Development of Prednisone:Polyethylene Glycol 6000 Fast-Release Tablets From Solid Dispersions: Solid-State Characterization, Dissolution Behavior, and Formulation Parameters

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ABSTRACT

The aim of the current study was to design oral fast-release polymeric tablets of prednisone and to optimize the drug dissolution profile by modifying the carrier concentration. Solid dispersions were prepared by the solvent evaporation method at different drug:polymer ratios (wt/wt). The physical state and drug:carrier interactions were analyzed by X-ray diffraction, infrared spectroscopy, and scanning electron microscopy. The dissolution rate of prednisone from solid dispersions was markedly enhanced by increasing the polymer concentration. The tablets were prepared from solid dispersion systems using polyethylene glycol (PEG) 6000 as a carrier at low and high concentration. The results showed that PEG 6000-based tablets exhibited a significantly higher prednisone dissolution (80% within 30 minutes) than did conventional tablets prepared without PEG 6000 (<25% within 30 minutes). In addition, the good disintegration and very good dissolution performance of the developed tablets without the addition of superdisintegrant highlighted the suitability of these formulated dosage forms. The stability studies performed in normal and accelerated conditions during 12 months showed that prednisone exhibited high stability in PEG 6000 solid dispersion powders and tablets. The X-ray diffraction showed that the degree of crystallinity of prednisone in solid dispersions decreased when the ratio of the polymer increased, suggesting that the drug is present inside the samples in different physical states. The Fourier transform infrared spectroscopic studies showed the stability of prednisone and the absence of well-defined drug:polymer interactions. Scanning electron microscopy images showed a novel morphology of the dispersed systems in comparison with the pure components.

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KEYWORDS: Solid dispersions, PEG 6000, prednisone, dissolution rate, tablets.

INTRODUCTION

Prednisone is usually considered the oral glucocorticoid of choice for anti-inflammatory or immunosuppressant effects.[1] It is indicated in conditions where corticosteroid therapy is likely to be beneficial, including allergic disorders, asthma, leukemia, thrombocytopenic purpura, insulin resistance in diabetes mellitus, immunosuppression, liver disorders, and ulcerative colitis.[2] It is also used in cancer chemotherapy[3] and is a therapeutic choice for systemic lupus erythematosus.[4] Prednisone is slightly soluble in water and, as a consequence, it can exhibit low and/or variable bioavailability after oral administration.[5] Therefore, a well-designed formulation must be capable of presenting a therapeutically effective amount of the hydrophobic drug to the desired absorption site, in an absorbable form. One technique that can be applied to increase the dissolution rate is the formation of the solid dispersion (SD) with polymeric carriers, such as polyethylene glycol (PEG) derivatives,[6] polyvinylpyrrolidone (PVP),[7] and hydroxypropyl methylcellulose.[8] In particular, PEG 6000 has been used as a carrier for increasing the dissolution rate of several poorly water-soluble drugs, such as tacrolimus,[9] diclofenac,[10] itraconazole,[11] and rofecoxib.[12] SD techniques are very useful in pharmaceutical sciences because of the increasing number of novel drug candidates that are poorly soluble, but there is still limited information available on their ability to be processed into the final dosage forms.[13] Although SDs of prednisone have been studied, the physicochemical properties and the development of tablets from those dispersed systems have not. Allen et al described the preparation of SDs of several glucocorticoids using dextrose, galactose, or sucrose as a carrier (1:40 drug:carrier ratio), but the required high concentration of those carriers would be an important disadvantage for preparing convenient dosage forms of administrable size.[14] Later, Allen et al reported an enhancement of the dissolution rates of hydrocortisone and prednisone by means of the fusion method, using sorbitol, sucrose, or PEG 6000 at a 1:19 drug:carrier ratio.[15] Enhancement of dissolution rates of prednisone by

