



Studies on Dissolution Enhancement of Prednisolone, a Poorly Water-Soluble Drug by Solid Dispersion Technique

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ABSTRACT

Introduction: Prednisolone is a class II substance according to the Biopharmaceutics Classification System. It is a poorly water soluble agent. The aim of the present study was to improve dissolution rate of a poorly water-soluble drug, prednisolone, by a solid dispersion technique. **Methods:** Solid dispersion of prednisolone was prepared with PEG 6000 or different carbohydrates such as lactose and dextrin with various ratios of the drug to carrier i.e., 1:10, 1:20 and 1:40. Solid dispersions were prepared by coevaporation method. The evaluation of the properties of the dispersions was performed using dissolution studies, Fourier-transform infrared spectroscopy and x-ray powder diffractometry. **Results:** The results indicated that lactose is suitable carriers to enhance the in vitro dissolution rate of prednisolone. The data from the x-ray diffraction showed that the drug was still detectable in its solid state in all solid dispersions except solid dispersions prepared by dextrin as carrier. The results from infrared spectroscopy showed no well-defined drug-carrier interactions for coevaporates. **Conclusion:** Solid dispersion of a poorly water-soluble drug, prednisolone may alleviate the problems of delayed and inconsistent rate of dissolution of the drug.

Introduction

Improvement of the dissolution rates of water-insoluble drugs is one of the most challenging issues of drug development, because the enhanced dissolution rates can enhance drug oral bioavailability.¹ The solid dispersion technique for water-insoluble drugs developed by Chiou and Reigelman² supplies an effective way to increase the dissolution rates of drugs.^{3,4} Details of different types of solid dispersion systems and the mechanisms of drug release from these systems have been reviewed in details.² Solid dispersion can be prepared by formulating

supersaturated systems of the drug employing various types of carriers, ranging widely from water-soluble to amphiphilic and lipid-soluble ones.⁴⁻⁷ Drugs molecularly dispersed in proper carriers may reach the maximum levels of particle size reduction, therefore the surface area increase, which results in enhanced dissolution rates.⁸

Numerous attempts⁹⁻¹⁶ have been made to improve the dissolution rate of prednisolone, a very slightly water soluble glucocorticoid to obtain more rapid and complete

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absorption. One of the limitations of common solvent method is the need for a solvent that dissolves hydrophilic carrier and hydrophobic drug at the same time which may not be applicable for some carriers such as carbohydrates. In our previous investigations we have demonstrated that co-evaporates with hydrophilic carriers could be prepared by using two different but mutually soluble solvents.^{17,18} Therefore the need for a common solvent of drug and carrier is not considered as an absolute requisite for preparation of co-evaporates. This broadens the application of the co-evaporation technique for more extensive range of drugs and carriers. In the present study, efforts were made to improve the dissolution behavior and consequently absorption, of prednisolone by applying the solid dispersion technique using lactose, dextrin, and PEG 6000 as hydrophilic carriers.

Materials and methods

Materials

For preparation of solid dispersions the following materials were used: lactose monohydrate (DMV, Netherland); mannitol, dextrin, PEG 2000, PEG 4000, PEG 6000 (Merck, Germany); prednisolone (Abureihan, Iran); Chemicals used for buffer preparation were reagent grade. All other materials used were of analytical or high performance liquid chromatography (HPLC) grade and were purchased from Merck (Germany).

Preparation of solid dispersions, physical mixtures and treated physical mixtures

Physical mixtures were prepared by mixing prednisolone with the hydrophilic carriers for 5 min in 100 mL bottles, until a homogenous mixture was obtained. The resulting mixture was sieved and the 105–250 micron particle size fraction was obtained using 60-140 mesh screens. The powders were stored in a screw-cap vial at room temperature.

Treated physical mixtures were prepared by mixing treated drug and treated carriers in 100-mL bottles. Treated drug was prepared by mixing alcoholic solution of prednisolone with distilled water until a homogenous mixture was obtained. Treated carrier was prepared by dissolving it in water and adding alcohol 96% until a homogenous mixture was obtained.

The objective of preparation of treated physical mixtures is to investigate if evaporation of the drug and carrier separately may affect release of the drug from solid dispersions.

