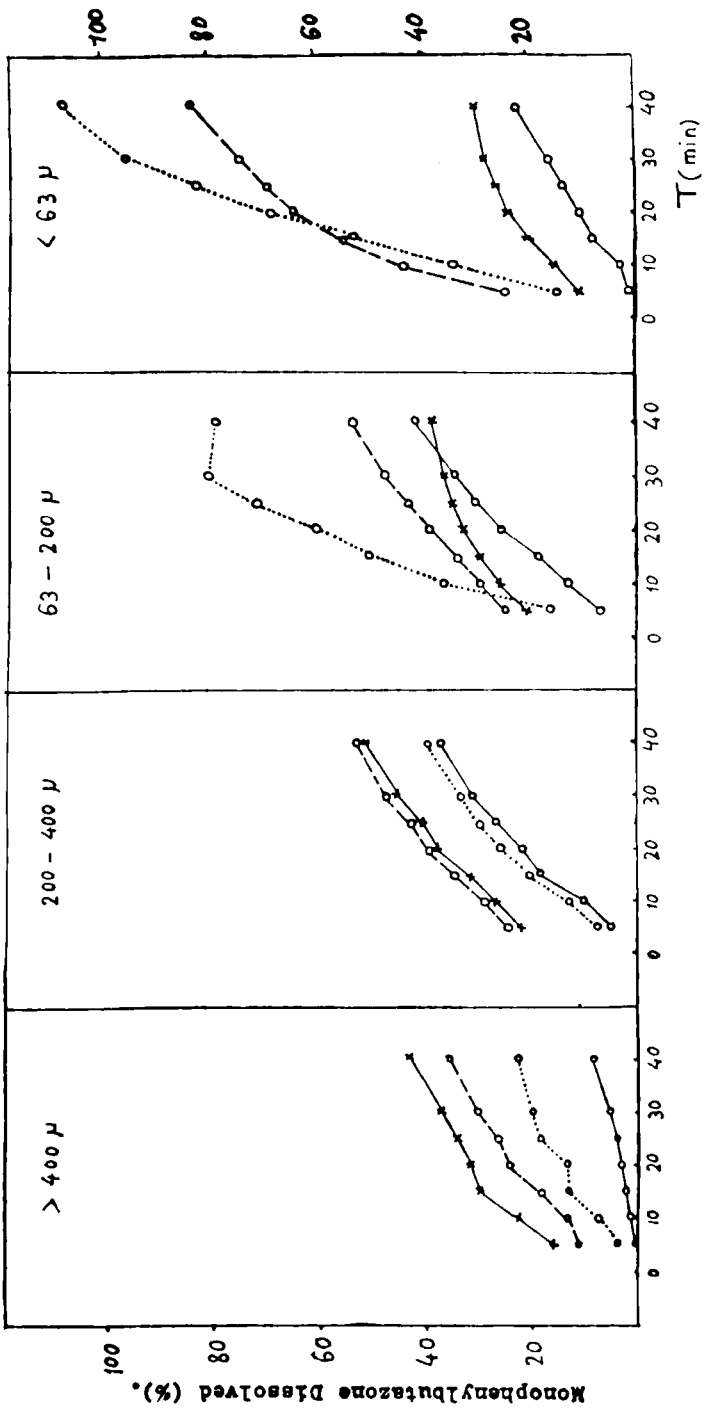

FIGURE 1

Effect of particle size on the dissolution rate of monophenylbutazone
o—o in 0.1 N Hcl; o·····o in 0.1 N Hcl containing 0.005% tween 80;
o- - -o solid dispersion with urea and x——x solid dispersion with PEG4000 (at eutectic ratio).

