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Characteristics of Bicalutamide Solid Dispersions and Improvement of the Dissolution

Fuzheng Ren, Qiufang Jing, Yanhui Tang, Yongjia Shen, Jialei Chen, Feng Gao and Jingbin Cui
Department of Pharmaceutical Engineering, School of Chemistry and Pharmaceutics, East China University of Science and Technology, Shanghai, 200237, China

ABSTRACT The purpose of our study was to formulate and evaluate bicalutamide (BL) solid dispersions (SD). The physicochemical properties were evaluated by differential scanning calorimetry (DSC), Fourier-Transform infrared (FT-IR) spectroscopy, Powder X-ray diffractometry (PXRD), dissolution studies, and stability studies. The dissolution studies demonstrated that the dissolution of BL from BL-SD increased with an increase in carrier content (PVP K30). X-ray assays and DSC results both confirmed the amorphous state of BL in BL-SD. Stability studies conducted after 6 months showed that BL exhibited excellent stability in the solid dispersion of PVP K30 (1:5).

KEYWORDS Bicalutamide, Solid dispersion, PVP K30, Dissolution rate, Amorphous state

INTRODUCTION

Bicalutamide (BL) is a specific nonsteroidal antiandrogen for use in combination therapy, with medical castration, for advanced prostate cancer. It has no other known progestational activities and does not cause the side effects associated with steroidal antiandrogens such as cyproterone acetate. It has a long plasma elimination half-life of approximately one week, and is therefore compatible with once-daily dosing. Two other notable advantages of bicalutamide are the retention of libido and sexual potency when the drug is administered as a single agent and a lower incidence rate of diarrhea compared with flutamide (Furr & Tucker, 1996). A commercial product for administering BL is CASODEX® Tablets. It is used for oral administration and each tablet contains 50 mg of BL (Goa & Spencer, 1998). Fig. 1 shows the structure of BL.

BL is a lipophilic drug (log $P_{octanol/water}$ 2.92, where P is the partition coefficient) and has a very low aqueous solubility (<5 mg/L) (Cockshott, 2004) . It is generally considered that compounds with very low aqueous solubility will show dissolution rate-limited absorption (Proudfoot, 1991). The bioavailability of BL is probably limited mainly by its dissolution rate for oral solid-dosage forms. The approaches that can be used for poorly soluble drugs include: (1) solutions using good solvents or cosolvent mixtures, (2) solid

Address correspondence to Qiufang Jing, Department of Pharmaceutical Engineering, East China University of Science and Technology, 363#, No. 130, Meilong Rd., Shanghai 200237, China; Tel: +86-21-64252241; Fax: +86-21-64253255; E-mail: jingqiufang@126.com

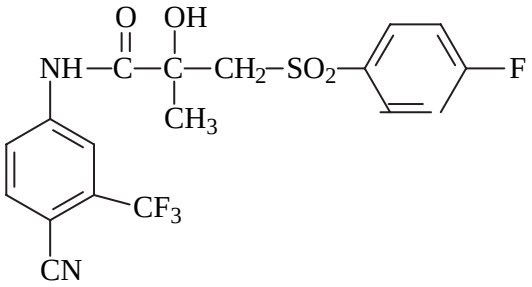

FIGURE 1 **The Structure of BL.**

state manipulation, (3) particle engineering, (4)solubilization by lipids, and (5) solubilization with complexing agents. Although micronised BL used to produce clinical trial tablets was extensively absorbed after oral administration (Cockshott, 2004), solid dispersion (SD) of BL was not reported.

SD can be defined as a distribution of active ingredients in molecular, amorphous, and/or microcrystalline forms surrounded by inert carriers (Chiou & Riegelman, 1971). Formulation of poorly water-soluble drugs such as SD can lead to a marked improvement in their dissolution rates and is often accompanied by an increase in their relative bioavailabilities (Serajuddin, 1999; Leuner & Dressman, 2000; Sethia & Squillante, 2003). The aim of the present study was to investigate the dissolution of BL from BL-SD, and to characterize the solid dispersions made up of PVP K30 and BL using differential scanning calorimetry, infrared spectroscopy, and power X-ray diffractometry. Solid dispersions were prepared by solvent evaporation.