crystallization in aqueous surfactant solutions was described by Chiou et al.[16] Landin et al investigated the influence of microcrystalline cellulose on the tableting behavior and the stability of prednisone formulations. It was found that prednisone dissolution rate varied significantly with polymeric particle size.[17] Subsequently, Ferrari et al reported the optimization of a prednisone tablet using croscarmellose sodium and 2 filler-binders, dicalcium phosphate dihydrate and anhydrous lactose. It was concluded that using a superdisintegrant excipient is a valid approach to improving drug dissolution.[18] Taking all these factors into account and considering the increased use of oral prednisone in immunosuppressive therapy in combination with other active compounds,[19] we decided to evaluate an alternative formulation for improving prednisone dissolution behavior. The aim of this work was to study the potential of SDs for development of fast-release tablets of prednisone using PEG 6000 as the hydrophilic carrier. The dissolution profile of prednisone from PEG 6000 tablets was compared with that of a reference prednisone tablet without PEG 6000. Also, the long-term stability of prednisone was explored. The morphology of the polymeric systems was studied using scanning electron microscopy (SEM). Furthermore, infrared (IR) spectroscopy and X-ray powder diffraction were used to investigate possible interactions between the components.

Materials and Methods

Materials

Prednisone (Hainan Zhongxin Chemical Co Ltd, Haikou, China), PEG 6000 (Aldrich Chemical Co, Milwaukee, WI), lactose (Foremost Whey Products, Div Wisconsin Dairies, Baraboo, WI), and PVP with molecular weight of 35 000 (Merck, Darmstadt, Germany) were used. All other materials and reagents were of analytical or pharmaceutical grade.

Methods

Preparation of SDs

SDs of prednisone:PEG 6000 at 1:1, 1:3, 1:5, 1:7, and 1:9 weight ratios were prepared by the solvent method. Prednisone was dissolved in 1 mL of ethanol, and the polymer was dissolved in 2 mL of water. The solutions were mixed under magnetic stirring for 30 minutes. Next, the solvents were evaporated under reduced pressure and dried at 40°C until constant weight. The powders were sieved through a 420-μm mesh and then stored in a desiccator at room temperature.

Preparation of Tablets

The composition of prednisone:PEG 6000 (1:1, 1:5, and 1:9 drug:polymer ratio) tablets and the conventional tablet (CT) is given in Table 1. Drug concentration was kept constant at 6.25% (10 mg), and the PEG 6000 concentration was 6.25% (10 mg), 31.25% (50 mg), or 56% (90 mg), respectively. Prednisone:PEG 6000 powders, lactose, and starch were manually blended in a mortar for 10 minutes. Thereafter, the powders were granulated with 10% wt/vol PVP ethanolic solution using a mortar and pestle and passed through a 14-mesh sieve; the granules were dried in a hot air oven at 40°C for 3 hours. Finally, magnesium stearate was added and the granules were passed through a 12-mesh sieve before tableting. A prednisone CT formulation without PEG 6000 was also prepared in a similar manner using the same excipients. Tablets were compressed with a compression force of 12 kN using a single punch–tableting machine (Erweka, Heusenstamm, Germany), equipped with 7-mm concave punches.

Table 1. Composition of Prednisone 10 mg SD Tablets at Various Drug:Polymer Ratios*

Components	1:1	1:5	1:9	CT
PEG 6000 (mg)	10	50	90	—
Lactose (mg)	106	66	26	116
Starch (mg)	20	20	20	20
PVP/EtOH (mg)	0.6	0.6	0.6	0.8

*All tablets contain 3.3 mg of magnesium stearate. SD indicates solid dispersion; CT, conventional tablet; PEG, polyethylene glycol; PVP, polyvinylpyrrolidone; EtOH, ethanol.

Flow Properties of Granulates

Flow properties were measured by the angle of repose φ, by pouring the granules through a glass funnel onto a flat surface. Each granulate was placed in a 100 mL funnel with an orifice of 6 mm, and the powder was allowed to flow under the force of gravity. The amount of powder used was 50 g, and the height of the funnel was 10 cm.

Characterization of Tablets

Disintegration time of the different tablet formulations was determined with an apparatus (UC-21 Disintegration Test System, Hanson Research, Ontario, Canada) according to US Pharmacopeia (USP) testing standards. The disintegration medium was degassed distilled water at 37°C. The friability of the tablet samples was measured using the Roche friabilator, which complies with USP testing standards. Forty tablets of each sample were weighed, placed into the friabilator, and rotated for 4 minutes at a speed of 25 rpm. The tablets were removed from the equipment, brushed gently to remove any loose dust from their surface, and again collectively weighed. Friability of the tablets was calculated as a percentage according to the following equation:

$$Friability(\%) = \frac{Initial\ weight - Final\ weight}{Initial\ weight} \times 100 \quad (1)$$

Thickness was determined using a micrometer (Roche, Basel, Switzerland). Ten individual tablets of each formulation were used. Content uniformity was ensured by weighing the 10 tablets individually, and the drug was extracted in water at 37°C. The drug content was determined by UV analysis (Ultrospec II, LKB-UV spectrophotometer, Cambridge, UK) at 244 nm.

