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SOLID DISPERSION CONTROLLED RELEASE: EFFECT OF PARTICLE SIZE, COMPRESSION FORCE AND TEMPERATURE

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ABSTRACT

Solid dispersions are dynamic systems, a careful control of processing variables is required to produce desired physico-chemical properties of these systems.

The influence of drug particle size, dispersion temperature and compression force on the release rate of theophylline from solid dispersed system tablets was studied. Theophylline base (micronized and granulate) were embedded into a polymeric mixture of PEG and acrylic/methacrylic esters at controlled temperature and shock cooled. Tablets were made at two compressional forces and drug release was measured spectrophotometrically over a period of fifteen hours.

The release rate of drug dispersed in these insoluble matrices was independent of particle size but not of hardness.

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However, variations in ratios of polymeric mixture and dispersion temperature controls the drug release rate from inert matrix more effectively than such factors as drug particle size and lower range of tablet hardness. The fast cooling produced excellent reproducibility of drug content throughout the entire entrapment product. X-ray diffraction study demonstrated no changes in crystalline form of theophylline.

INTRODUCTION

A number of reviews have been published on the problems of controlled drug delivery,[1,2,3,4,5] and the theoretical advantages of controlled release for a variety of drugs are well documented.[6,7,8,9] In order to ensure a constant rate of release of a given drug it is desirable that zero-order kinetics should apply to the system. In general the drug may be physically incorporated into a polymeric matrix and compressed. Solid dispersion techniques have obvious applications in providing a homogeneous distribution of the drug together with ease of mixing, reproducibility, predictability and control of release profiles.[10,11,12]

Drug release from solid dispersions in insoluble polymeric matrices is dependent on the rate of drug diffusion and usually follows the square root law equation.[13] Recent studies of such dispersions have shown that soluble complexes are formed. The difference in crystallinity between solid dispersions and physical mix of drug and carrier has also been demonstrated.[14,15] The cooling conditions of molten dispersed systems influences the release kinetics,[16] due to change in polymorphic properties of the drug.

It is difficult to control rate of drug release from solid dispersed systems. Release kinetics are directly influenced by formulation and physico-chemical factors. In a solid dispersed system dynamic events are complex and optimization of preselected

delivery rate may only be achieved by careful control of processing parameters.

This paper is concerned with the effects of formulation and those important parameters which may influence the dissolution profile of Theophylline from insoluble polymeric matrices into an aqueous environment. Theophylline was chosen because of its low solubility, ease of assay, and short half life, although many problems have been reported in producing controlled release dosage forms.

MATERIALS AND EQUIPMENT

The following materials were used; PEG 6000 (BDH-Chemical Ltd., Poole, England), Ethyl cellulose (Hercules Powder Company Ltd.), Eudragit retard - BN 70041 and Theophylline crystals commercial grade, Lot 1028 and 51647. U.V. spectrophotometer-Perkin Elmer 554, Manesty tablet machine type F3, Hardness tester (Engineering systems CT40 Nottingham), x-ray diffraction type pw 1120/90, (Phillips, England). Theophylline size analysis was performed using a HIAC-PA720, 24 channel particle size analyser[17] (Northey Int. Systems Ltd., London).

EXPERIMENTAL

Two formulae were used for compression as shown in Table 1. PEG 6000 and ethyl cellulose were melted and mixed in a china dish on a hotplate at controlled temperatures of 75°, 85° and 90° for 10 minutes. Methacrylate polymer was added to the homogeneous melt and mixed for a further 10 minutes. Then, theophylline was added to the molten mixtures and stirring continued for another 10 minutes at the selected temperatures to achieve a uniform distribution.

The mixtures were immediately poured onto glass plates, maintained at 0°C and allowed to congeal. Each solidified mass was transferred to a ceramic mortar and finely ground for 15

TABLE 1.

FORMULAS USED

	I	II
Theophylline	20	20
PEG 6000	55	40
Ethyl cellulose	10	15
Acrylic/Methacrylic Esters	15	25

Quantities listed are percentage by weight.

minutes and then sieved. The fraction finer than 420μm was used. The resultant powder was compressed at two pressures using a round convex punch 7.5mm diameter on a Manesty type F3 tablet machine. Tablets were produced weighing 200mg and having hardnesses of 3.5 and 4.8 kg. Uniformity of tablet weight and hardness were within 5 per cent.

