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INFLUENCE OF SELECTED WATER SOLUBLE CARBOHYDRATES ON THE DISSOLUTION PROFILE OF PREDNISOLONE

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ABSTRACT

The utilization of three water soluble carbohydrates as carrier to improve the dissolution rate of prednisolone was studied. Coprecipitates and physical mixtures of the drug and the carriers in three different proportions were prepared and their dissolution profile was compared with the dissolution profile of the pure drug. The remarkably fast and erratic dissolution of prenisolone observed from the coprecipitates was possible due to the conversion of prednisolone into its metastable or amorphous form durning the coprecipitation process. The dissolution rate of the drug from the physical mixtures was much higher than from the pure drug itself. Effect of aging of the coprecipitate on the dissolution profile showed an increasing tendency of

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the dissolution curve to match with that of the corresponding physical mixture.

INTRODUCTION

Prednisolone is a poorly water-soluble adrinocortical steroid. The corticosteroids have demonstrated unpredictable, and irregular dissolution rates (1-5). Several investtigators have shown that the formation of solid dispersions or coprecipitates of relatively hydrophobic drugs with various pharmacologically inert hydrophilic carriers may significantly increase their in vitro dissolution rates (6-22). However, the use of carbohydrates or sugars, as carrier in the solid dispersion system has received limited attention in the literature (21,22). These investigators reported solid dispersions of drug-sugar using the melting method. The use of sugar in the melting has an inherent problem of its own, i.e., during the heating at the preparation temperature sugars may decompose causing an amber coloration. The solvent or coprecipitation method may overcome this problem. However, the literature is completely devoid of such technique using mono or poly-saccharides. The present study describes the use of some selected sugars namely fructose, xylose, and polydextrose using the solvent or coprecipitation method to improve the dissolution profile of the hydrophobic drug prednisolone.

EXPERIMENTAL

MATERIALS

Prednisolone[1], fructose[1], xylose[1], polydextrose[2], and alcohol USP[3] were used as received without further treatment.

PRODUCT PREPARATION

Coprecipitates and physical mixtures of prednisolone and the carriers were prepared using 1:5, 1:10, and 1:20 (w/w) drug:carrier proportions. Two different methods were used to prepare the coprecipitates depending on the availability of suitable solvent(s) for the drug and the carriers.

Coprecipitates with fructose and xylose

The required amount of prednisolone and fructose or xylose to yield drug-carrier proportions of 1:5, 1:10, and 1:20 were dissolved in a minimum volume of alcohol USP by the application of heat using a water bath. Heating was continued and the solution was vigorously stirred until a translucent to white viscous gummy mass formed. The mass was transferred to a vacuum desiccator with a heating device, kept at 95° for 30-45 minutes and finally at 25° overnight for products containing xylose and 48-72 hours for products containging fructose. The solid mass was pulverized and passed through a 60 mesh screen and kept in a screw-capped glass vial.

1. Sigma Chemical Company, St. Louis, MO.
2. Pfizer Chemical Division, NY.
3. New York Laboratory Supply Company, NY.

Coprecipitates with Polydextrose:

The 1:5, 1:10 and 1:20 prednisolone-polydextrose coprecipitates were prepared by dissolving the components separately in a minimim volume of alcohol USP and distilled water respectively. The aqueous solution of polydextrose was poured into the alcoholic solution of prednisolone with continous stirring when a clear solution was obtained. The system was heated in a water bath with vigorous stirring when initially a transparent to a translucent viscous mass and finally an off-white coprecipitate formed. The moist mass was transferred to a vacuum disiccator with heating device and kept at 95^{o} for 30 minutes. The solid mass was pulverized and passed through a 60 mesh screen and stored in a screw-capped glass vial.

