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# THE INFLUENCE OF VARIOUS DISPERSING AGENTS ON THE DISSOLUTION RATE OF HYDROCHLOROTHIAZIDE

Deshpande, A. V. & Agrawal, D. K.

Department of Pharmaceutics
Faculty of Pharmaceutical Sciences
Ahmadu Bello University
Zaria (Nigeria)

## ABSTRACT

The solvent and melt methods were employed to prepare solid dispersions with various water soluble carriers and sparingly soluble drug, hydrochlorothiazide. The carriers investigated included dextrose, sorbitol, tartaric acid and urea. Dispersion with urea was superior to other carriers in releasing the drug into solution. Dextrose - melt showed decomposition of the drug. Sorbitol drug physical mixture produced a faster rate of dissolution of the drug than the melt dispersions. The eutectic mixture of urea and drug cooled at room temperature ($28^{o}$) produced a faster dissolution rate of the drug than the mixture cooled at $-2^{o}$.

## INTRODUCTION

It is well established that dissolution is frequently the rate limiting step in the gastro-intestinal absorption of a drug from a solid dosage form. The relationship between solution rate and absorption is particularly distinct when considering drugs of low solubility.

Burner and Tolloczke (1) were the earliest workers to show that dissolution rate was a function of the surface area exposed to the dissolution medium. Accordingly, a drug will dissolve more rapidly when its specific surface area is increased i.e. decreased particle size. Leavy (2) has considered a number of methods by which drug may be exposed to the gastro-intestinal fluid in finely divided form. The most common and direct method is the micronization of the particles which may be administered as a dosage form. This particular approach has got disadvantage of wettibility which may lead to erratic and incomplete absorption. A second method involves administration of drug from solutions from which, upon dilution with gastric fluids, the dissolved drug will precipitate in the form of fine particles; but this may not solve the problem of stability if it is likely to occur. Recently more unique ways of increasing the dissolution rate have been reported by dispersion techniques and by adsorption

on various clays. These techniques have been considerably used by various research workers (3 - 16). The definitions, methods of preparation and pharmaceutical applications of these dispersions were thoroughly reviewed by Chiou and Riegelman (17).

In our previous investigation (18) we had taken six benzothiadiazine derivatives (one of them was hydrochlorothiazide) and polyethylene glycol 6000, as a carrier for increasing the dissolution rate. We observed that bendroflumethiazide and methylclothiazide showed decomposition by either methods, while chlorothiazide, hydrochlorothiazide, flumethiazide and cyclopenthiazide showed excellent increase in dissolution rate without any decomposition. Based on these facts, we have decided to carry out further investigations using one drug and different carriers. Thus the present communication examines five water soluble carriers, dextrose, PEG 6000, sorbitol, tartaric acid, and urea, and compares the dissolution characteristics of pure drug vis-a-vis solid dispersions prepared by either solvent or melt methods, employing the slightly soluble hydrochlorothiazide as the model compound.

## EXPERIMENTAL

Materials - The following materials used were of highest purity and were obtained from standard sources viz. -

dextrose, PEG 6000, sorbitol, tartaric acid, urea and hydrochlorothiazide.*

Preparation of samples - Dispersions with each carrier and hydrochlorothiazide were made either by solvent or melt methods (depending upon the stability of the hydrochlorothiazide by either of the process) as described earlier (18).

The dispersed mixture of the drug with tartaric acid was prepared by coprecipitate method while with urea, sorbitol and PEG 6000, melt method was used. The drug dextrose dispersion prepared by either of the method was found to be unstable after drying. The eutectic composition of urea and the drug were also prepared by melt method but were cooled at two temperatures - one at 28° and the other at -2°. The rest of the procedure was followed as mentioned earlier (18). The details about method, composition, carrier and other parameters are shown in table 1. The dried mixtures were pulverized and after sieving, the fraction which passed through sieve 350 μm and retained on sieve 250 μm was further considered for dissolution studies.

Dissolution studies - The dissolution rate studies were carried out as described earlier (18) by using 50 mg. of pure hydrochlorothiazide and solid dispersions contain-

*Supplied by Ciba-Geigy, Basel, (Switzerland).