TESTING

Release profiles were obtained immediately after tablet manufacture. Rate of release was monitored using a flow-through UV spectrophotometric technique, under sink conditions, with distilled water as dissolution medium.

For each determination a tablet was placed in a basket rotated at 60rpm, the dissolution medium maintained at 37°C, and spectrophotometric measurements made at 271nm. It was found that the presence of other ingredients used in the formulation did not interfere with the drug assay.

RESULTS AND DISCUSSION

Particle size profiles by volume for granulated and micronised samples of theophylline with their median values are given in figure 1.

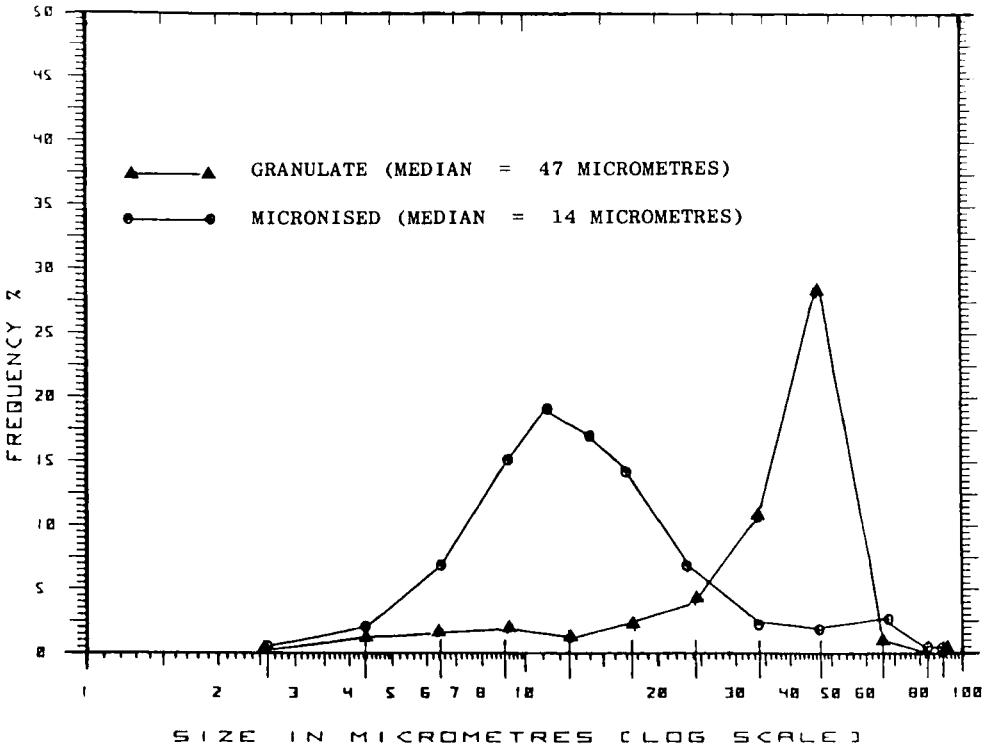


FIGURE 1 Particle size distribution curves for granulated and micronised samples of Theophylline with median values.

Table 2 shows the values for theophylline content, hardness and weight of tablets. The consistency of theophylline content in both formulations I and II indicates the uniform distribution of the drug.

The dissolution curves obtained are shown in figures 2 - 5 and are typical release profiles. The characteristics of these curves reflect the parameters involved such as polymer concentration and hardness, in agreement with previous reports.[18]

Figure 2 shows the influence of hardness on drug release from tablets of two formulations produced to give low (3.5 kg) & high (4.8 kg) hardness. It is to be expected that hardness would

TABLE 2.

Theophylline content, Hardness & Weight

FORMULATION	DISPERSION TEMPERATURE °C	Theophylline content/tablet ± SD[a] (% weight) MICRONIZED	Theophylline content/tablet ± SD[a] (% weight) GRANULATE	Hardness kg[b] LOW	Hardness kg[b] HIGH	Weight mg[c]
I	75°	19.5 ± 0.8	19.8 ± 0.4	3.5	4.75	205
	85°	19.7 ± 0.5	19.7 ± 0.7	3.5	4.8	200
	90°	19.6 ± 0.4	19.9 ± 0.4	3.6	4.82	202
II	75°	19.5 ± 0.9	20 ± 0.6	3.45	4.82	206
	85°	20.2 ± 0.3	19.7 ± 0.5	3.55	4.8	205
	90°	19.4 ± 0.4	19.4 ± 0.6	3.52	4.8	202

(a) Average of 5 determinations (Theoretical = 20%), (b) & (c) are average of 10 determinations.