MATERIALS AND EXPERIMENTAL METHODS

Materials and Reagents

Polyvinylpyrrolidone (PVP) was used as received from ISP Technologies, Inc. (Wayne, NJ, USA). All solvents used were of analytical grade. The BL used to prepare the formulations was in the form of a fine powder and it was a generous gift from the Shanghai Institute of Pharmaceutical Industry (Shanghai, China).

Preparation of SD and Physical Mixture

The BL-SD with PVP K30 (1:3, 1:4, 1:5, w/w) was prepared by conventional solvent evaporation. The required amount of PVP K30 was dissolved in ethyl alcohol absolute (containing 20% PVP) in a round-bottom flask with stirring. An appropriate weight of BL powder was dissolved in acetone (containing 15% BL). The two solutions were mixed by stirring. The solvents were evaporated at 50°C under reduced pressure in a rotavapor and they were further dried in a vacuum desiccator over silica gel for 24 h to remove all the residual solvents. The dried mass was lightly ground and sieved. The powder fraction corresponding to a mesh size of less than 80 (180 μm) was collected for further investigation. The dispersions were stored in glass bottles and in a glass desiccator over silica gel at room temperature to avoid changes of the physical structure of the samples between preparation and the measurements. To evaluate the effect of the loading of the drug and the SD carrier, dispersions of various ratios of BL and PVP K30 (1:3, 1:4 and 1:5) were prepared as described above.

Physical mixtures were prepared by simple geometric mixing of the two pure solid components with a spatula, followed by sieving the mixture five times through a 60 mesh sieve.

Dissolution Rate Testing

The drug dissolution profiles of the drug alone, the SD powder and the corresponding physical mixture of BL and PVP K30 were examined according to the USP paddle method. SD equivalent to 50 mg of BL was added to the dissolution medium (900 ml). The dissolution medium consisted of water with 0.6% w/v sodium lauryl sulfate (SLS) at a temperature of 37 ± 0.2°C. The solution was stirred with a rotating paddle at 75 rpm. Samples were withdrawn from each vessel at predetermined time intervals, filtered over a cellulose acetate filter of 0.45 μm (received from Millipore Corp., Billerica, MA, USA), appropriately diluted and assayed using a UV spectrophotometer at 272 nm. The same volume and temperature of fresh medium was replaced and correction for cumulative dilution was calculated. The percent of BL dissolved for each formula ($n = 6$) was plotted versus time. It should be noted that PVP K30 showed negligible absorption at this wavelength.

Powder X-ray Diffractometry (PXRD)

PXRD patterns of the pure ingredients, the SD in the PVP K30 matrix, and the corresponding physical

mixture were recorded using an X-ray diffractometer (model Rigaku D/max 2550 VB/PC, Rigaku, Japan) with Cu/K-α1 line as the source of radiation. The angular range 3–50° 2θ was scanned in step-scan mode (with step width at 0.02°). The diffraction pattern was measured with a voltage of 40 kV and a current of 100 mA.

Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (model Universal V2.3C TA, DSC 2910 Modulated, TA Instruments, New Castle, DE, USA) was used to obtain the DSC curves representing the rates of heat uptake with respect to temperature. About 10 mg of sample was weighed in a standard open aluminum pan. An empty pan of the same type was utilized as the reference. Samples were heated from 25°C to 250°C at a heating rate of 10°C/min., while being purged with dry nitrogen (50 ml/min). Temperature and heat flow calibrations were performed with indium.

Fourier-Transform Infrared (FT-IR) Spectroscopy

The infrared spectra of samples were obtained using an FT-IR spectrometer (Model IR200, Thermo Nicolet Instrument Corp., Fitchburg, WI, USA). About 1~2 mg of the sample was mixed with dry potassium bromide (100~200 mg) using the KBr disk method. The scanning range was 4000–400 cm^{-1}.

