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EVALUATION OF THE IN VITRO RELEASE PROFILE OF DIGOXIN FROM DRUG-CARBOHYDRATE COPRECIPITATES

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ABSTRACT

An improvement in the dissolution profile of digoxin by coprecipitating the drug with fructose, polydextrose or xylose is reported. The results of this investigation indicate that the need of a common solvent for the drug and the carrier is not necessarily an absolute requirement for the preparation of coprecipitates. The use of two mutually soluble solvents was found suitable to prepare polydextrose coprecipitates. The increase in the dissolution rate was attributed to the increased wettability and/or the presence of a very fine state of subdivision of the drug particles. A linear relationship was obtained when percent drug released was plotted as a function of log time. Both the slope and the intercept values of the linearized plot were used to compare the release profile of different formulations. Aging of a coprecipitate exhibited slower dissolution than the freshly prepared product.

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INTRODUCTION

The gastrointestinal absorption of hydrophobic drugs is generally rate limited by dissolution. Digoxin is a poorly water-soluble drug and has demonstrated unpredictable and irregular absorption from tablets produced by various manufacturers (1-3). Furthermore, significant variations in blood levels were noted between batches made by the same manufacturer (1). Several reports have confirmed the existence of a close correlation between in vitro dissolution and plasma digoxin levels (4-6).

The solid dispersions and coprecipitates of hydrophobic drugs with various water-soluble pharmacologically inert carriers have been shown to significantly increase their in vitro release rates (7-20).

The purpose of this study was to improve the in vitro dissolution profile of digoxin by preparing coprecipitates of the drug in nontoxic pharmacologically inert carbohydrates, namely, fructose, polydextrose, and xylose. The preference of the coprecipitation method over the melting method was based upon the fact that exposure of the drug and the carriers to a high temperature used during the melting method may have some injurious effect on the product, especially on the carbohydrates and high melting point drugs.

EXPERIMENTAL

Materials

Digoxin, Fructose, Xylose (Sigma Chemical Co.), Polydextrose (Pfizer Chemical Division), Concentrated Hydrochloric acid, and Alcohol USP (J.T. Baker Chemical Company.) were used as received without further treatment.

Product Preparation

The 1:5, 1:10 and 1:20 (w/w) drug-carrier physical mixtures and coprecipitates were prepared using the method reported in an earlier investigation (19).

Dissolution Study

Dissolution profiles were determined using USP XXI Dissolution apparatus, Method I (basket method) desribed in an earlier

investigation (19) using 500 milliliters of 0.1 N hydrochloric acid maintained at 37 ± 0.5° and stirred at 120 ± 2 rpm. Drug concentrations were measured spectrophotometrically at 221 nm using 0.1 N hydrochloric acid as the blank.

Effects of Aging

The freshly prepared coprecipitate that showed the fastest release pattern was selected to study the effect of six months aging on the dissolution profile. During this study, the coprecipitate was stored in a screw capped vial at room temperature and the dissolution profile was obtained every two months using the dissolution method described above.

RESULTS AND DISCUSSION

All dissolution tests were run in triplicate. The percent drug dissolved at each time interval was within 5% of the mean value of the three readings. The concentration of digoxin in the dissolution medium obeyed Beer's law at 221 nm. Incorporation of 20 fold excess of carriers did not alter the absorbance maximum of the drug. The amount of drug in the dissolution medium was maintained at sink condition.

As shown in Figure 1, at each time interval, marked differences existed between the percent digoxin released from all coprecipitates studied and the pure drug. An increase in the proportion of the water soluble carrier hastened dissolution of digoxin from the coprecipitates.

Figure 2 indicates that the digoxin-carrier physical mixtures did not show considerable improvement in the dissolution profile. Neither the change in the carrier nor the change in the proportion of the carrier made any considerable difference in the profile.

Figure 3 shows the effect of the same proportion of different carriers on the dissolution profile of the drug from the coprecipitateas. Fructose appeared to be more effective than the other two carriers in its ability to improve the dissolution profile of digoxin.