DISSOLUTION STUDIES

The dissolution profiles were determined by using USP XXI Dissolution apparatus, Method I (basket method). Nine hundred milliliters of freshly prepared distilled water was maintained at 37 ± 0.5^{o} and stirred at 100 ± 1rpm. An accurately weighed sample equivalent to 9 mg of prednisolone was spread over the surface of the dissolution medium at zero time. Any large aggregates, if formed, were lightly broken up with a microspatula within a few seconds after adding the sample. At predetermined time intervals, 10 ml of aliquots were withdrawn and were filtered through 0.45 u Millipore

filter. To replace the volume of the sample withdrawn for assay, 10 ml of distilled water was added to the dissolution flask each time after the sampling. Drug concentrations were measured spectrophotometrically at 246 nm using distilled water as the blank. Cumulative corrections were made for the volume of sample solutions previously withdrawn.

EFFECT OF AGING

The effect of six month aging on the dissolution profile of the coprecipitate which showed the fastest dissolution in the freshly prepared form was studied. The coprecipitate was stored in a screw-capped vial at room temperature. Dissolution profile was obtained every two months using the USP dissolution apparatus, rotating basket method as described above.

RESULTS AND DISCUSSIONS

Each curve showing the dissolution profile is drawn through points which represent an average of three dissolution runs. The percent drug dissolved at each time interval was within 5% of the mean value of the three readings. The amount of drug in the dissolution medium maintained sink condition and the concentration of the drug in the dissolution study obeyed Beer's law at 246 nm (λ max of prenisolone in water). Incorporation of a 20 fold excess of the carrier did not alter the absorbance maximum of the drug.

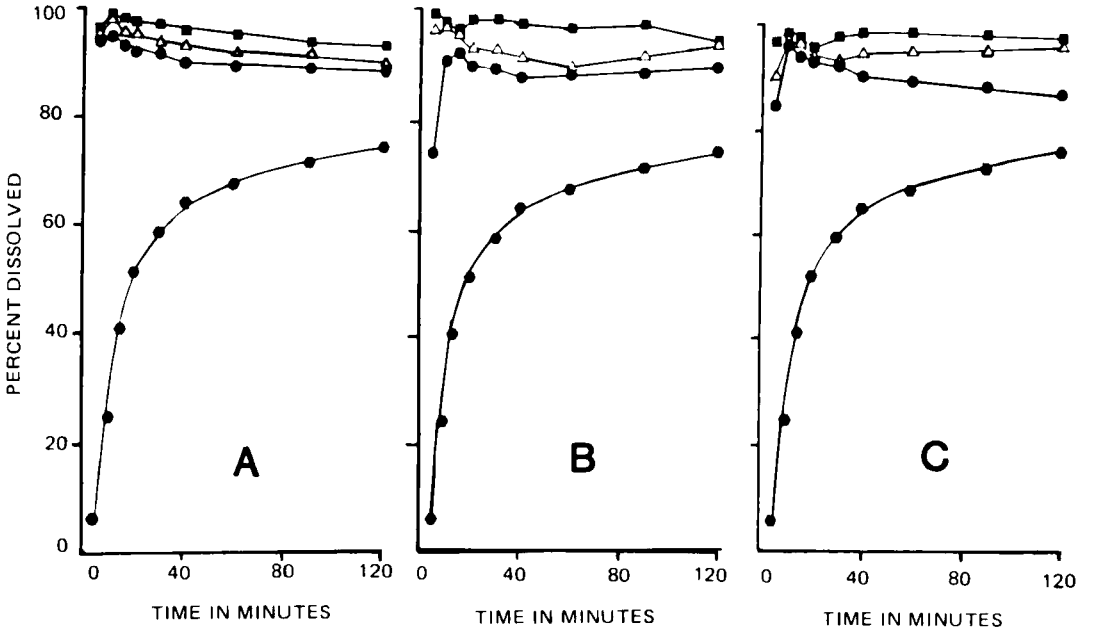

Figure 1. Dissolution profile of prednisolone and its coprecipitates with (A) fructose, (B)xylose, and (C) polydextrose in various proportions. Key: ◆ pure drug; drug:carrier proportion of ● 1:5; ▲ 1:10, ■ 1:20.