Table 1. Time in Minutes for 50 and 75 Percent of the Drug Hydrochlorothiazide to Pass into Solution from Solid Dispersions

| Carrier | Ratio of Drug: Carrier | Method | $T_{50}$ a | $T_{50}$ b | $T_{75}$ a | $T_{75}$ b | Remarks |
|---|---|---|---|---|---|---|---|
| Dextrose | 1:20 | Melt and coprecipitate | - | | - | | Significant decomposition |
| PEG 6000 | 1:20 | Melt | 17 | 46 | 28 | 60 | |
| Sorbitol | 1:20 | Melt | 55 | 42 | 70 | 58 | |
| Tartaric acid | 1:20 | Coprecipitate | 25 | 60 | 40 | 75 | |
| Urea | 1:20 | Melt | 1 | 42 | 1.6 | 60 | |
| Urea | Eutectic mixture | Melt cooled at room temp. | 12 | 70 | 36.5 | 120 | |
| Urea | " " | Melt cooled at $-2^{\circ}$ | 60 | 60 | | | |
| Control | 1:0 | | 60 | 80 | | | |

a - Processed drug

b - Physical mixture.

ing equivalent amount of the pure drug. A fixed amount of the dissolution media was withdrawn at fixed time intervals and was replaced by equivalent amount of same media maintained at 37°. After appropriate dilution with water, the absorbance was recorded at 317 nm. A control experiment was also run using same amount of the pure drug of same particle size.

Following the same procedures the physical mixtures of drug and carrier were subjected to dissolution rate studies.

Eutectic mixtures of urea and drug were also considered for dissolution rate studies. This experiment was conducted to study the effect of cooling temperature on dissolution rate of the eutectic mixture. The reported data is the average of at least duplicate runs and results were reproducible.

## RESULTS AND DISCUSSION

Solid dispersion of PEG 6000 and Sorbitol - Polyethylene glycol 6000, has been extensively used for preparing solid dispersions with both liquid (19) and solid drugs (9, 11, 13) and has been shown to increase the dissolution rate of poorly soluble drugs. We have earlier observed (18) that dispersions prepared by corprecipitate method with PEG 6000 did not dry completely even when they were kept for almost 6 to 7 weeks. The release rate of hydrochlorothiazide from