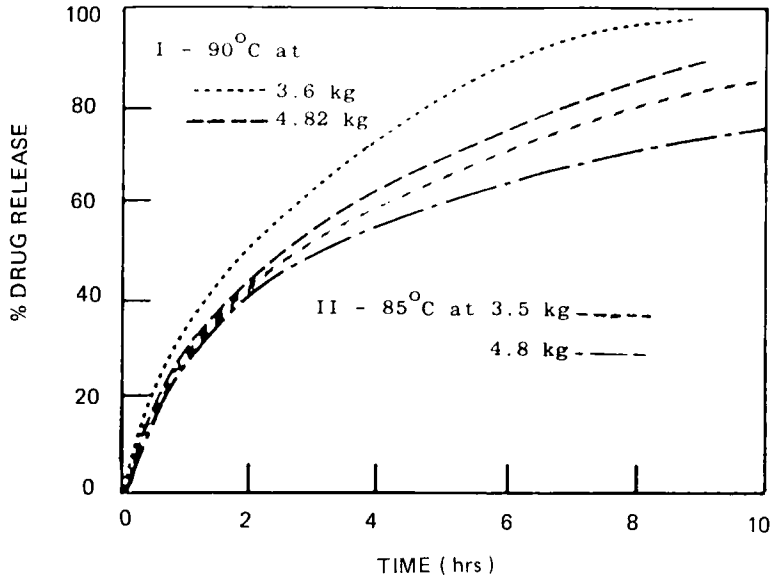


Fig. 2 RELEASE CURVES FOR EACH OF THE COMPRESSED SOLID DISPERSED POLYMERIC SYSTEMS (FORMULATION I & II).

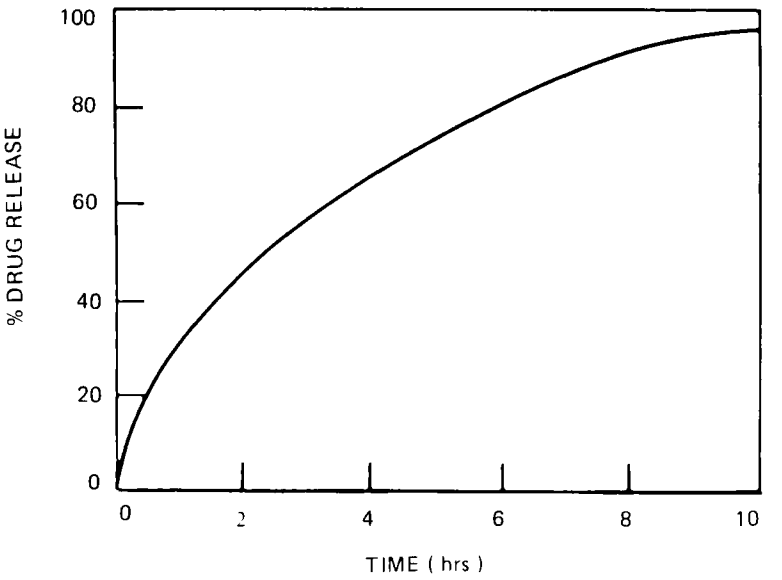


Fig. 3 AMOUNT OF THEOPHYLLINE RELEASED VERSUS TIME FOR TABLETS PREPARED AT 3.55 kg (FORMULATION I AND 90°C, MICRONIZED AND GRANULATE).