Stability Studies

The stability testing was conducted under the International Conference on Harmonization (ICH) stability conditions (Matthews, 1999). An appropriate amount of SD sample powder was placed into glass vials with aluminum-lined caps, stored in a sealed desiccator at 25°C/ 60% RH for 6 months and characterized as a function of exposed time. Sealed desiccators containing saturated salt solutions ($NaNO_2$) were equilibrated at 25°C.

RESULTS AND DISCUSSION

Dissolution Testing

Fig. 2 shows the dissolution profiles of the SD, the physical mixtures (BL-PVP-M) (1:5) and the pure BL.

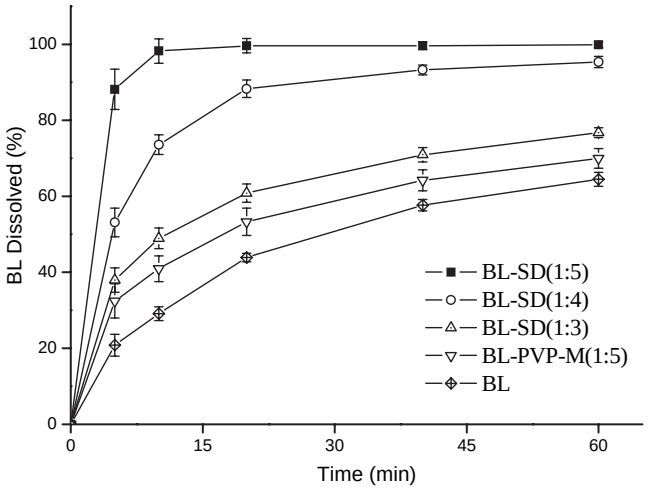

FIGURE 2 **Dissolution Profiles of BL-SD, Physical Mixtures (BL-PVP-M) (1:5) and Pure BL. (*n*=6) Error Bars Represent the Standard Deviation.**

All the solid dispersions (SD) showed higher amounts of the drug being released compared with pure BL and with the corresponding physical mixture (1:5). The amount released increased with an increasing proportion of PVP K30. The SD of BL-SD (1:5) showed the highest cumulative released percentage (about 98% during the initial 10 min.), followed by the 1:4 and 1:3 dispersions. The bioavailability of BL is mainly limited by its dissolution rate. The amount released for physical mixtures (1:5) was lower than solid dispersions (1:3, 1:4, 1:5), but higher than pure BL. Several reasons may account for the increased dissolution: the formation of amorphous BL within the SD; presence of BL in the form of very small crystallites within the SD; a soluble complex formation between the drug and the water-soluble carrier such as PVP K30 (Craig, 2002; Abdul-Fattah & Bhargava, 2002). Next, studies were conducted in order to identify the cause of enhanced BL dissolution from the SD.

Powder X-ray Diffractometry(PXRD)

The presence of crystals in BL at room temperature was clearly confirmed by XRD data. X-ray patterns (Fig. 3) showed no sharp peaks attributable to BL in the BL-SD (1:5), indicating that BL crystals were transformed to an amorphous state during the cosolvent process. In the case of the BL-SD (1:3, 1:4), small peaks were observed, which indicated a crystalline fraction in the BL-SD (1:3, 1:4). It seemed that they could show the transference of crystalline BL to the