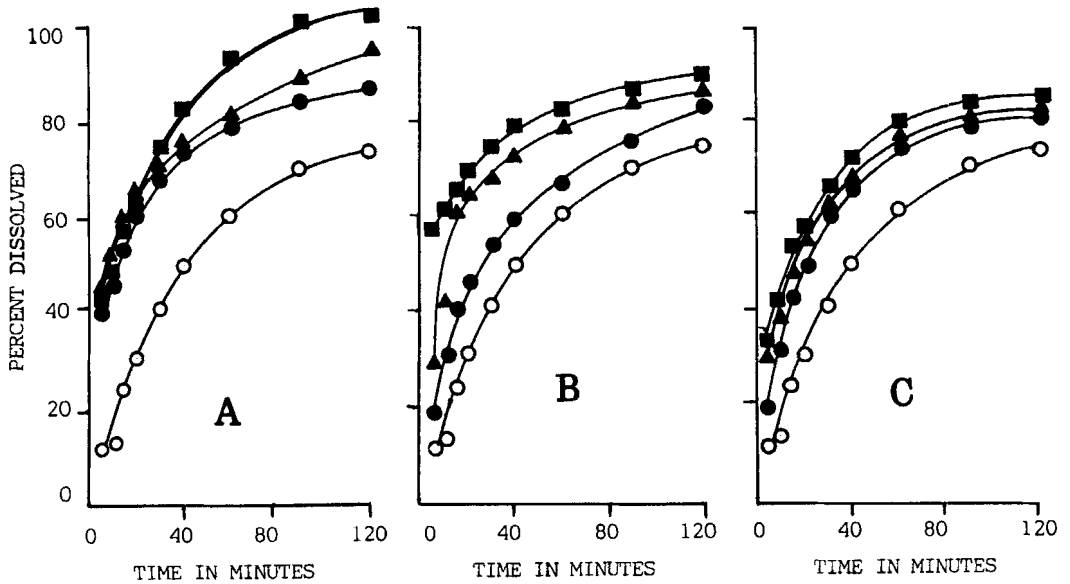

Figure 1. Dissolution profile of digoxin and its coprecipitates with (A) fructose, (B) polydextrose, and (C) xylose in various proportions. Key: ○ pure drug; drug:carrier proportion of ● 1:5; ▲ 1:10; ■ 1:20.

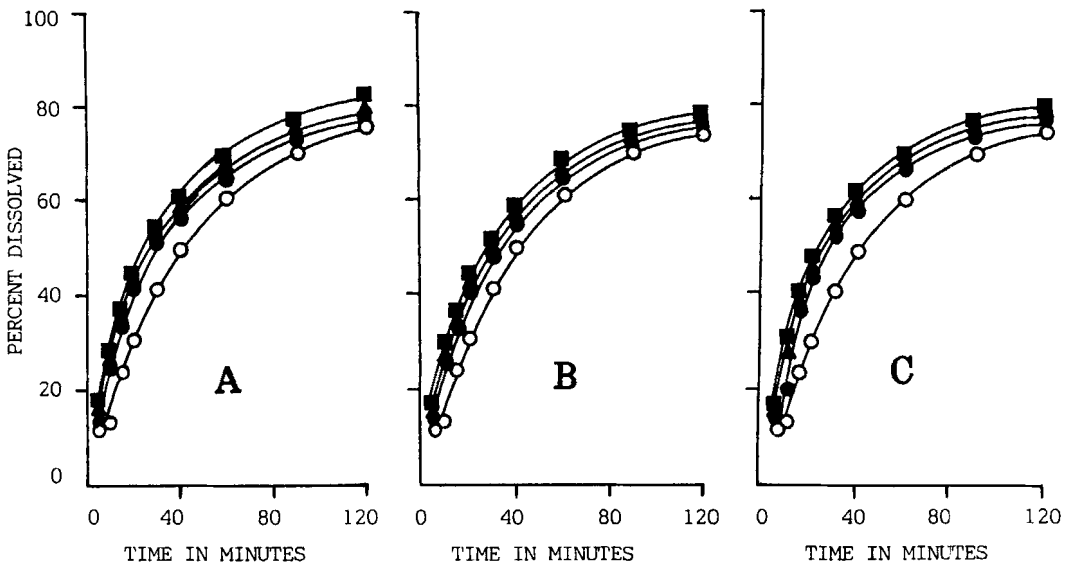

Figure 2. Dissolution profile of digoxin and its physical mixtures with (A) fructose, (B) polydextrose, and (C) Xylose. Key: ○ pure drug; drug:carrier proportion of ● 1:5; ▲ 1:10; ■ 1:20.