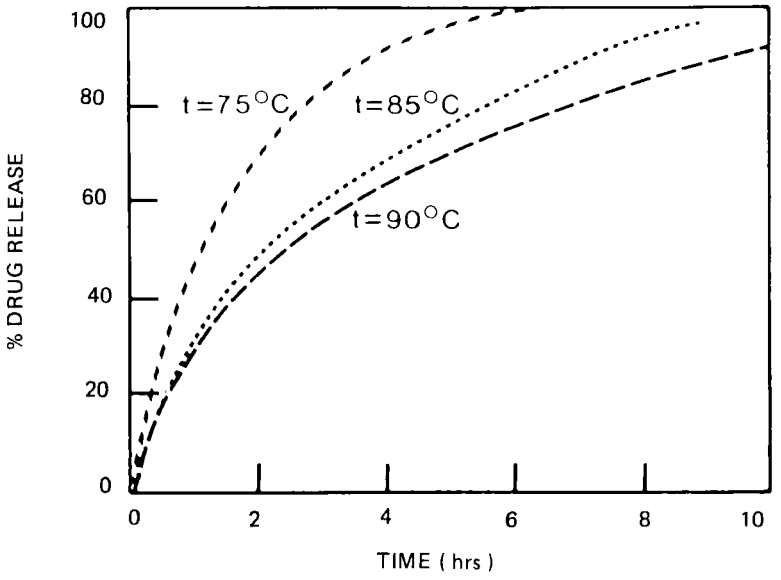


Fig 4 EFFECT OF DISPERSION TEMPERATURE ON RELEASE RATE OF THEOPHYLLINE FROM TABLETS PREPARED AT 3.5Kg, FORMULATION I.

affect the rate of release, as porosity and degree of tortuosity in the system influences the release rate kinetics.

Figure 3 gives the release profiles from tablets prepared at 3.55 kg, formulation I, 90°C, using micronized and granulated theophylline base. Particle size did not affect rate of drug release from tablets, however, when the same quantities of micronized and granulated theophylline base, as such, were dissolved in water at the same temperature (37°C), higher concentrations of the micronized drug went into solution. Thus, in the solid dispersion technique described the solubility of the granulated drug is as high as that of the micronized. This phenomena has been described elsewhere for other low soluble drugs.[19]

Figure 4 indicates the influence of dispersion temperature during processing. Release rate kinetic changes are significant,

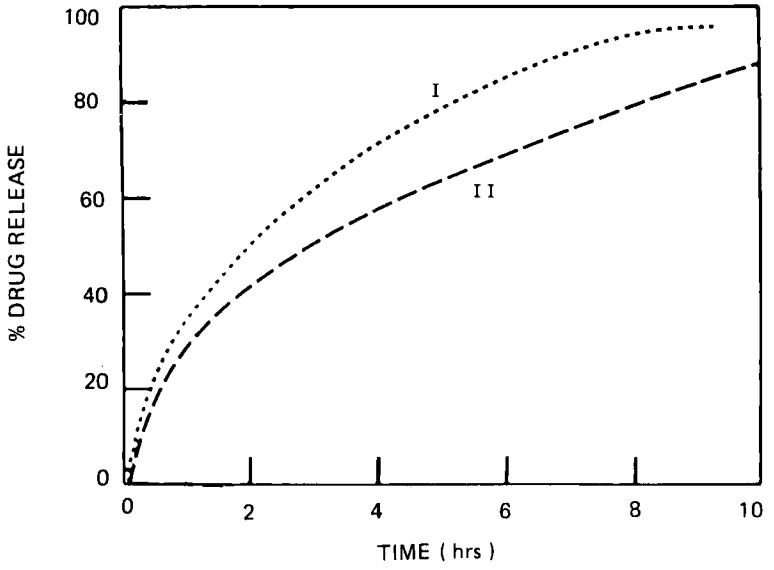
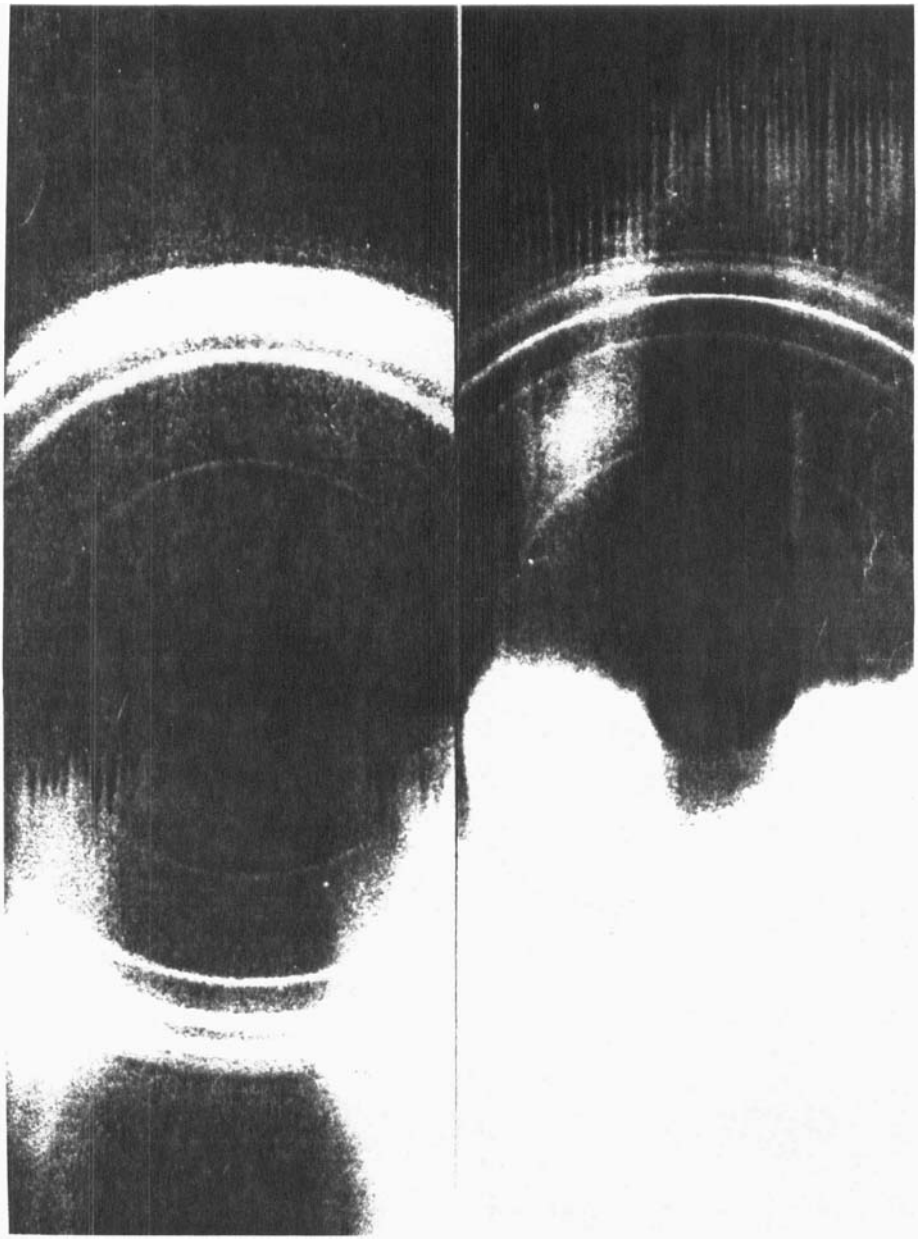