Co-evaporates were prepared in the following prednisolone-carrier ratios: 1:10, 1:20, and 1:40 (w/w). Co-evaporates were prepared by dissolving the components separately in a minimum volume of ethanol or distilled water, respectively. The alcoholic solution of

prednisolone was then poured into the aqueous solution of the carrier under continuous stirring. The mixture was then heated in a water bath (70°C) under vacuum and vigorous stirring.

Initially, a transparent to a translucent viscous mass was observed and finally a pale yellow coevaporate was formed. The moist mass was transferred to a vacuum desiccator and kept at 50°C overnight. The solid mass was ground and the particle size fraction of 105–250 micron was separated using 60-140 mesh screens and kept in a screw-capped glass vial until use.

Dissolution studies

Hand-filled, hard gelatin capsules of the formulations, containing 5 mg of the drug, were used for the dissolution studies. The test was conducted using USP 30 Apparatus I at 50 rpm. The dissolution medium consisted of 900 ml distilled water which was maintained at 37 (± 0.5) °C. The duration of the test was 30 minutes. A 5-ml aliquots were withdrawn at appropriate time intervals, and replaced with a 5 ml of distilled water and assayed by UV spectrophotometry at 246.8 nm. Cumulative percentages of the drug dissolved from the preparations were calculated. Three replicates of each dissolution test were carried out.

Mean percent dissolution (MPD) and dissolution efficiency (DE)¹⁹, were used to compare dissolution profiles of binary systems Eq. (1):

$$MPD = \frac{\sum_{i=1}^n (PD)_i}{n} \quad (1)$$

Where i is the sample number, n is the number of dissolution sample times and PD is the percent drug dissolved at time intervals Eq. (2):

$$DE = \frac{\int_0^T Y \times dt}{Y_{100} \times T} \times 100\% \quad (2)$$

Where Y is percent drug released as a function of time, T is the total time of drug release and Y_{100} is 100 percent drug released.

Powder X-ray diffraction

The powder X-ray diffraction (PXRD) pattern of all ingredients and all binary systems were recorded using an automated siemens X-ray diffractometer (Siemens D5000, Munich, Germany). Cross sections of the ingredients and all binary systems were taken and held in place on a quartz plate to Cu K α radiation of wave length 1.5406 Å. The samples were analyzed at room temperature over a range of 5-70° 2 θ with sampling intervals of 0.02° 2 θ and scanning rate of 6°/min.

Fourier-transform infrared spectroscopy

Fourier-transform infrared Spectroscopy (FT-IR) were obtained on a Bomem 2000 FT-IR system (Bomem Quebec, Canada) using the KBr disk method. Samples were mixed with KBr powder and compressed to 10-mm discs by hydraulic press at pressure of 10 tons for 30 seconds. The scanning range was 450-4000 cm⁻¹ and resolution was 2 cm⁻¹.

Results and discussion

Dissolution studies

The release of prednisolone from solid dispersions, physical mixtures and treated physical mixtures was determined in distilled water. DE and MPD values are represented in Table 1.

Table 1. DE and MPD of prednisolone-carrier binary systems (standard deviations were all less than 10%).

Sample	Pure drug	Solid dispersion			Treated Physical mixture	Physical mixture			
Drug Carrier Ratio		1:10	1:20	1:40	1:40	1:10	1:20	1:40	
Without carrier	DE	20.65	-	-	-	-	-	-	
	MPD	18.32	-	-	-	-	-	-	
Lactose	DE	-	80.98	83.18	80.71	71.24	65.39	73.73	70.24
	MPD	-	73.05	75.12	72.95	63.77	57.80	66.60	62.45
Dextrin	DE	-	50.62	62.49	68.82	65.28	31.42	38.11	39.51
	MPD	-	45.10	56.00	61.31	58.37	27.47	33.68	34.41
PEG 6000	DE	-	60.93	60.78	53.74	55.18	42.36	51.61	43.25
	MPD	-	53.95	52.90	46.05	48.42	35.76	44.14	37.17

It is evident that the dissolution rate of the solid dispersions of prednisolone prepared with lactose, dextrin and PEG 6000, are higher than that of pure drug and physical mixtures of ingredients. Moreover the dissolution rate of treated physical mixtures was higher compared to related physical mixtures.

Possible explanations of the increased dissolution rate of solid dispersions have been proposed by Craig and Ford^{20,21}, which include: reduction of drug crystallite size, a solubilization effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of the drug, dissolution of the drug in the hydrophilic carrier, conversion of the drug to the amorphous state and finally the combination of the above mentioned mechanisms.

