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DISSOLUTION OF CHLORPROPAMIDE TABLETS IN A METHANOL - WATER BINARY SOLVENT SYSTEM

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ABSTRACT

The dissolution of 250mg chlorpropamide tablets has been investigated in aqueous methanol co-solvent systems. Dissolution in the mixed solvent systems, despite sink conditions being obtained, was reduced over non-sink conditions in the pure aqueous system due to impaired tablet disintegration. However, tablet disintegration was improved at low methanol volume fractions due to improved wetting and fluid flux into the tablet mass.

A dissolution system was devised using an appropriate amount and order of addition of methanol to the dissolution fluid.

INTRODUCTION

Dissolution of high dose relatively insoluble drugs such as chlorpropamide can be problematic due to difficulties of

maintaining the sink condition of the dissolution test. In such occasions, where a readily accessible ionisation centre to enhance solubility is not available, the formulator then considers adding a non-aqueous co-solvent such as an alcohol to the dissolution fluid.

Poirier and others (1983) have conducted studies on low dose chlorthalidone in an aqueous-ethanol co-solvent system and have pointed out that the nature of the co-solvent, and time of addition of the co-solvent to the dissolution fluid, can influence the resultant dissolution profile.

This paper reports an investigation of a water-methanol co-solvent dissolution test for tablets of a high dose hydrophobic drug (250mg chlorpropamide).

EXPERIMENTAL

Materials

Chlorpropamide tablets (250mg Diabinese(R)) from Pfizer Ltd., Sandwich, U.K. The chlorpropamide bulk used for the standards was to BP grade and obtained from Francis SpA, Italy. The methanol employed was Analar grade obtained from Hopkins and Williams.

Methods

Drug solubility and determination of the sink condition

Chlorpropamide(C) has a low solubility in water (0.27mg/ml at 37C) and therefore exceeds the sink condition, defined as 10% saturation, in the conventional USP paddle dissolution test. The amount of drug that can dissolve under sink conditions (900ml) in a USP dissolution test is approximately 24mg. Thus, dissolution of

250mg tablets will require the addition of a co-solvent to the dissolution fluid to maintain sink conditions.

Solubilities of C were conducted at 37(+-1)C by equilibrating excess drug with 10ml of the binary aqueous methanol co-solvent system. Following equilibration, the solutions were filtered (Acrodisc, 0.2um) and diluted to a suitable concentration with methanol to allow spectrophotometric analysis at 230.9nm.

Dissolution

Dissolution tests were conducted on a pre-calibrated dissolution bath (Caleva model 7ST, G.B. Caleva, Ascot, UK) according to the method in USP XXI using paddles at 50rpm. The values reported are the mean of six determinations.

Disintegration

Tablet disintegrations were measured using the BP test using one tablet per tube. Each value reported is the mean of six determinations. The fluids employed were pure water and binary 10% v/v, 20% v/v, 40% v/v and 60% v/v methanol-water systems.

RESULTS AND DISCUSSIONS

Dissolution of the tablets under non-sink conditions in distilled water is shown in Figure 1. As expected, dissolution is slow and incomplete with only 50% of the drug dissolved in 60 mins. Measurement of the solubility of C at 37C in an aqueous methanol system (Figure 2) indicates that sink conditions are obtained with approximately 40% v/v methanol in the dissolution fluid. However, dissolution in the binary co-solvent system, even when sink conditions are maintained, leads to a more retarded dissolution profile (only 40% of the C dissolving in 60 minutes) than in the pure aqueous fluid.