0.005% Tween 80 was added. Finholt and Solvang (9) showed that the effect of surfactants on the mass transfer of drugs was mainly due to their ability to decrease the interfacial tension between the drug and the dissolution medium, and only to a small extent to the solubilizing power of the surfactant. It is clear from the results that in presence of surface active agent, the dissolution rate of the medicament from the different sieve fractions increases as the powder becomes more fine, this is contrary to the results obtained in absence of Tween 80 specially with 63 μ particles. Figure 1 reveals the influence of Tween 80 on the dissolution efficiency/particle diameter correlations and illustrates that in presence of Tween 80, the specific surface area of the drug particles controls drug dissolution. Thus, it can be concluded that size reduction of monophenylbutazone increases the specific surface area, but brings about a simultaneous and more pronounced reduction of the effective surface area which out weighs the effect of increased surface area. The findings indicated the uselessness of the approach of simple particle size reduction to enhance the dissolution rate of monophenylbutazone probably due to the exaggerative of secondary attractive forces acting on the surface. Accordingly it would be plausible that such an approach would help only if particle size reduction is coupled with modification of the surface properties of the powder by inclusion in matrix materials. This what was happened in this study. The phase diagram of monophenylbutazone- urea system reveals a pattern which is typical for simple eutectic mixtures. The eutectic composition in this case is : monophenylbutazone 90% and urea 10%, the eutectic point is 85°. For monophenylbutazone-polyethylene glycol 4000 system, the eutectic composition is : monophenylbutazone 30% and PEG 4000, 70% the eutectic point is 54°. Figure

1 illustrates the dissolution profiles of the various sieve fractions of monophenylbutazone-urea solid dispersion. It is clearly evident from the obtained results that the dissolution of monophenylbutazone from its solid dispersion with urea at eutectic composition was enhanced as compared to a control sample of medicament powder. The dissolution rate of the medicament from the solid dispersion varies according to the sieve fraction used. It increased with the reduction of particle size. This behaviour can be attributed to the rapid dissolution of urea in the solid dispersion of the more fine powder.

The amount of the medicament dissolved from various sieve fractions of monophenylbutazone-PEG 4000 solid dispersion of eutectic composition in comparison with that of the drug powder is represented also in Figure 1, It is clear that the amount dissolved was greater as compared to that dissolved from a control sample of monophenylbutazone powder. The dissolution rate of the medicament from the solid dispersions varies according to the sieve fraction used. It increased with increasing the particle size up to a sieve fraction of 200-400 μ, beyond which (>400 μ) the dissolution rate decreased. This enhancement in dissolution of a comparatively coarser sample of the solid dispersion sieve fraction 200-400 μ, might be attributed to that the carier, PEG 4000, in this case dissolves with a comparatively low rate from the matrix and thus counteracting the aggregation for a longer time and facilitating dissolution. While in particle size >400 μ the decrease in dissolution rate is due to the decrease in the surface area subjected to the dissolution medium.

Figure 2, compares the dissolution behaviour of monophenylbutazone from solid dispersions and physical mixtures. All samples being of the same sieve fraction