Dry mixing of prednisolone with carrier brings the drug in close contact with the hydrophilic carrier. The increased dissolution rate observed in these cases can be contributed to several factors such as a solubilization effect of the carrier, improved wettability of the drug and inhibition of particle aggregation.

Dissolution profiles of solid dispersions with lactose showed an increase in the dissolution rate of prednisolone with respect to the drug by itself which could be due to high hydrophilicity of lactose (Figure 1). Also, increasing the weight fraction of prednisolone in the solid dispersions did not affect noticeably the dissolution rate of the dispersions prepared with lactose (Figure 2).

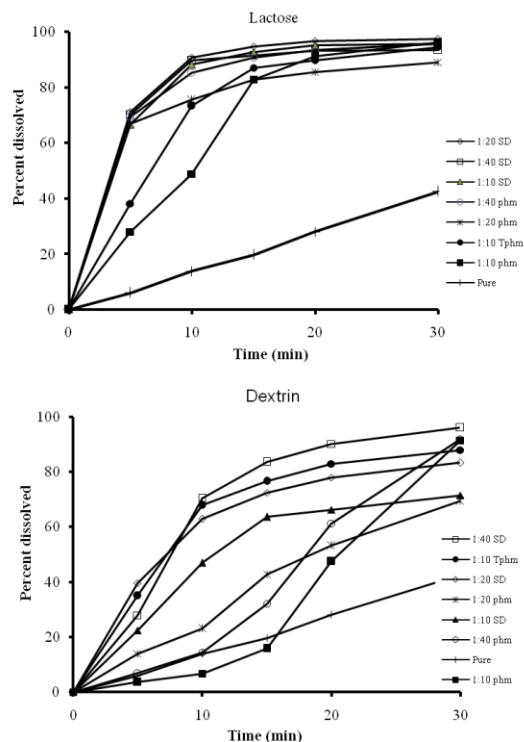


Figure 1. Dissolution profiles of physical mixtures (PM), treated physical mixtures (TPM) and solid dispersions (SD) of prednisolone with lactose and Dextrin.

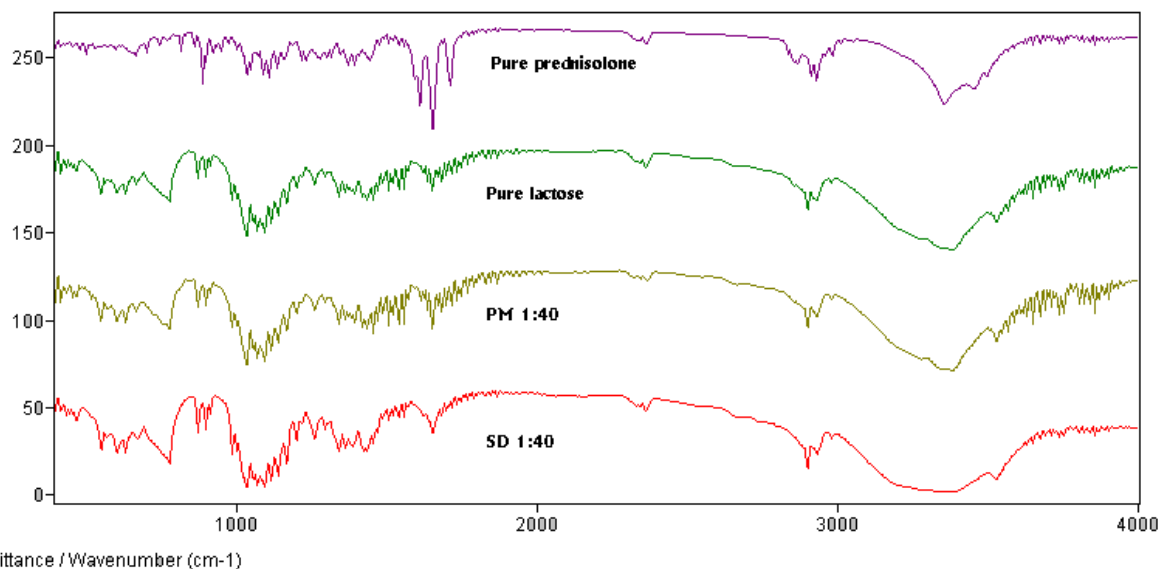


Figure 2. FT-IR spectra of pure prednisolone, lactose, 1:40 physical mixture (PM) of prednisolone with lactose, and 1:40 solid dispersion (SD) of prednisolone with lactose

This is not unexpected, as it has been previously shown that an increase in the weight fraction of the drug does not necessarily decrease the dissolution rate.^{17, 22} Hence utilizing lactose in a ratio of 1:10 should be enough for reaching higher dissolution rate.