Dissolution Studies

Dissolution studies of prednisone from SDs and tablets were performed according to the method described in USP XXIV, using apparatus 2 (Hanson Research, SR8 8-Flask Bath, Ontario, Canada) with the paddle rotating at 50 rpm in 500 mL of degassed distilled water, at 37°C. SD powders containing 10 mg of prednisone were dispersed on the surface of the dissolution medium while tablets were introduced in the flask and the time 0 was recorded. At different time intervals, 5 mL samples were withdrawn through a filter. The amount of released prednisone was determined by UV analysis at 244 nm. It was found that PEG 6000 did not interfere with the assay at this wavelength. The results presented are mean values of 3 determinations.

Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to various models such as first-order,[20] Higuchi,[21] and Hixson-Crowell,[22] to ascertain the kinetic modeling of drug release.

Morphological Examination of Tablets During Dissolution Studies

Photo imaging was performed on SD tablets $TSD_{1:1}$ and $TSD_{1:9}$ formulations at different times. Tablets were taken out from the medium (degassed distilled water at 37°C) and were imaged by a digital camera (Olympus SP 350, Tokyo, Japan) equipped with zoom lens 3× (38-114 mm).

Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FT-IR) spectra were obtained by an FT-IR-Prestige-21 (Shimadzu, Tokyo, Japan) using the KBr disk method (2 mg sample in 100 mg KBr). Scanning range was 800 to 3800 cm^{-1} with a resolution of 1 per cm^{-1}.

X-Ray Powder Diffraction

Data collection was performed in transmission mode on an automated STOE Powder Diffractometer (STOE and CieGMBH, Darmstadt, Germany). Samples were enclosed between 2 polyacetate films held together by double-sided adhesive tape. Data acquisition and evaluation was performed with the STOE Powder Diffraction Software package, Version 2.75 (STOE and CieGMBH, Darmstadt, Germany).

SEM

The morphology of prednisone:PEG 6000 systems was investigated by means of an AMR 1000 Scanning Microscope (Amray, Bedford, MA). Samples were previously sputter-coated with a gold layer in order to make them conductive. Pictures were taken at an excitation voltage of 20 kV and a magnification of 550×.

Stability Study

Representative samples ($TSD_{1:1}$ and $TSD_{1:9}$) were placed in a controlled temperature cabinet at 25°C, 40°C, and 60°C; the relative humidity was 60%. The content of prednisone was analyzed monthly by UV spectroscopy.

RESULTS AND DISCUSSION

Dissolution Rate Studies of Prednisone:PEG 6000 SDs

Figure 1 shows the in vitro dissolution profiles of prednisone from SDs containing various ratios of drug to carrier. Prednisone is slightly soluble in water,[18] which is reflected in the extent of drug dissolved after 10 minutes (12%). Its hydrophobic property caused the powder to float on the surface of the dissolution medium and prevented the surface powder from contacting the medium. In contrast, the dissolution rate of prednisone from all the PEG 6000 SDs was significantly higher than that of prednisone alone. As the proportion of PEG increased, prednisone dissolution rates increased. The results indicated that $SD_{1:9}$ exhibited 100% drug dissolution within 10 minutes. The hydrophilic properties of