Fig. 5 EFFECT OF FORMULATION COMPONENTS ON DRUG RELEASE FROM POLYMERIC MATRICES (FORMULATION I AND II AT 3.5Kg AND DISPERSION TEMPERATURE OF 85°C.

such that, at higher dispersion temperature an increase in the relative flatness of the pseudo-steady state portion of the curves improves markedly with time. This situation could be explained since, at higher temperature drug particles dissolve or disperse at equilibrium in the matrix. The solid particles held within the polymeric system allow a high level of dispersion and a large surface area to be achieved forming a unique reservoir for drug entrapment. The release of the drug from this device is of a desorption type following the usual square root law kinetics.

Figure 5 illustrates the release profiles from tablets containing various concentrations of polymers at one hardness. Prolongation of release is enhanced by increasing the polymer concentration. The release pattern approaches a limiting value as polymer concentration increases and work is in progress to elucidate this relationship.



A Figure 6 B

X-ray diffraction patterns of Theophylline, (A) before melting. (B) after it has been shock cooled.

X-ray diffraction patterns of theophylline used were taken from samples that were shock cooled, figure 6. The rate of cooling did not influence the crystallinity of theophylline as identified from x-ray diffraction profiles which remained constant. However, to a large extent drug is embedded amorphously in the polymers.

CONCLUSIONS

The production of solid dispersions may present a thermodynamically more active form of drug substance and directly influences the diffusion and release rate.

In design of these delivery systems, balancing the ratio of polymers (hydrophilic or lipophilic) must be coupled with the variables by which active drug is entrapped, along with the influence of physico-chemical and mechanical factors on release kinetics.

Selection of polymer, channelling agent, method of incorporation, ratio of drug to polymer, formulation constraints and dispersion temperature are important determining factors on release rate. In matrix type formulations, which generally follow square root law release kinetics, the desired zero-order release may be achieved by control of these reported parameters and special geometric forms.

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