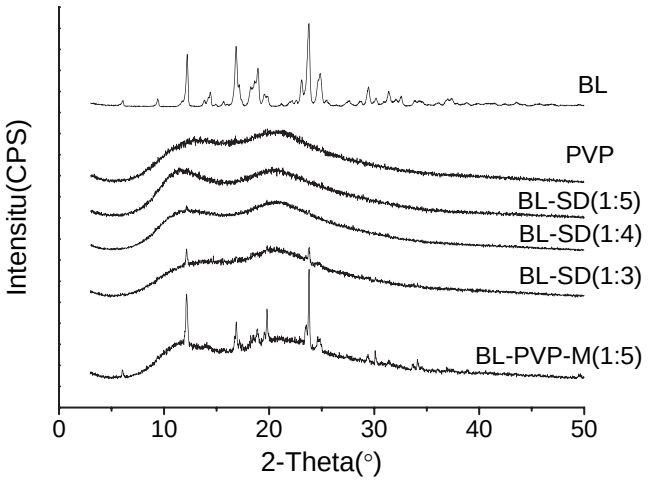

FIGURE 3 **X-ray Diffraction Patterns of BL, BL-SD (1:5) and PVP K30.**

amorphous state. X-ray diffraction data of BL in a physical mixture with PVP K30 still showed crystallinity, which suggested that the mere presence of PVP K30 in the physical mixture had no influence on the physical state of BL.

Differential Scanning Calorimetry (DSC)

The DSC curves of the pure components, the representative physical mixture and the solid dispersions are shown in Fig. 4. A characteristic fusion endotherm appeared for pure BL, with a peak melting point at 195°C, and ΔH 108.5 J/g. During the scanning of PVP K30, a broad endotherm around 90°C was observed, indicating the loss of water due to the extremely hygroscopic nature of PVP polymers (Nair et al., 2002). Because of the amorphous structure of the polymer, no peak melting point was seen in the thermograms. The thermograms of the BL-SD (1:3, 1:4, 1:5) also showed similar broad endotherms around 90°C. In the case of the BL-SD (1:3), a small endotherm was observed near the melting point of BL, with ΔH (1.308 J/g). In contrast, the BL-SD (1:4) showed a weak melting peak around 195°C, and its ΔH was not detected. In the case of the BL-SD (1:5), no endotherm was observed around the melting point of BL. There was a concomitant reduction of its enthalpy with the increase of carrier content in the SD. This change indicated the formation of an SD. The peak melting point at 195°C of BL was observed in the thermogram of the corresponding physical mixture (BL-PVP-M) (1:5). However, there was an observable change in ΔH (10.15 J /g) which probably indicated some interaction between BL and PVP K30 even in the BL-PVP-M. Total disappearance of the drug melting endotherm indicated that BL might be in an amorphous state in BL-SD (1:5). The probable reason was the inhibition of the crystallization of BL by polymers in the SD. Various studies have shown that PVP inhibits crystallization of drugs in SD, resulting in amorphous form of the drug in the SD (Taylor & Zografi, 1997; Matsumoto & Zografi, 1999; Van den Mooter et al., 2001). The mechanism of crystallization inhibition by povidone is often set off by specific interactions, especially hydrogen-bonding between the drug and the polymer. The extent of the inhibition depends on the proportion of the polymer in the SD, with higher proportions resulting in more inhibition. Moreover, DSC-results were in agreement with those of X-ray assays.

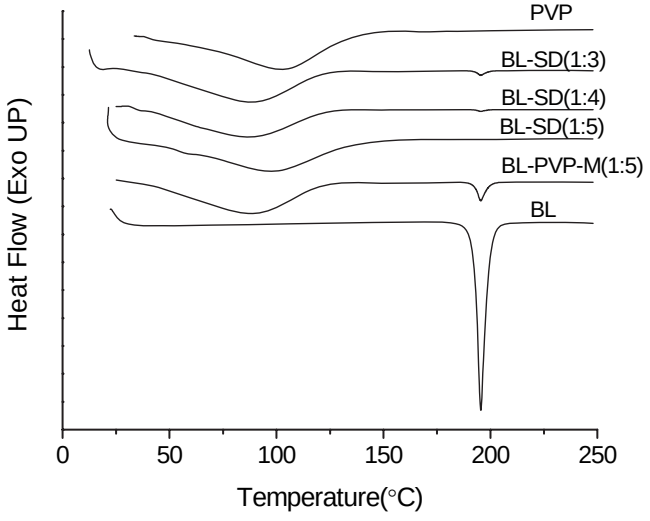

FIGURE 4 **DSC Plots of BL-SD (1:5), Corresponding Physical Mixture (BL-PVP-M) (1:5), Pure BL and PVP K30.**