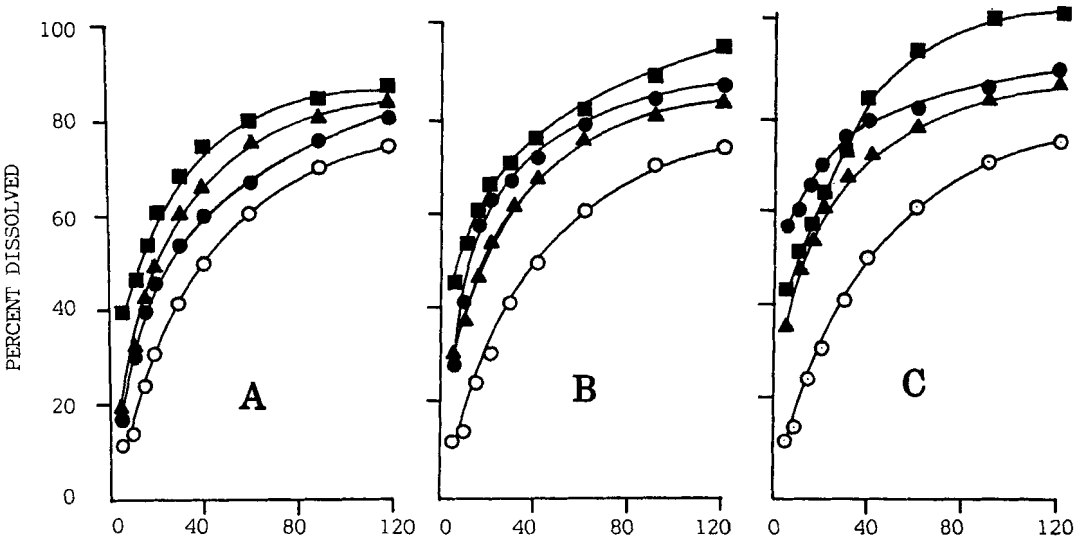

Figure 3. Dissolution profile of digoxin and its coprecipitates with different carriers in the proportion of (A) 1:5, (B) 1:10, and (C) 1:20. Key: ○ pure drug; ■ digoxin-fructose; ● digoxin-polydextrose; ▲ digoxin-xylose.

The faster dissolution of digoxin from the coprecipitates may be attributed to the increased wettability and reduced particle size of the drug. The hydrophobic drug particles were apparently preferentially surrounded by the water soluble carriers during the coprecipitation process. When these coprecipitates were exposed to the aqueous medium, the surrounding water-soluble carrier dissolved rapidly and facilitated the wetting of the drug particle. Thus, under these circumstances, the hydrophobic drug particles did not behave as hydrophobic as they would have in the absence of the surrounded water-soluble carrier. Therefore rapid dissolution was promoted.

The in vitro release profile of different coprecipitates were therefore compared following a method reported by McTaggert et al. (21). A linear relationship was observed only when percent drug dissolved was plotted as a function of log time (Figure 4). This relationship can be expressed by the equation of the straight line