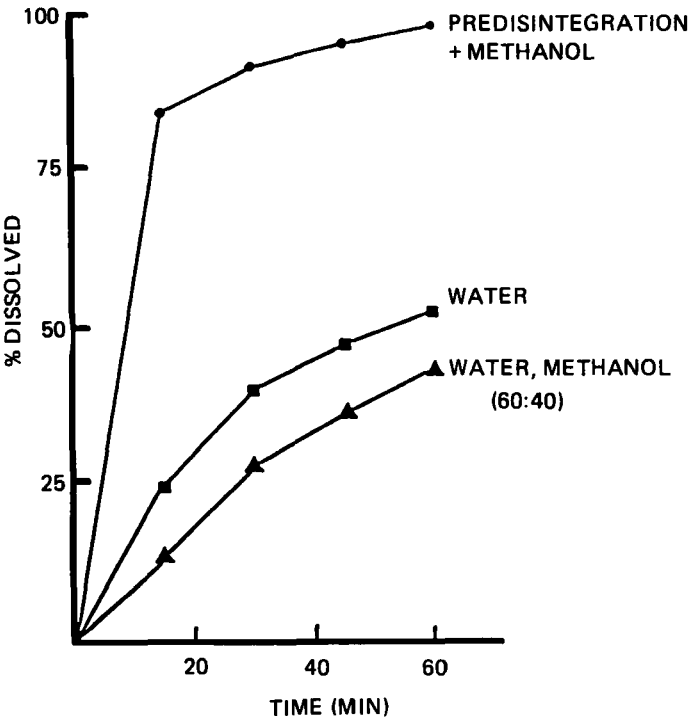

FIGURE 1

DISSOLUTION OF 250mg CHLORPROPAMIDE TABLETS IN VARIOUS FLUIDS

These dissolution results can be explained by the effect of methanol on the disintegration time of the tablets and is a result in accord with the work of Poirier and others (1983), and also Guyot-Hermann and Ringard (1981). This was confirmed by measurement of the disintegration times of the C tablets at varying methanol levels in the aqueous fluid used for disintegration test. The results (Figure 3) show that, as expected, tablet disintegration in 40% methanol is some 20% longer than in pure water. The disintegration time is essentially doubled in 60% methanol.