Figure 1 shows the dissolution profile of prednisolone from the pure drug and from the coprecipitates of the drug with the three hydrophilic carriers in various proportions. As can be seen in this figure, the dissolution of prednisolone was faster from the coprecipitates than from the pure drug. With the exception of xylose and polydextrose 1:5 drug-carrier combinations, all the coprecipitates showed more than 90% dissolution within 5 minutes, the first sampling time. The xylose and polydextrose coprecipitates showed more than 90% dissolution within 10 minutes.

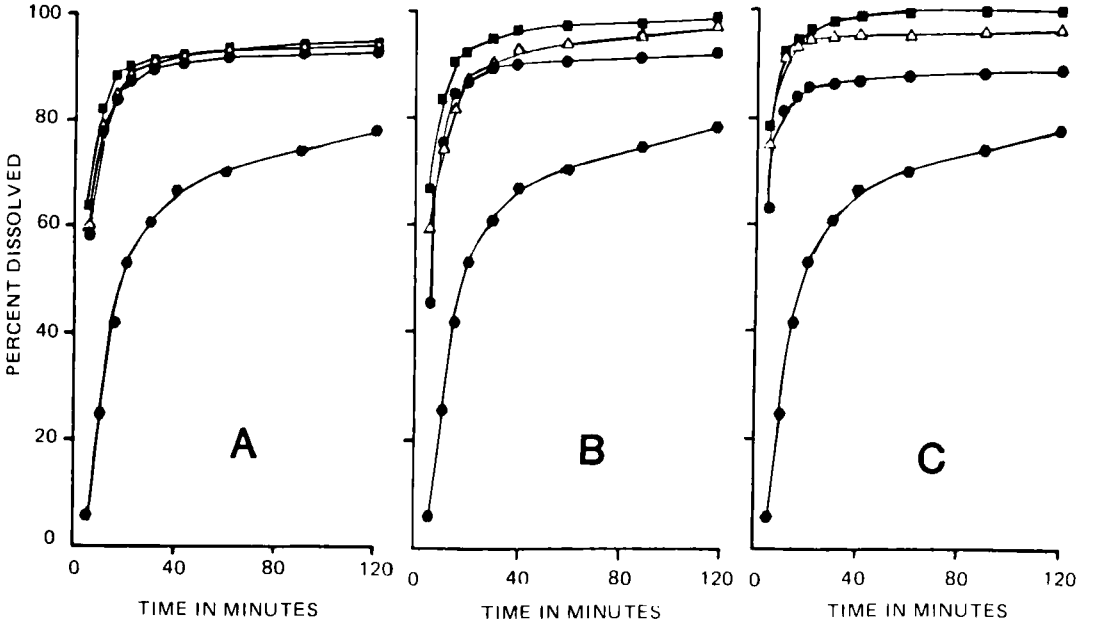

Figure 2. Dissolution profile of prednisolone and its physical mixtures with (A) fructose, (B) xylose, and (C) polydextrose. Key: ● pure drug; drug:carrier proportion of ● 1:5, △ 1:10, ■ 1:20.

Increase in the proportion of the carriers appeared to hasten the dissolution of all the products studied. However, since the dissolution of the coprecipitates were very fast, the observed difference in the proportion of the carriers may not be considered remakable.

The dissolution of prednisolone from its physical mixture with the three carriers (Figure 2) was also faster than the observed form the pure drug. While the fructose physical mixtures did not discriminate between the concentration of the carrier level (Figure 2A), the dissolution