$$D = m \ln T + D_1 \qquad \text{(equation 1)}$$

where D is the percent drug dissolved at any time T, D_1 is the

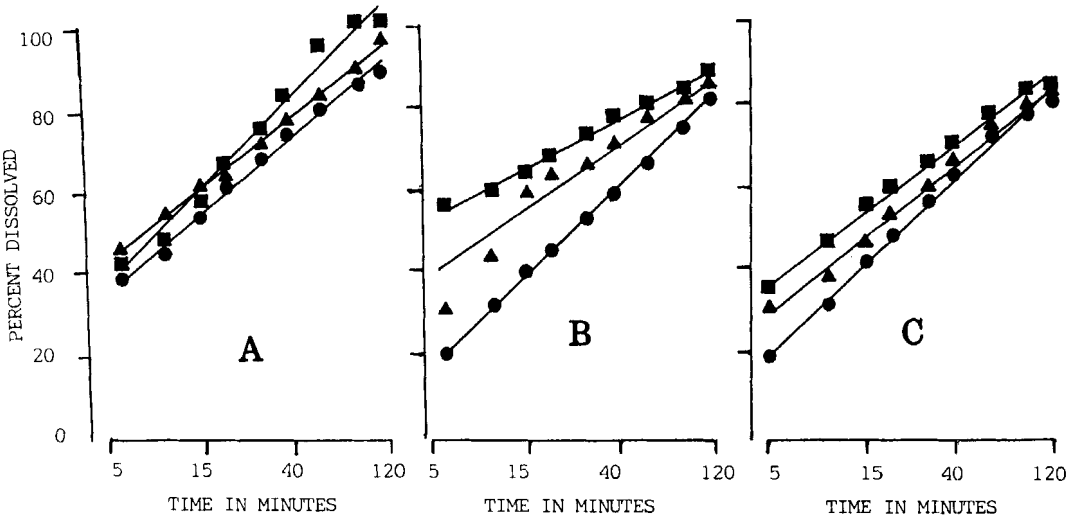

Figure 4. Linearized dissolution profile of digoxin coprecipitates with (A) fructose, (B) polydextrose, and (C) xylose. Key: Drug:carrier proportion of ● 1:5; ▲ 1:10; ■ 1:20.

intercept which is a measure of the percent drug released in one minute, and m is the slope and is related to the release rate of drug from the particular formulation. Normally, high values of both, the slope and the intercept would be an indication of rapid release. However, since a very high value of slope with a low intercept value, as well as a very high intercept value with a low value of slope could also represent a very fast release, we feel that the formulations should be evaluated using both the slope and the intercept values. For this purpose an equation (equation 2) is derived from equation 1, from which the time required for the dissolution of any amount of drug (say, for 75% drug released we use $D_1 = 75$) can be calculated using the slope and the intercept values. Since the slope and the intercept of the linearized graph describes the complete dissolution profile, the time for 75% of the drug released from the formulations can be evaluated by using equation 2.

$$T = \exp (75 - D_1 / m) \qquad \text{(equation 2)}$$

Table I shows the correlation coefficient (r), slope, intercept, and T_{75} (time for 75% drug dissolution) values for the coprecipitates

TABLE I

Values of parameters of equation $D = m \ln T + D_1$ for physical mixtures and coprecipitates of digoxin with different carriers in various proportions.

CARRIERS USED	PROPORTIONS	r	SLOPE	INTERCEPT	T_{75}
		PHYSICAL MIXTURES			
FRUCTOSE	1:5	0.9956	20.65	-20.66	103
	1:10	0.9992	21.64	-21.63	87
	1:20	0.9992	21.98	-21.61	81
POLY-DEXTROSE	1:5	0.9972	20.52	-20.91	107
	1:10	0.9973	20.32	-19.32	104
	1:20	0.9966	20.09	-16.63	96
XYLOSE	1:5	0.9914	21.03	-17.34	81
	1:10	0.9975	20.45	-16.29	87
	1:20	0.9960	21.51	-17.44	74
		COPRECIPITATES			
FRUCTOSE	1:5	0.9923	16.48	10.89	49
	1:10	0.9973	16.00	17.74	36
	1:20	0.9867	22.47	0.04	28
POLY-DEXTROSE	1:5	0.9993	20.32	-15.24	85
	1:10	0.9706	17.27	5.00	58
	1:20	0.9901	10.65	37.82	33
XYLOSE	1:5	0.9920	21.11	-14.52	69
	1:10	0.9908	18.12	- 0.63	65
	1:20	0.9954	16.33	10.63	52