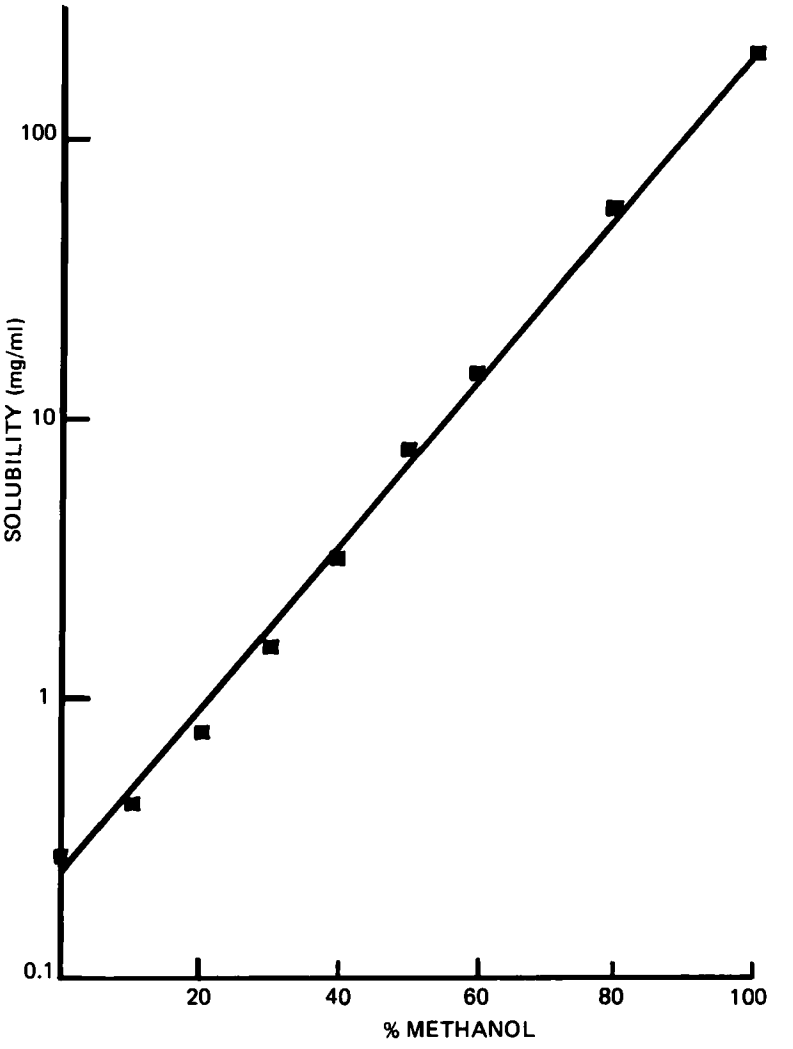

FIGURE 2

SOLUBILITY OF CHLORPROPAMIDE IN BINARY WATER-METHANOL CO-SOLVENT SYSTEM

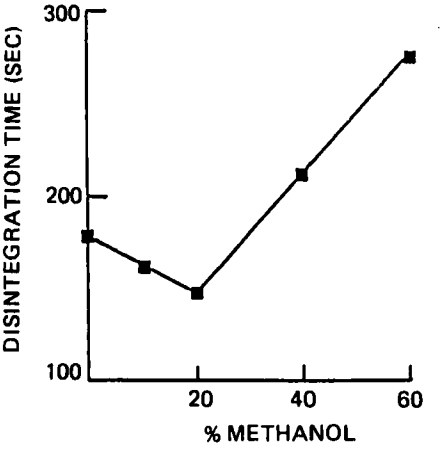

FIGURE 3

DISINTEGRATION TIMES OF 250mg CHLORPROPAMIDE TABLETS IN BINARY METHANOL-WATER SYSTEM

Interestingly, and conversely to the previous work with low dose chlorthalidone (Poirier and others 1983), disintegration of C tablets in 20% methanol are some 20% faster than in pure water. Thus, in this tablet system, there appear to be two opposing forces governing tablet disintegration in the mixed solvent system. Addition of the co-solvent appears to prolong disintegration by hindering disintegrant swelling, but this is balanced against the improved wettability and resultant wicking of the disintegrating fluid into the tablet. This appears to occur with a fluid containing 30% v/v methanol which possesses a surface tension of 44 mNm^{-1}. It is perhaps worthy of note that this balance of properties could be different in wet massed systems if the tablet contain intra- or extragranularly located disintegrant.

The balance of the disintegration phase in the mixed solvent, with the limitations from non-sink conditions in the tablet dissolution process was next examined by conducting studies using 20, 30, 40 and 60% aqueous-methanol systems. Dissolution of C from the tablets was found to be fastest with a fluid of 30% methanol (Figure 4); the composition of optimal tablet disintegration. However, even at 30% methanol, dissolution is relatively slow with only 58% C dissolving in 60 minutes, due to the methanol component being below that (40%) required for sink conditions.

Dissolution was next examined by allowing tablet disintegration within the aqueous component of the fluid (540ml) followed by addition of the methanol component after 10 minutes. A full dissolution profile from the tablets was obtained with over 90% of the drug released in 30 minutes (Figure 1). Thus, allowing for unimpaired disintegration and maintaining the sink condition, full dissolution of the dosage forms can be demonstrated.

Conducting the same procedure with a 30% methanol system (non-sink) resulted, as before in incomplete dissolution (77% C dissolved in 60 minutes) whereas the procedure using 60% methanol, produced an identical dissolution profile to that using 40% methanol (Table 1).

However, there are a few artefacts of the solvent addition method that are worthy of note. In the first phase of the dissolution, during the mandatory aqueous disintegration phase, the hydrodynamics of the test are substantially altered by the reduced