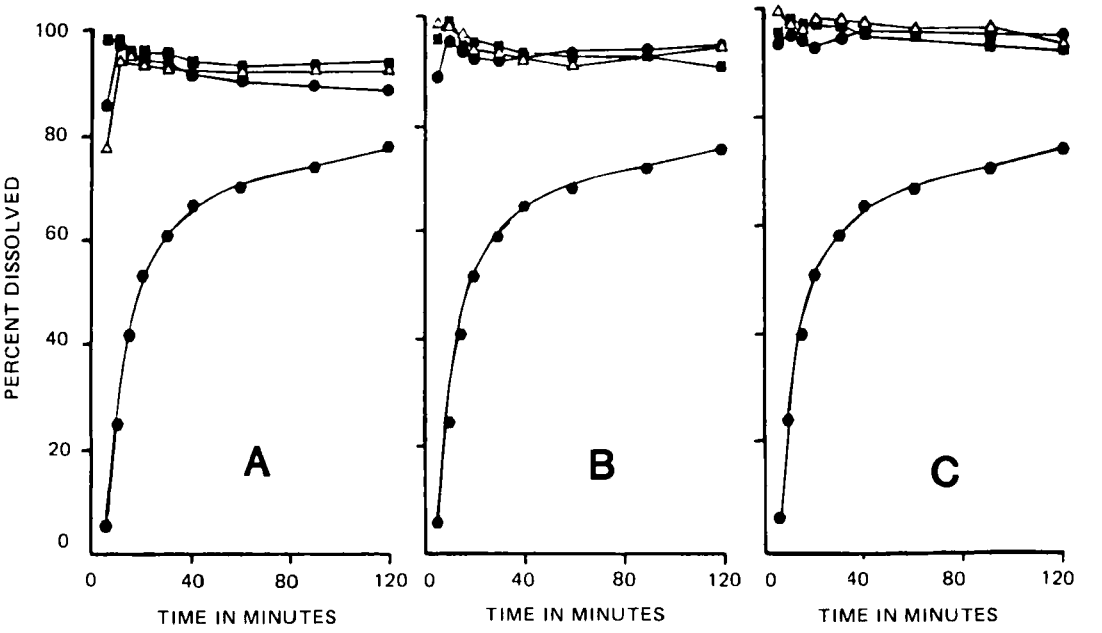

Figure 3. Dissolution profile of prednisolone and its coprecipitates with different carriers in the proportion of (A) 1:5, (B) 1:10, and (C) 1:20. Key: ⬣ pure drug; ■ prednisolone-fructose; ● prednisolone-polydextrose; △ prednisolone-xylose.

followed 1:20 > 1:10 > 1:5 in the case of physical mixtures prepared with polydextrose and xylose.

The effect of the same proportion of different carriers on the dissolution profile of prednisolone from the coprecipitates is shown in figure 3. In the 1:10 and 1:20 drug-carrier coprecipitates, xylose appeared to have the highest effect to upgrade the dissolution profile followed by fructose and polydextrose. Again, due to the very fast dissol-