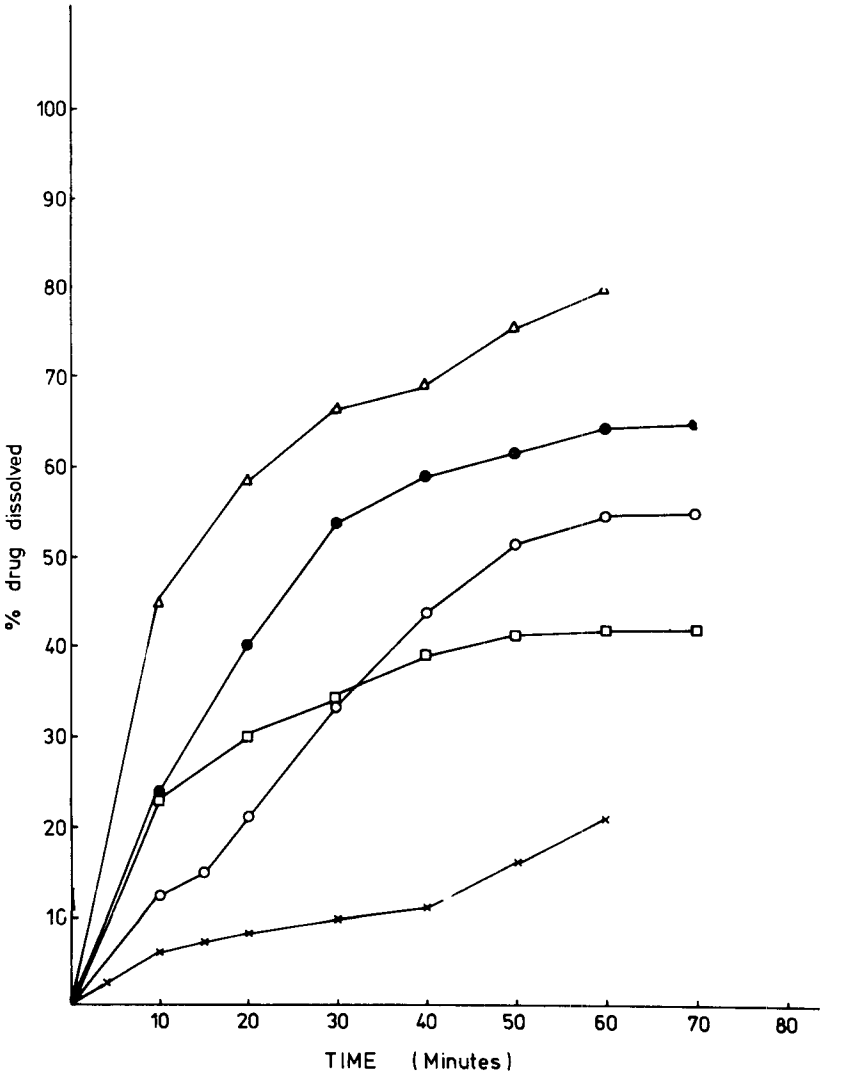


FIGURE 1

Dissolution profiles of hydrochlorothiazide, hydrochlorothiazide - PEG 6000 and hydrochlorothiazide - sorbitol dispersions. × Pure hydrochlorothiazide. △ PEG 6000 melt. ● PEG 6000 physical mixture. ○ Sorbitol physical mixture. □ Sorbitol melt.

melt dispersion is shown in fig. 1. Chiou and Riegelman (9) found that in the griseofulvin PEG 6000 system, drug release was fastest from dispersion prepared by melt method. These findings are quite contradictory to those reported by Mcginity et. al (20) who have shown faster dissolution of sulphabenzamide and indomethacin by coprecipitate technique. These particular reports could not be compared with our findings due to non drying of the coprecipitate dispersed mixtures. However, the slower dissolution rate of PEG melt as compared to dispersed mixture prepared by using urea as a carrier by the same method, could be due to the fact that the drug might have embedded in the matrix of the glycol as a result of the melt method, and the release of the drug could be achieved by two possible mechanisms including the diffusion of drug from undissolved glycol and the dissolution rate of PEG 6000 itself (24). It is proved that the dissolution of PEG 6000, is much slower than urea under experimental conditions, possibly this might be one of the reasons for faster dissolution of urea-hydrochlorothiazide dispersed mixture.

Mannitol as a dispersing agent has been considerably used in increasing the dissolution rate (21), but on the other hand sorbitol has not been tried so often. This might be due to the problem of its poor solu-

bility in common solvents and charring at high temperature. In our findings, sorbitol has shown to form two immissible phases upon solidification from the liquid state. The dissolution rate of the drug from melt was not significantly increased, which might be due to the fact that hydrochlorothiazide was not completely dissolved in sorbitol; and due to the formation of two immissible phases instead of clear glass solution. It is interesting to note that the physical mixture of the same composition of sorbitol and drug have shown faster dissolution rate than the processed drug fig. 1. This might be due to the complex formation between drug and sorbitol, which has shown poor solubility. Further studies are being currently carried out to investigate the reason behind poor solubility of sorbitol drug dispersed mixture.

Solid Dispersion with Urea - Urea as dispersing agent for increasing the dissolution rate of poorly soluble drug has been well demonstrated (2, 5, 8, 23). Fig 2 shows the great increase in the dissolution rate of hydrochlorothiazide. As a matter of fact, urea has shown by far the best result when compared with other carriers. Further in over-all operation of preparing samples, urea did not pose any problem. On this criteria therefore, it was decided to prepare eutectic