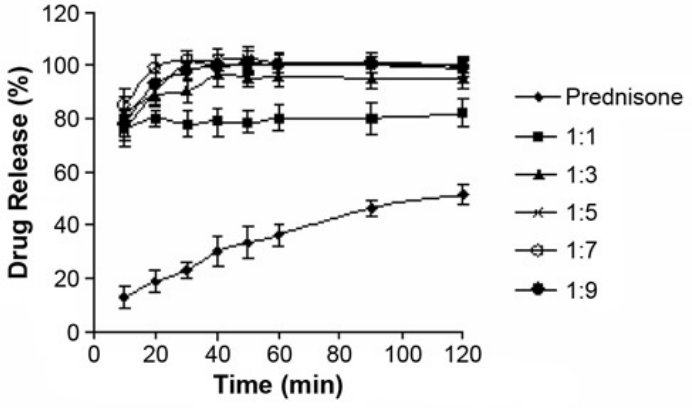

Figure 1. Dissolution profiles of prednisone from prednisone: polyethylene glycol 6000 solid dispersions at 1:1, 1:3, 1:5, 1:7, and 1:9 drug:polymer ratio and prednisone alone.

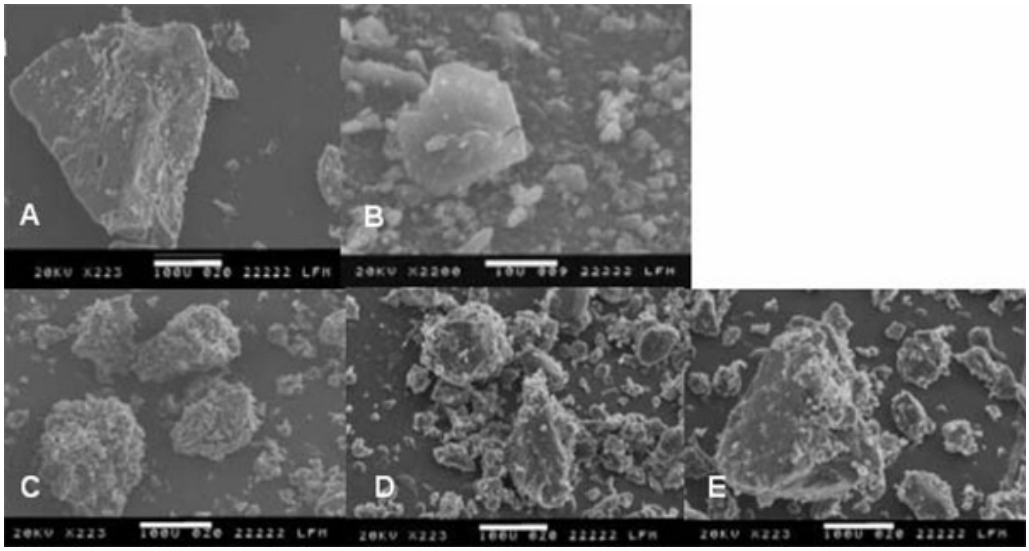

Figure 2. Scanning electron microscopy images of PEG 6000 (A), prednisone (B), and prednisone:PEG 6000 solid dispersions at 1:1 (C), 1:5 (D), and 1:9 (E) drug:polymer ratio. PEG indicates polyethylene glycol.

PEG 6000 probably led to greater wetting and increased surface available for dissolution by reducing interfacial tension between the hydrophobic drug and the dissolution medium.[23]

Solid-State Characterization of Prednisone: PEG 6000 Systems

SEM

Figure 2 shows SEM images of the pure components and SD systems. PEG 6000 (Figure 2A) existed in a crystalline mixture of smooth-surfaced particles (100-300 μm) with few smaller particles (20-40 μm), while prednisone (Figure 2B) existed as small irregular particles (10-20 μm). On the contrary, $SD_{1:1}$ (Figure 2C) consisted of more spherical particles of rather irregular surface. In the case of $SD_{1:5}$ (Figure 2D) and $SD_{1:9}$ (Figure 2E), where the polymer ratio was increased, the particles presented a surface morphology similar to that of pure PEG 6000. These micrographs demonstrate the homogeneity of SDs; it is impossible to distinguish the presence of prednisone crystals among the PEG particles. The novel arrangements between prednisone and PEG particles might be responsible for the enhanced drug dissolution rate found for SD systems, in comparison with pure prednisone. To our knowledge, we are the first to attempt to characterize the morphology of prednisone:PEG 6000 systems.