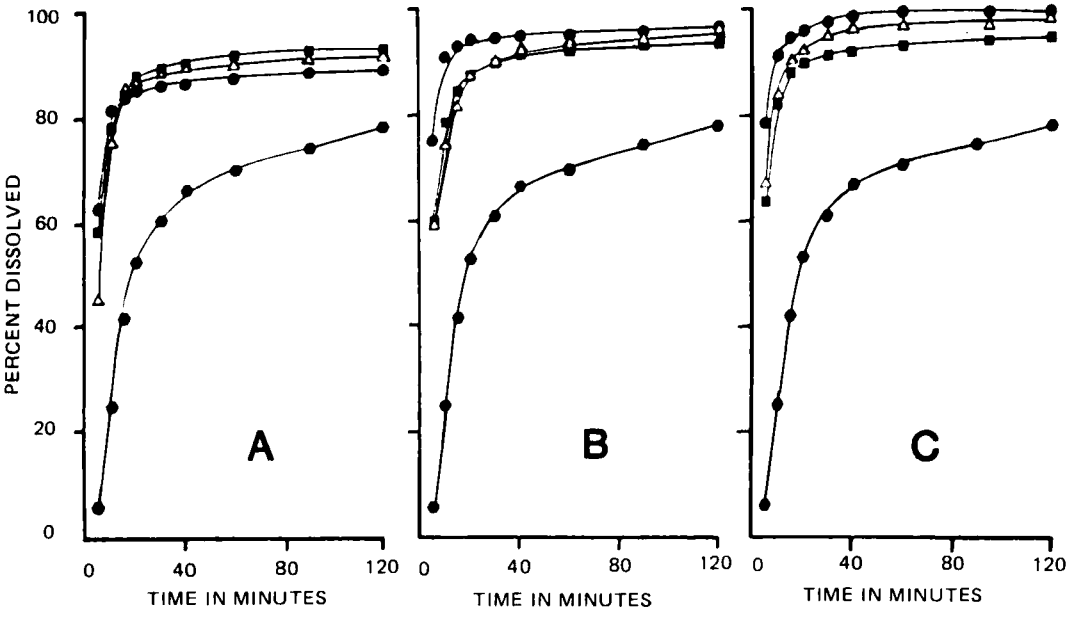

Figure 4. Dissolution profile of prednisolone and its physical mixtures with different carriers in the proportion of (A) 1:5, (B) 1:10, (C) 1:20. Key: ⬢ pure drug; ■ prednisolone-fructose; ● prednisolone-polydextrose; Δ prednisolone-xylose.

ution fo the coprecipitates ,the observed difference may not be considered remarkable.

The effect of the same proportion of different carriers on the dissolution profile of prednisolone from the physical mixtures (Figure 4) reveals that the ability of the carriers to improve the dissolution rate of prednisolone from most of the drug-carrier physical mixtures follwed the order polydextrose > xylose > fructose.

The time in minutes for the dissolution of 50%, 70%, and 90% of prednisolone (from the pure drug, its coprecipitates and physical mixtures with different carriers) as indicated by t_{50}, t_{70}, t_{90} respectively are shown in Table I. The t_{90} of most of the coprecipitates was less than 5 minutes, whereas that of the pure microfine drug was more than 120 minutes, i.e. more than 24 times faster release rate form the coprecipitates. Physical mixtures, especially the 1:10 and 1:20 drug-polydextrose combinations showed remarkable fast release profiles.

It is noticeable that the dissolution profile of prednisolone from the coprecipitates (Figure 1) showed a trend different from the usual consistant increase in concentration of the drug in the dissolution medium as a function of time. The percent drug dissolved increased in the beginning and than showed a tendency to decrease. Similar decline of the dissolution profile has been reported by other investigators in their studies (23-26) with different drugs. These authors have explained the decline due to the nonhomogeneity of the amorphous form of the drug in the coprecipitates (23), crystallization of gelatinous drug precipitates (24), and the presence of metastable polymorphic form (25, 26). A comparison of the dissolution profile of the coprecipitates with those of the corresponding physical mixtures show "a matching up" tendency of the former

TABLE I

Time for 50%, 70%, and 90% dissolution of prednisolone from pure drug and from coprecipitates and physical mixture of the drug with different carriers in various proportions.

PRODUCT	CARRIERS	PROPORTIONS (Drug:Carrier)	DISSOLUTION TIME IN MINUTES		
			t_{50}	t_{70}	t_{90}
PURE DRUG	None		19	60	>120
COPRECIPITATES	Fructose	1:5	<5	<5	<5
	"	1:10	<5	<5	<5
	"	1:20	<5	<5	<5
	Polydextrose	1:5	<5	<5	7
	"	1:10	<5	<5	<5
	"	1:20	<5	<5	<5
	Xylose	1:5	<5	<5	9
	"	1:10	<5	<5	<5
	"	1:20	<5	<5	<5
PHYSICAL MIXTURES	Fructose	1:5	<5	8	35
	"	1:10	<5	7	31
	"	1:20	<5	6	21
	Polydextrose	1:5	<5	6	>120
	"	1:10	<5	<5	10
	"	1:20	<5	<5	10
	Xylose	1:5	6	10	60
	"	1:10	<5	9	30
	"	1:20	<5	6	15