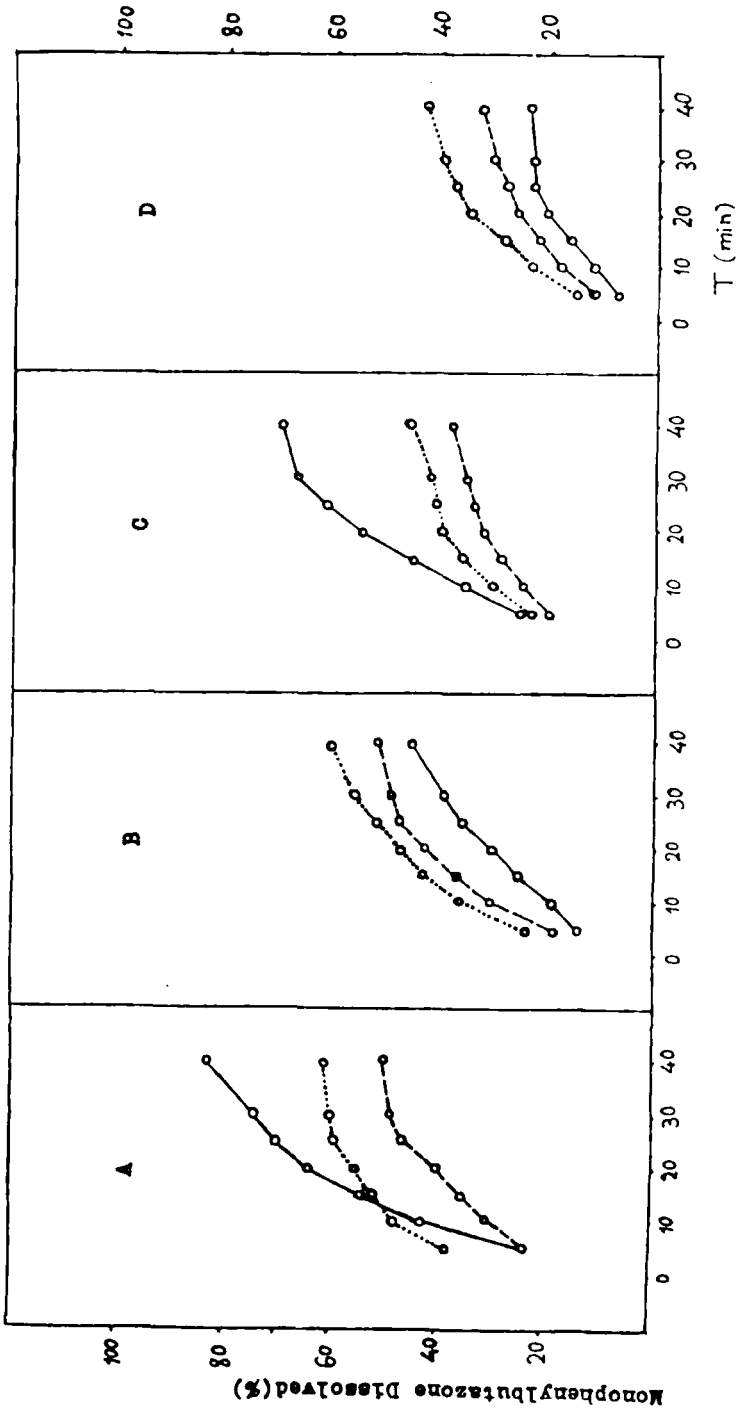

FIGURE 2

Dissolution rate of different ratios of monophenylbutazone solid dispersion and physical mixture at particle size < 63 μm, o—o 5% drug, 95% Carrier, o·····o 50% drug, 50% Carrier, o— —o 80% drug, 20% Carrier. A &B, drug-Urea solid dispersion and physical mixture respectively, C&D drug- PEG 4000 solid dispersion and physical mixture respectively.

(< 63 μ). The drug carrier ratios were : 5: 95, 50:50 and 80:20. It is evident that the dissolution rate of the medicament from the solid dispersions with either urea or PEG 4000 was higher than that from the corresponding physical mixtures. The dissolution rate of the medicament from the solid dispersion of the drug-carrier ratio 5:95% is markedly higher than that of the composition 50: 50. The ratio of 80: 20 gave the least dissolution rate of the medicament. In case of physical mixtures: the composition 50:50 produced the highest dissolution rate followed by the composition 80:20 and then 5:95%.

The drug-urea either solid dispersions or physical mixtures in the different compositions produced generally higher dissolution rates than that produced with PEG 4000. This may be due to the higher solubilizing effect of urea towards monophenylbutazone. On the other hand, the general increase in the dissolution rate of the solid dispersion of the drug more than that of the corresponding physical mixture may be attributed to the increase in the effective surface area of the medicament in these dispersions. In conclusion, where the dissolution rate is affected by particle size, the present investigation shows that, factors other than initial particle size need to be controlled in order to get a reproducible rate of the drug.

The nature and proportion of the carrier, the manufacturing process, i.e. solid dispersion or physical mixture, and the presence or absence of surfactant may all influence the particle size in the final product and thus apparently minor changes in formulation and manufacture may have a significant influence on the efficacy of the product.

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