Fourier Transform IR Spectroscopy

FT-IR spectra of pure components and SD systems are depicted in Figure 3. PEG 6000 showed a C-H stretching at 2890 cm^{-1}, a C-O stretching at 1110 cm^{-1}, and an OH stretching at 3350 cm^{-1}. Prednisone presented 3 characteristic bands for carbonyl groups at 1622 cm^{-1} (α-β-unsaturated), 1688 cm^{-1} (aliphatic), and 1707 cm^{-1} (cyclic) and a characteristic broad band of a hydroxyl group around 3365 to 3260 cm^{-1}. In agreement with their chemical structures, formation of hydrogen bonds between the carbonyl groups of

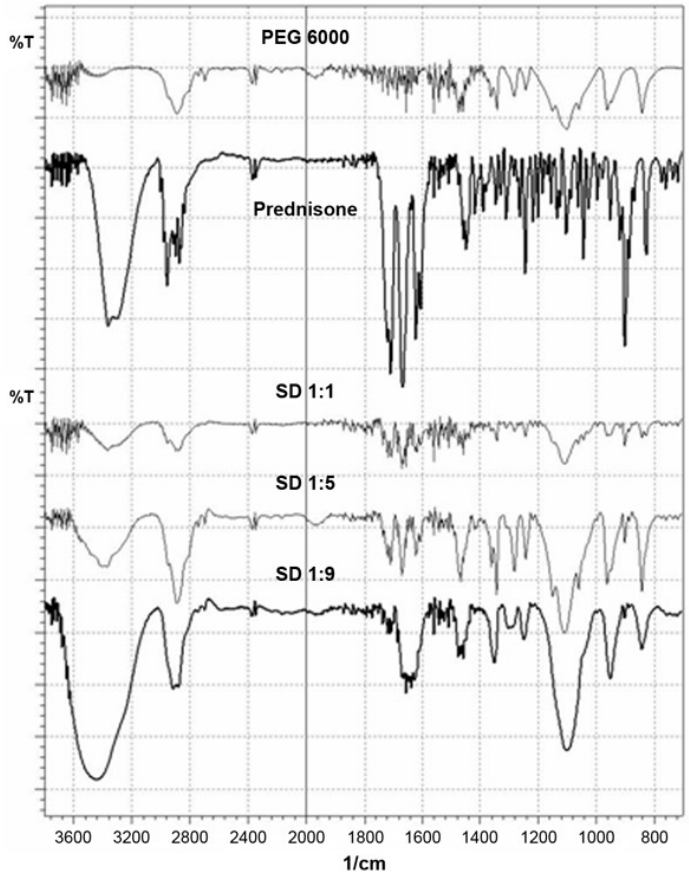

Figure 3. Infrared spectra of PEG 6000, prednisone, and prednisone:PEG 6000 SDs at 1:1, 1:5, and 1:9 drug:polymer ratio. PEG indicates polyethylene glycol; SD, solid dispersion.

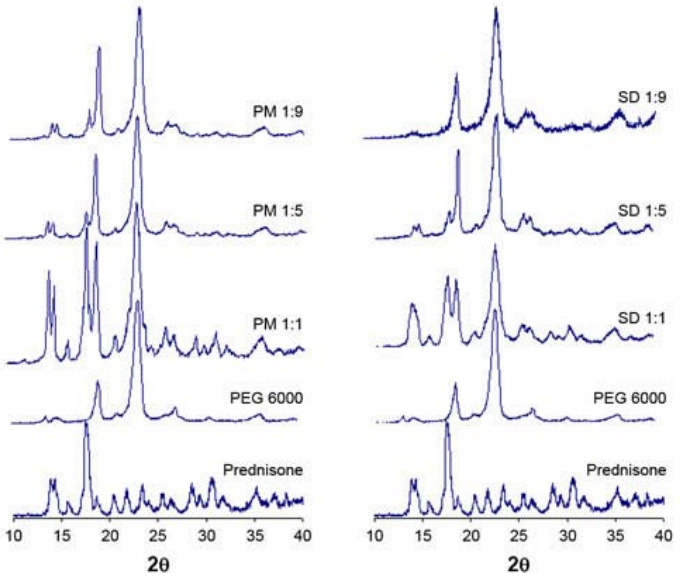

Figure 4. X-ray powder diffraction patterns of prednisone, PEG 6000, prednisone:PEG 6000 PM, and SDs at 1:1, 1:5, and 1:9 drug:polymer ratio. PM indicates physical mixture; SD, solid dispersion; PEG, polyethylene glycol.