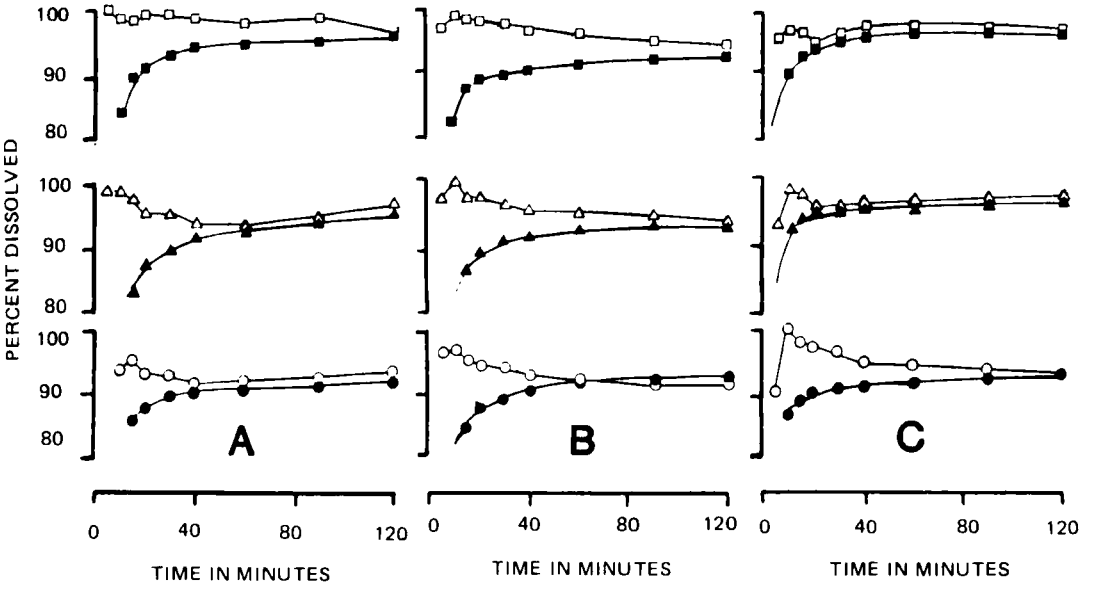

Figure 5. Comparison of the dissolution profile of the coprecipitates; ○ 1:5, △ 1:10, □ 1:20; Physical mixtures; ● 1:5, ▲ 1:10, ■ 1:20.

with that of the latter (Figure 5). This type of dissolution profile indicates a strong possibility of the presence of a metastable polymorphic form of prednisolone in the coprecipitates. Furthermore, during the study of the effect of aging on the dissolution profile of the prednisolone coprecipitate, it was found that the tendency of the dissolution profile of coprecipitate to align with that of the corresponding physical mixture increased with the aging of the coprecipitate. This also indicates the possibility of the presence of a metastable

polymorphic form which on aging probably changed to a stable form similar to that present in the physical mixture.

The lag time required by the dissolution profile of the coprecipitates to "match up" with the corresponding physical mixture was found to be different with different coprecipitates. For example, with the xylose and fructose coprecipitates, a decrease in the proportion of the carrier decreased the lag time for the match up (Figures 5A and 5B), whereas the reverse was the case with the polydextrose coprecipitates (Figure 5C). One possible explanation for this behavior is as follows.

If the decline of the dissolution profile is assumed to be due to the presence of metastable or amorphous form, the "match up" can then be the result of possible conversion of the metastable or amorphous form to the stable polymorphic form that may place in the stagnent boundary (diffusion layer) around the dissolving particle. Once the conversion was completed, the dissolution profile took the trend of that of thecorresponding physical mixture. Thus the time required for this "match up" (completion of conversion) would be expected to be proportional to the amount and/or stability of the metastabe or amorphous form.