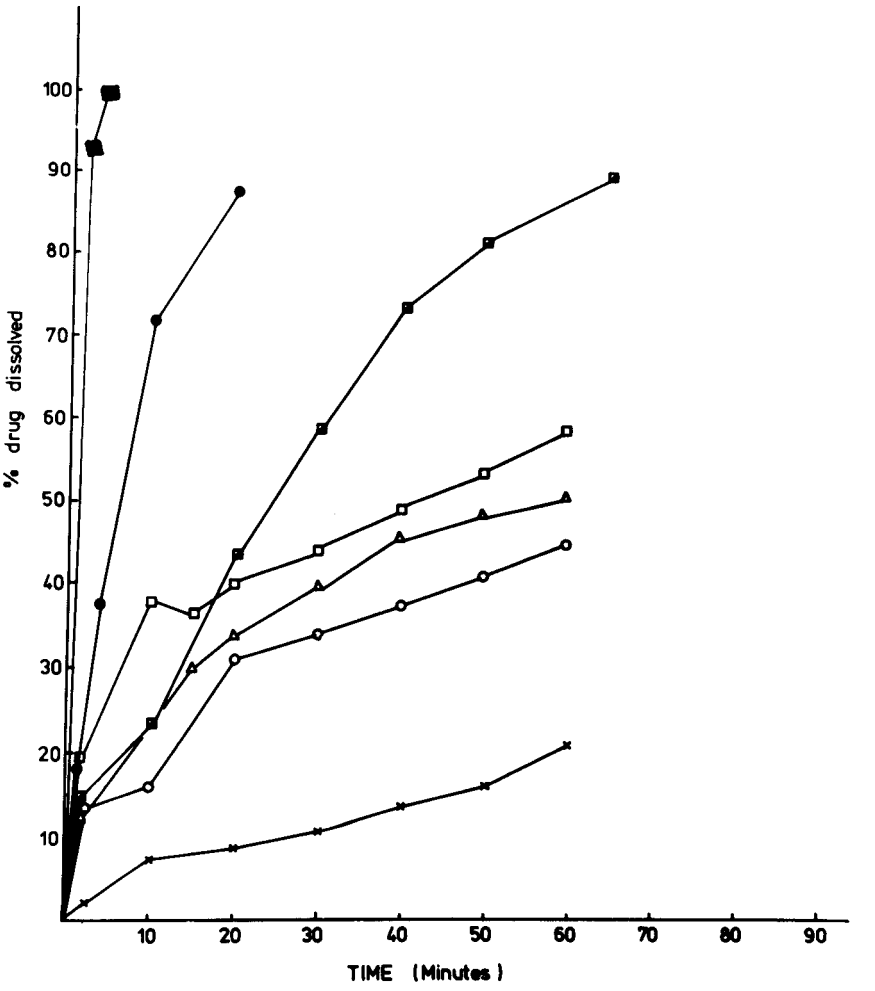


FIGURE 2

Dissolution profiles of hydrochlorothiazide, hydrochlorothiazide - urea, and hydrochlorothiazide-tartaric acid dispersions. × Pure hydrochlorothiazide. ■ Urea melt. ● Eutectic mixture with urea cooled at room temp. ○ Eutectic mixture with urea cooled at -2°. □ Urea physical mixture. ◪ Tartaric acid co-ppt. △ Tartaric acid physical mixture.

mixture of the drug and study the effect of cooling at two different temperatures. The dissolution studies of eutectic mixture prepared either at $28^{o}$ and $-2^{o}$ did not show any significant improvement in dissolution of the drug over drug urea melt prepared initially at 10% concentration. But it was observed that the method of preparation of eutectic mixtures may have a significant effect on the efficiency of this techniqu for particle size reduction. In our findings (fig. 1), the eutectic mixture cooled at room temperature have shown faster dissolution rate than the same mixture cooled at $-2^{o}$. This significant difference in dissolution could be due to the difference in type and shape of crystals formed during the process of cooling. It is a well known fact that, sudden cooling results in formation of bigger and non uniform crystals as compared to slow and uniform cooling which results in uniform size and shape of crystals. In our case it might be true also, in addition to that, urea might have formed crystals faster than the drug and this might have resulted in formation of two layers of crystals i.e. one of the urea itself and other that of the drug. In dissolution this combination seems to have shown poor dissolution though these facts are not yet proved experimentally. So presently studies are being carried out on the nature of the crystals formed by eutectic mixture when

cooled at different temperatures and its effect on the over-all dissolution, and also the type of solution it has formed if any.

Solid dispersion with Tartaric Acid - Melt samples of the drug and tartaric acid showed degradation of the drug. Alternatively coprecipitate method was tried of which the results are shown in fig. 2. Chiou and Riegelman (9) showed citric acid to be an excellent carrier for griseofulvin and also superior to PEG 6000 with the same drug, however, in this case PEG 6000 has shown better dissolution characteristics than tartaric acid.

## SUMMARY AND CONCLUSION

A comparison of coprecipitate and melt methods and soluble carriers used to prepare solid dispersions on the dissolution rate of hydrochlorothiazide showed that melt of hydrochlorothiazide and urea were superior to all the other dispersions prepared by either method. Sorbitol and hydrochlorothiazide physical mixture showed better dissolution than the processed drug with the same carrier. The eutectic mixture did not show any superior property of dissolution in this study. It is significant to note that the melt of urea and the drug shows the free flowing property of the powder, so this processed drug can be further developed for practical applications.

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