As it can be seen from Figure 1, the solid dispersion of the drug with dextrin showed enhanced dissolution rate.^{17, 18}

Compared to the drug alone, an improvement in the dissolution rate was achieved for the formulations containing PEG 6000. Dissolution rate was decreased increasing the ratio of PEG 6000. This phenomenon may be attributed to formation of viscous boundary layer at the surface of the polymer at higher carrier ratios. However, the release of prednisolone from treated physical mixtures in the ratio of (1:40) was slightly faster than the release from coevaporates. This could be due to the fact that dissolution mechanism of solid dispersion with PEG 6000 might be predominantly diffusion-controlled, and presumably the high viscosity of this carrier in stagnate layer is the main factor to control the dissolution rate.

Powder X-Ray Diffraction (PXRD)

The extent of crystallinity affects dissolution of drugs. An amorphous or metastable form will dissolve promptly because of its higher internal energy and greater molecular motion, which increase thermodynamic properties compared to crystalline materials.^{23,24} Crystallinity was determined by comparing

some representative peak heights in diffraction patterns of the solid dispersions with those of physical mixtures. Our findings revealed that prednisolone was in its crystalline forms in the physical mixtures and solid dispersions prepared with lactose without any change compared to the corresponding treated physical mixtures and physical mixtures of the drug. On the contrary solid dispersions prepared with dextrin were characterized by the complete absence of any diffraction peaks, suggesting a complete amorphization in the amorphous carrier. In the case of solid dispersions prepared with PEG 6000, prednisolone was still detectable in crystalline form. Therefore no complete amorphization occurred.

Fourier-transform infrared spectroscopy

Fourier-transform infrared (FT-IR) spectroscopy was used to further characterize possible interactions between the drug and carrier in the solid state. From the structures of the prednisolone, lactose, dextrin and PEG 6000, it can be assumed that possible interaction could occur between the hydroxyl or carbonyl group of prednisolone and the hydroxyl group of these carriers. Any sign of interaction would be reflected by a change in the position of C=O vibration and disappearance of O-H stretching depending on the extent of interaction.

The results from FT-IR spectroscopy showed that incorporation of prednisolone into PEG 6000, lactose, did not modify their peak positions and trends. These results further indicate the absence of well-defined

interaction between prednisolone and PEG 6000, lactose as already confirmed from the X-ray diffraction study. The spectrum of prednisolone showed characteristic bands of the OH group which were found at 3200-3500 cm^{-1} (OH involved in intermolecular association). Two carbonyl stretching peaks appears as a very strong band at 1708 cm^{-1} and 1654 cm^{-1} . The spectrum of dextrin showed, amongst others, important bands at 2953 cm^{-1} (C-H stretching) and 1109 cm^{-1} (C-O stretching). A very broad band was also visible at 3446 cm^{-1} , which was attributed to the presence of water. Important vibrations detected in the spectrum of PEG 6000 are the C-H stretching at 2890 cm^{-1} and the C-O stretching at 1110 cm^{-1} and OH stretching at 3350 cm^{-1} . Comparing the spectra of physical mixtures and solid dispersions of prednisolone with lactose, PEG 6000, and dextrin no difference was shown in the position of the absorption bands. The spectra can be simply regarded as the superposition of those of prednisolone and carrier. Although it could be expected to have hydrogen bonding between the hydrogen atom of the OH of the drug and one of the lone pairs of the oxygen atom in carrier, this could not be demonstrated.

Conclusion

An increased dissolution rate of prednisolone solid dispersions was observed with increasing the ratio of dextrin to the drug. Controversially, the dissolution rate of the drug was not varied upon increasing the ratio of the carrier to the drug when the drug was dispersed in lactose. However decreased dissolution rate of the solid dispersions was achieved by increasing the ratio of PEG 6000.

In conclusion improving the dissolution rate of prednisolone solid dispersions using polysaccharides like lactose is more appropriate than using dextrin and PEG 6000.

Conflict of interests

The authors declare no conflict of interests.

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