It is known that the nature of the solvent, its boiling point, rate of evaporation, viscosity of the medium and the nature and the concentration of the other solutes present in

the system influences the formation of polymorphic forms (27). Coprecipitates of fructose and xylose were prepared using Alcohol USP (which is azeotropic) as the only solvent. An increase in the proportion of the carriers increased the carrier concentration in the solution system from which the coprecipitates were prepared by evaporating the solvent. Apparently the increased concentration of the carriers hastened the precipitation process (by supersaturating the system) which may have caused the formation of an increasing proportion of metastable polymorphic form. On the other hand polydextrose coprecipitates were prepared using a water and Alcohol USP solvent system (not azeotropic) where the water content was more than the present in Alcohol USP. For the solubilization of any increased proportion of polydextrose, it was necessary to add an increasing proportion of water. Since an increasing proportion of water in the solvent system decreased the rate of evaporation, it is possible that a slower rate of evaporation might yield a higher proportion of stable (and lower proportion of metastable) polymorphic form; therefore an increased proportion of polydextrose in the coprecipitate yielded a decreased proportion of metastable form resulting in a decrease in time in the dissolution profile of the coprecipitates to match the corresponding physical mixtures.

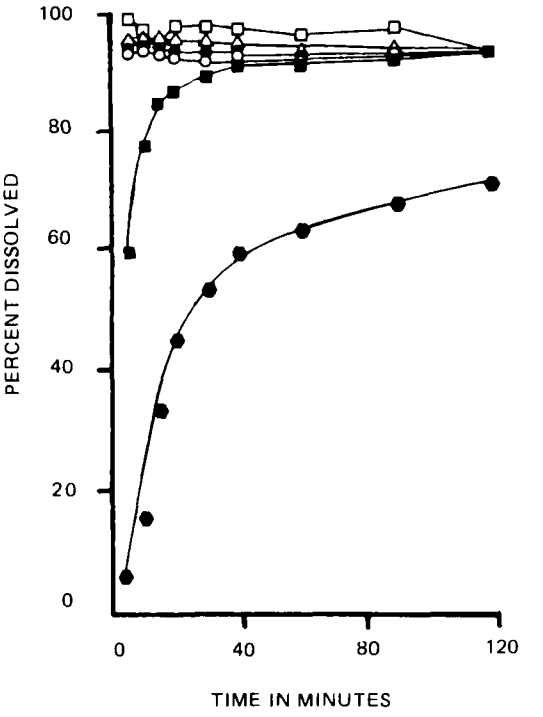

Figure 6. Effect of aging on the dissolution profile of prednisolone-xylose 1:20 coprecipitate. Key: □ freshly prepared; △ after two months; ● after four months; ○ after six months; ■ physical mixture; ● pure drug.

EFFECT OF AGING

Since the product with the highest dissolution profile was of particular interest, the 1:20 prednisolone-xylose coprecipitate, which in the freshly prepared stage appeared to show the fastest dissolution, was subjected to dissolution test every two months, for a period of six months (Figure 6). The lag time for the alignment of the dissolution profile of

the coprecipitates with that of the corresponding physical mixture appeared to decrease with aging of the product. It is possible that with the aging of the product increasing amounts of metastable polymorphic form may convert to the more stable polymorphic form similar to that present in the physical mixture. From the dissolution behavior of the coprecipitate at different ages, it appears that in freshly prepared coprecipitate the fraction of the metastable form was higher which exhibited the unpredictable or erratic dissolution profile. Durning aging, due to the possible conversion of a considerable fraction of the metastable form the time for the "match up" of the dissolution profile of the aged coprecipitate to that of the corresponding physical mixture decreased.

CONCLUSIONS

Coprecipitates of prednisolone showed remarkably fast dissolution, releasing more than 90% of the drug in less than 10 minutes, compared to about 75% drug dissolved in two hours from the untreated drug. Dissolution profiles of the formulations indicated the possibility of the presence of amorphous or metastable polymorphic form in the coprecipitates. Crystal behavior transformation during coprecipitation is not very surprising in case of a drug such as prednisolone which is liable to undergo polymorphic changes.

It is evident from this study that although coprecipitation technique is very promising to improve the dissolution rate of poorly water soluble drugs, a major stability problem may arise if the drug is liable to polymorphic change. From the results of this study it is concluded that dissolution sampling for drugs which are sensitive to polymorphism should be continued for a resonable time after about 90% drug has dissolved in order to exclude any possibility of either the presence of, or the conversion of the drug to its other polymorphic form(s).

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