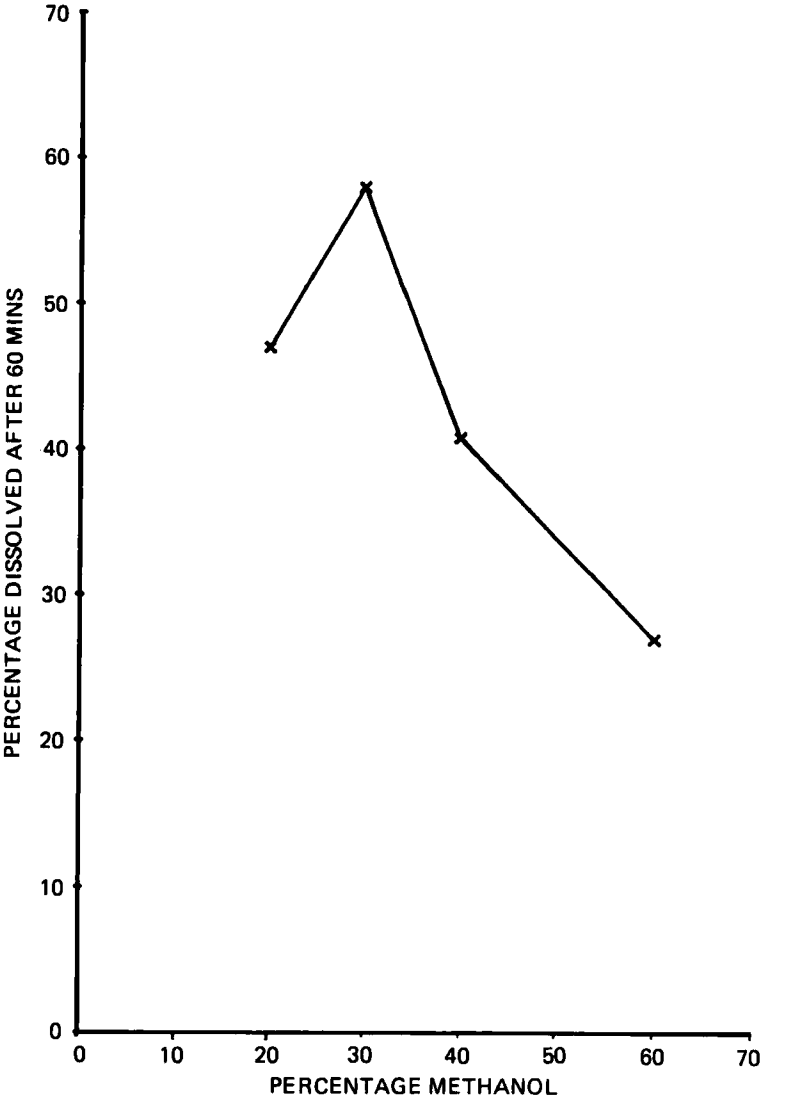

FIGURE 4

PERCENTAGE CHLORPROPAMIDE DISSOLVED IN 60 MINUTES

Table 1

% Dissolved From C Tablets Using Pre-disintegration Technique With Varying Methanol Levels in Binary Solvent

% Methanol Time/Mins	30	40	60
		% Dissolved	
15	38 ± 9	75 ± 5	77 ± 2
30	66 ± 2	90 ± 3	96 ± 3
45	74 ± 1	94 ± 3	99 ± 3
60	77 ± 1	96 ± 2	100 ± 4

fluid volume. Following tablet disintegration, a further disruption in the solution hydrodynamics occurs due to the addition of the non-aqueous phase. Perhaps, most importantly, following the second phase of solvent introduction, a temperature increase of 5C occurs due to exothermic heat of mixing of the two solvents. To investigate the above, a pre-disintegration dissolution test was conducted using water at 42C as the added secondary phase. An increase in dissolution was indeed observed (62% vs 50% dissolved in 60 minutes), but the enhancement was significantly smaller than that produced with the co-solvent addition.

CONCLUSION

This study has investigated the influence of a binary co-solvent fluid on the disintegration phase within the dissolution process of a high dose solid dosage form of a relatively insoluble hydrophobic drug. Different tablet disintegration phenomena appear

to apply depending on the level of the non-aqueous component of the mixed solvent system. However, despite tablet disintegration being improved at some solvent compositions, a phase of pre-disintegration of solid dosage forms should be incorporated in dissolution tests employing binary solvent mixtures.

REFERENCES

Guyot-Hermann A.M. and Ringard J.; "Disintegration Mechanisms of Tablets Containing Starches. Hypothesis About The Particle-particle Repulsive Force", Drug Dev. Ind. Pharm. 7 (1981) 155-177.

Poirier H., Lewis G.A., Shott M.J. and Stevens H.N.E.; "Problems With a Pharmacopoeial Dissolution Test Using a Binary Medium", Drug Dev. Ind. Pharm. 9 (1983) 442-452.