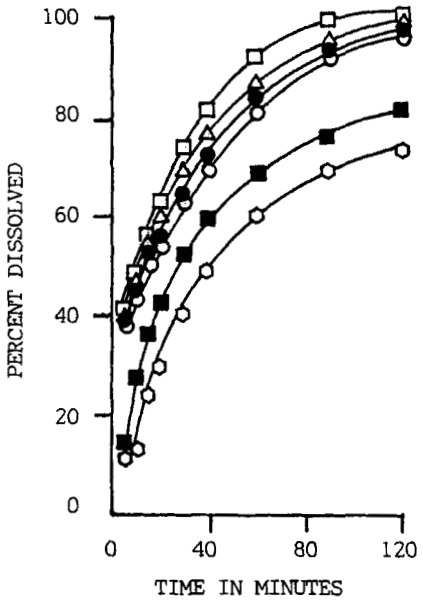

Figure 5. Effect of aging on the dissolution profile of digoxin-fructose 1:20 coprecipitate. Key: □ freshly prepared; △ two months ● four months; ○ six months; ■ digoxin: fructose 1:20 physical mixture; ⬡ pure drug.

and the physical mixtures. The T_{75} values in Table I could be useful to judge the superiority of a coprecipitate in its ability to release the drug during the dissolution process. The standard deviations of the slopes (0.66) and intercepts (2.13) of the physical mixtures were much smaller then the corresponding values of the coprecipitates (3.49 and 16.39 respectively) probably because the release profile from the physical mixtures did not show discrepancy on changing the type of content of the carriers.

Effect of Aging

The digoxin-fructose 1:20 coprecipitate which, in the freshly prepared state, showed the fastest dissolution was selected for the study, since the product with the fastest dissolution profile was of particular interest. The effect of six months of aging as studied at

TABLE II

Effect of aging on the parameters of the equation

$D = m \ln T + D_1$ and T_{75} values

AGE (Months)	r	SLOPE	INTERCEPT	T_{75} (MINUTES)
0	0.9867	22.4692	0.04	22.11
2	0.9943	21.7156	-0.92	33.04
4	0.9983	20.8985	-1.02	38.00
6	0.9974	20.4483	-1.11	41.35

TABLE III

Least Significant Difference (LSD) test for T_{75} values obtained from coprecipitate at different stages of aging.

AGING PERIOD	DIFFERENCE IN T_{75} VALUES	CONFIDENCE LEVEL 1%	5%
0 - 2	33.04 - 28.11 = 4.93	N.S	S
0 - 4	38.00 - 28.11 = 9.89	S	S
0 - 6	41.35 - 28.11 = 13.24	S	S
2 - 4	38.00 - 33.04 = 4.96	N.S	S
2 - 6	41.35 - 33.04 = 8.31	S	S
4 - 6	41.35 - 38.00 = 3.35	N.S.	N.S

S = Significant
N.S = Not Significant

two month intervals is shown in Figure 5. In this Figure, the dissolution of digoxin from the corresponding physical mixture and from the pure drug have been included for comparison purposes. The dissolution profile at each stage of aging showed a good fit to equation 1, the correlation coefficient (r), slope, intercept, and T_{75} values of this coprecipitate at each stage of aging are shown in Table II. It would appear from Figure 5 and the T_{75} values in Table II that the

coprecipitate showed a decrease in release profile upon aging. ANOVA test at 5% level showed a significant increase in the T_{75} value. The Least Significant Difference (LSD) test (Table III) revealed that at 1% level the T_{75} values of the consecutively aged coprecipitate were not significantly different. However, at 5% level only T_{75} value for the last two months of aging was not significant.

CONCLUSIONS

The dissolution profile of digoxin can be improved by coprecipitating the drug with such water soluble carbohydrates as fructose, polydextrose and xylose. Since the coprecipitates with polydextrose could be prepared by using two different but mutually soluble solvents, the need of a common solvent for the drug and the carrier should not be considered an absolute requirement for the preparation of coprecipitates. The use of two mutually soluble solvent system will broaden the application of coprecipitation technique for a wider range of drugs and carriers otherwise not handleable. In the evaluation of in vitro release profiles from a linearized plot, consideration of both the slope and intercept is necessary except when all the intercept values are equal or the differences among the values are not significantly different.

The study of the effect of aging on the dissolution profile of solid dispersion is important, since the in vitro release profile from the coprecipitates may decrease upon aging of the products. Although aging affected the dissolution profile, even the six month aged coprecipitate showed appreciable superiority in the in vitro release profile over the corresponding physical mixture and the untreated microfine drug.

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