prednisone and the hydroxyl groups of PEG 6000 could be expected. In this case, any sign of interaction would be reflected by a change in the position of C=O vibration and disappearance of O-H stretching. When prednisone was dispersed into PEG, the absorption band at 3361 cm^{-1}, which is assigned to OH because of intermolecular association, appeared to decrease in intensity when the amount of carrier was increased. Both intramolecular hydrogen bonding between hydroxyl groups of prednisone and intermolecular hydrogen bonding between hydroxyl groups of prednisone and PEG were suspected. Examination of the IR spectra of prednisone:PEG 6000 SD at 1:1, 1:5, and 1:9 showed insignificant shifts in peaks for the 2 compounds, suggesting the absence of interaction between prednisone and PEG 6000.

X-Ray Powder Diffraction

Figure 4 shows the X-ray powder diffraction patterns of prednisone, PEG 6000, physical mixtures, and SDs at 1:1, 1:5, and 1:9 drug:polymer ratios. PEG 6000 revealed 2 distinct peaks at 19 and 23° 2θ, characteristic of its crystallinity.[24] Prednisone was characterized by 2 prominent diffraction peaks in the range of 10° to 30° 2θ. The diffraction patterns of prednisone in all physical mixtures were similar to those of the pure drug, indicating that the crystallinity of prednisone did not essentially change. The smaller intensity of some peaks of prednisone could be due to the dilution effect related to increasing the polymer ratio. On the other hand, diffraction patterns of SD systems showed fewer, broader, and less intense peaks. When PEG 6000 content was increased from 50% (1:1 SD) to 90% (1:9 SD), some characteristic peaks of prednisone (17.66°, 28.68°, and 30.78°) gradually decreased, while other peaks disappeared (ie, 13.56° and 14.34°). In addition, the positions of PEG 6000 patterns in SD systems were the same and superimposable, which ruled out the possibility of chemical interaction between prednisone and PEG 6000. These results suggest that prednisone is dispersed homogeneously in an amorphous state or dissolved into PEG 6000.[25]

Studies of Prednisone:PEG 6000 Tablets

Flow Characteristics

It is very well known that poorly flowing powders or granulations present several difficulties to the compression process. In general, pharmaceutical powders exhibit an angle of repose between 34° and 48°.[26] Thus, the flow of granulates containing different amounts of PEG 6000 (6.25%, 31.25%, and 56%) was determined by the angle of repose φ. Although PEG micrographs (Figure 2) showed crystals of irregular shape that could lead to poor flow characteristics because of friction and cohesiveness between particles,[27] these selected blends exhibited passable flow, with angles of repose between 41° and 44°.

Physical Characterization of PEG 6000 Tablets

The diameter, friability, thickness, and weight of formulated tablets are described in Table 2. To be acceptable by USP standards, the weight variation tolerance for uncoated tablets must be 7.5% or less. It was found that weight variation

Table 2. Technological Characterization of Prednisone 10 mg SD Tablets at Various Drug:Polymer Ratios*

	1:1	1:5	1:9	CT
Content uniformity (%)	98.82 ± 1.9	98.21 ± 1.7	97.86 ± 2.0	98.91 ± 2.3
Weight variation (%)	3.6 ± 0.2	4.2 ± 0.7	4.6 ± 0.4	2.9 ± 0.1
Friability (%)	0.35 ± 0.5	0.38 ± 0.1	0.43 ± 0.3	0.74 ± 0.2
Thickness (mm)	3.8 ± 0.2	3.8 ± 0.9	4.1 ± 0.4	3.5 ± 0.1
Diameter (mm)	7.0 ± 0.4	7.1 ± 0.5	7.0 ± 0.9	7.0 ± 0.5
Disintegration time (min)	4 ± 0.8	7 ± 0.1	8 ± 0.6	2 ± 0.5

*All values represent mean ± standard deviation (n = 3). SD indicates solid dispersion; CT, conventional tablet.