Fourier-Transform Infrared (FT-IR) Spectroscopy

In order to study interactions between the polymer and the BL, IR spectra of pure BL, PVP K30, and BL-SD (1:5) were conducted. These results are shown in Fig. 5. In compounds with a hydroxyl group, the OH group showed a stretching vibration as a broad band around 3400–3650 cm^{-1}. However, this was not the case with BL. No broad bands were observed and only slight peaks appeared around this region. The most

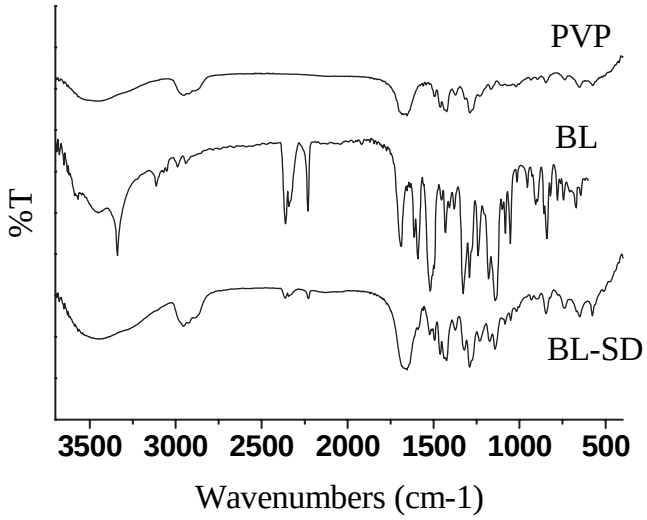

FIGURE 5 IR Spectra of Pure BL, PVP K30, BL-SD (1:5).

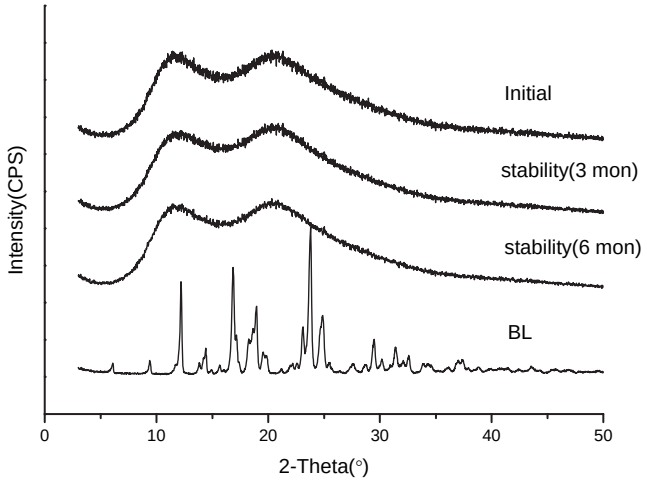

FIGURE 6 X-ray Diffraction Patterns of BL, BL-SD (1:5) Initial, BL-SD (1:5) Three Months at 25°C/60%RH, and BL-SD (1:5) Six Months at 25°C/60%RH.

probable reason was the involvement of the OH group in an intramolecular hydrogen bond with the lone pair of electrons of the carbonyl group. In return, this prevented the appearance of the characteristic band for the stretching vibration of the OH group.

The peak for the N-H group appeared around 3337 cm^{-1}, the peak for the CN group appeared around 2236 cm^{-1}, and the stretching vibration of the carbonyl group typically appeared around 1692 cm^{-1}. The most distinct peak of PVP K30 was the stretching vibration of the carbonyl group that would typically appear around 1715 cm^{-1}. Since the carbonyl group is part of a five-membered heterocyclic ring with a tertiary amide, the peak for the carbonyl group stretching appeared around 1655 cm^{-1}. This band was especially sharp, because of the dipolar nature of the N-C-O group (Weuts et al., 2004). Intermolecular hydrogen bonding was suspected between the hydroxyl group and the N-H group of BL and the carbonyl group of PVP K30. Careful examination of the IR spectra of the SD showed that the concentration of BL in the BL-SD was too low, resulting in a decrease in the intensity of the band. Moreover, the broad band around 3400 cm^{-1} in the PVP case would mask the peak for the N-H group in the spectrum of SD. Although the absence of the peak for the N-H group, the presence of a broad band around 3440 cm^{-1}, and the peak for C=O group shifted insignificantly around 1663 cm^{-1}, these did not constitute conclusive evidence to support the conclusion that intermolecular hydrogen bonding occurred between the polymer and the BL. It was concluded that the presence of an interaction in BL-SD could not be confirmed by FT-IR.