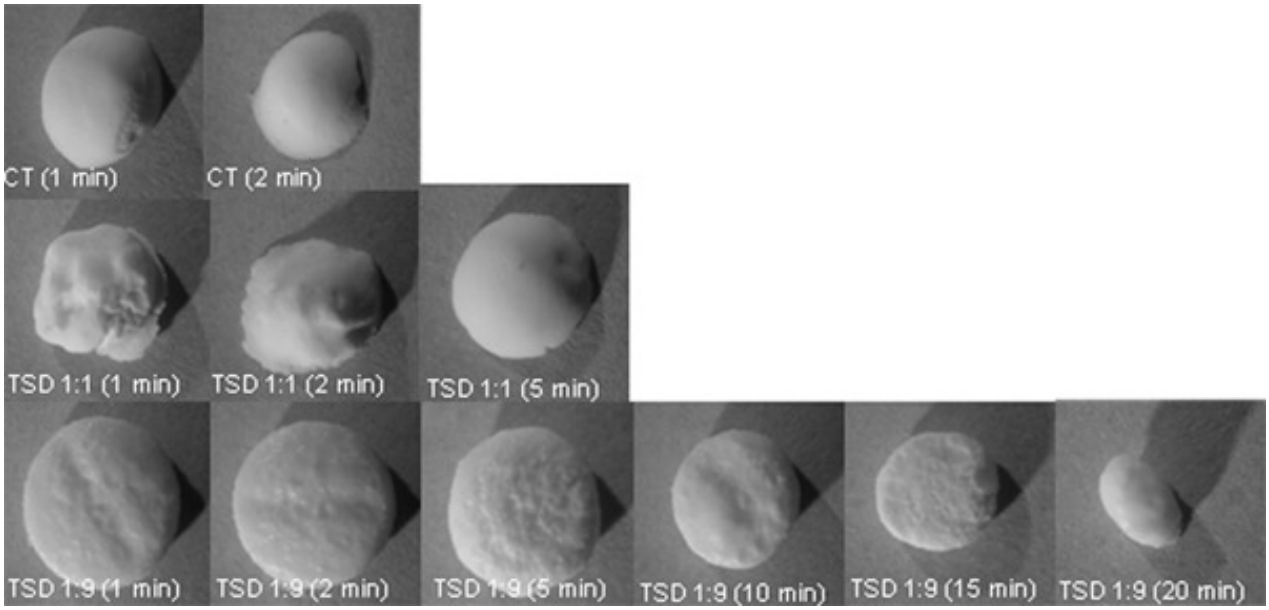

Figure 5. Morphology of prednisone CT and prednisone:PEG 6000 TSD at 1:1 and 1:9 drug:polymer ratio during dissolution studies. CT indicates conventional tablet; PEG, polyethylene glycol; TSD, solid dispersion tablet.

increased with the amount of PEG 6000, up to 4.6%. The friability obtained (<1%) confirmed the suitability of wet granulation technology. Good uniformity in drug content was found among different batches of tablets.

Disintegration Time

Previous studies indicated that PEG 4000[28] or PEG 6000[29,30] prolongs the disintegration time of tablets. As shown in Table 2, formulations $TSD_{1:5}$ and $TSD_{1:9}$, containing 31.25% and 56% PEG 6000, showed a disintegration time of 7 and 8 minutes, respectively. Tablets prepared with 6.25% PEG 6000 ($TSD_{1:1}$) had a disintegration time of 4 minutes. All tablet formulations fulfilled USP requirements (<15 minutes), but when there was a large amount of PEG, its binding properties were stronger than the swelling and disintegrating effect of the starch, slowing disintegration. In contrast, when there was a small amount of PEG ($TDS_{1:1}$), the effect of the starch was more pronounced, allowing for faster disintegration. As expected, the CT without PEG 6000 disintegrated rapidly (2 minutes).

Dissolution Studies of Tablets

Oral dosage forms containing PEG 6000 have been reported to increase as well as decrease the drug release.[31-33] It was expected that the dissolution times would follow the same pattern as the disintergration time (Table 2). Surprisingly, no correlation between disintegration time and dissolution of tablets with PEG 6000 was observed, in contrast with several previous reports describing a direct correlation between these 2 parameters.[34-36] As can be observed in Figure 5, PEG 6000 tablets appeared to disintegrate progressively, keeping almost the same shape, when they came into contact with the neutral medium. This phenomenon could be controlled by the binding effect of PEG 6000, which is more pronounced at high polymer ratio ($TSD_{1:9}$). In contrast, CTs disintegrated within 1 to 2 minutes, as could be expected for tablets formulated without PEG. Following a trend observed in the dissolution assay of SD powders, there was a significant enhancement of the dissolution rate of prednisone from tablets when the polymer concentration increased from 6.25% ($TSD_{1:1}$) to 56% ($TSD_{1:9}$). The released amount of prednisone from $TSD_{1:1}$, $TSD_{1:5}$, and $TSD_{1:9}$ was around 45% during the first 10 minutes, probably because of the lag time

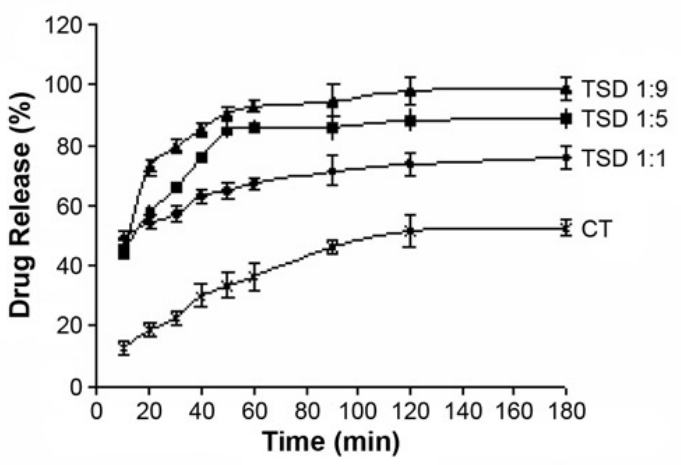

Figure 6. Dissolution profiles of prednisone from prednisone CT and from prednisone:PEG 6000 TSD at 1:1, 1:5, and 1:9 drug:polymer ratio. CT indicates conventional tablet; PEG, polyethylene glycol; TSD, solid dispersion tablet.

Table 3. Drug Release Kinetics of Prednisone 10 mg SD Tablets at Various Drug:Polymer Ratios*

Formulation	First-Order Model	Higuchi Model	Hixson-Crowell Model
1:1	0.9555	0.8918	0.9002
1:5	0.9804	0.9037	0.9023
1:9	0.9909	0.8770	0.8909

*SD indicates solid dispersion.

produced by the binding effect of the polymer and the disintegration process. At the end of the assay, the amount of prednisone released from $TSD_{1:9}$ was 99%. In comparison with CTs formulated without PEG 6000, SD tablets clearly performed better and a significant enhancement in dissolution characteristics was observed. Drug dissolution rate was faster for SD tablets ($TSD_{1:9}$), with 46% released within 10 minutes as compared with 13% for CT. After 120 minutes, drug released from $TSD_{1:9}$ was 99%, while drug released from CT was 50% (Figure 6). Dissolution profiles were also analyzed according to 3 release models: Hixson-Crowell, Higuchi, and first order. It was found that the first-order model produced the highest correlation coefficient (Table 3).

Stability

Data for stability studies performed for $TSD_{1:1}$ and $TSD_{1:9}$ formulations at 25°C, 40°C, and 60°C, with a relative humidity of 60%, revealed that no considerable differences in drug content were observed during 1 year. Mean stability for 1 year was above 95% at 40°C, and above 93% at 60°C.

Lot Reproducibility

Three batches of each formulation were prepared and the dissolution rate of prednisone was evaluated under the same conditions. The resulting drug release profiles from these 3 different batches showed no significant difference among the release profiles for each set of 3 batches, indicating that this manufacturing process is reliable and reproducible.

CONCLUSIONS

SDs of prednisone prepared with PEG 6000 by the solvent evaporation method resulted in greater increases in drug dissolution. As demonstrated by both X-ray diffraction and SEM, a decreased crystallinity of prednisone and the surface morphology of the polymeric particles explained this improved dissolution rate. Tablets containing those SD particles had drug dissolution profiles that were better than those of CTs without PEG 6000. Moreover, flow properties of the granules as well as disintegration analysis and technological parameters of the tablets indicated that PEG 6000 is a suitable excipient for the development of prednisone fast-release tablets.

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