Stability Studies of SD Powder

The current ICH guidelines recommend long-term stability testing to be conducted at 25°C/60% RH. A stability study was conducted for the BL-SD (1:5) at these conditions for 6 months. Sample powders were stored over a desiccant in glass vials with aluminum-lined caps. The XRD, DSC, and in vitro dissolution rates for the amorphous pharmaceutical solids were used to check their stability. The XRD (Fig. 6) of SD powder exhibited no change in peak intensity for BL, suggesting that the amorphous state of the BL was unchanged for 6 months. In addition, the DSC results showed that there were no endotherms at 195°C, which was the melting point of BL. Thus, the DSC results indicated that BL was amorphous after 6 months of storage. Fig. 7 demonstrates that the difference in the dissolution profiles between the initial sample and the six-month sample was insignificant. The results of the XRD patterns, the DSC, and the dissolution rates indicated excellent stability for the amorphous BL-SD powder (1:5) at 25°C/60% RH for six months. We did not find the more commonly observed decrease in dissolution during storage, which was a key limitation of solid dispersions.

CONCLUSIONS

The solid carrier played a significant role in the initial enhancement of drug dissolution in our studies. The above studies indicate that PVP inhibited

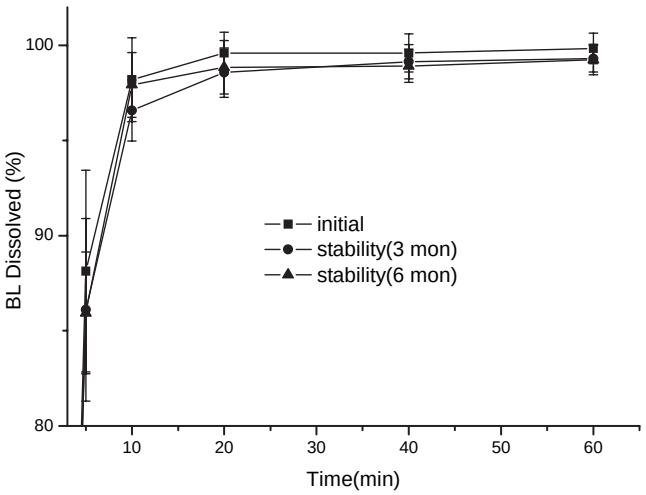

FIGURE 7 **Dissolution Profiles of BL-SD (1:5) Initial, BL-SD (1:5) Three Months at 25°C/60%RH, and BL-SD (1:5) Six Months at 25°C/60%RH. (*n*=6). Error Bars Represent the Standard Deviation.**

the crystallization of drugs, resulting in the amorphous state form of the drug in SD. The rate of the dissolution of BL from BL-SD depended on the concentration of the carrier. Dissolution of BL increased with an increase in carrier content (PVP K30). A high proportion of PVP in the SD could potentially resolve the processing issues that affect the improvement of the dissolution rate. However, using a high proportion of carrier may not be practical considering the increased size of the oral solid-dosage form (such as tablets). Therefore, the BL-SD (1:5) was chosen as the optimized formulation and is considered to be the best candidate for further studies. X-ray assays and DSC results both confirmed the amorphous state of BL in SD. The presence of an interaction in BL-SD could not be confirmed by FT-IR spectroscopy. Six-month stability studies at 25°C, 60% RH showed that BL exhibited excellent stability in the SD of PVP K30.

Overall, SD technology presents the industry with some extremely exciting possibilities with regard to the formulation of BL in order to improve its dissolution.

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