



Pharmaceutical Nanotechnology

Formation of bicalutamide nanodispersion for dissolution rate enhancement

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ABSTRACT

Bicalutamide was loaded on hydrophilic excipients to form nanodispersions via a combination of anti-solvent precipitation and spray drying method. The particle size, BET surface area, contact angles and dissolution rate of the nanodispersions were analyzed. The results indicated that lactose was a suitable matrix to prevent the bicalutamide particles growth and aggregation. The lactose loaded particles had a mean size of 330 nm within a narrow distribution. X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transform infrared (FT-IR) characterization indicated the nanodispersion exhibited unchanged crystalline and chemical structure. Dissolution rate of bicalutamide nanodispersion was significantly faster than that of commercial products. It increased to 94% in 10 min while both commercial formulas Casodex and bicalutamide tablets dissolved 60% and 38% respectively at the same period. It was proposed that the enhanced dissolution rate of bicalutamide nanodispersion contribute to high surface area and well-wetted state of drug particles.

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1. Introduction

It is estimated that above 40% or more of active substances being identified through combinatorial screening programs are poorly soluble in water, which is a critical determinant of oral bioavailability (Lipinski, 2001, 2002). The bioavailability of poor water-soluble hydrophobic drugs with high permeability through biomembrane can be increased by their dissolution rate in the gastrointestinal tract (Amidon et al., 1995). Common approaches to improve dissolution of poor water soluble drugs include application of cosolvents and lipids (Porter et al., 2007, 2008; Pole, 2008), complexing agents (Carrier et al., 2007; Brewster and Loftsson, 2007; Davis and Brewster, 2004), the formation of emulsions and solid dispersions (Fini et al., 2008; Kennedy et al., 2008; Tran et al., 2008; Lakshman et al., 2008), particle size reduction (Rabinow, 2004; Kesisoglou et al., 2007; Keck et al., 2007; Merskio-Liversidge and Liversidge, 2008) or lipid carriers (Tran et al., 2009; Simovic et al., 2009), or control of the API's polymorphic form (Crowley and Zografi, 2002; Schmidt et al., 2003; Strachan et al., 2004; Karjalainen et al., 2005; Masuda et al., 2006; Muster and Prestidge, 2002)

Currently, considerable studies have been conducted to increase the dissolution of drugs by creating active pharmaceutical ingredients (API) nanoparticles (Wang et al., 2007; Zhao et al., 2009; Yang et al., 2008; Zhang and Shen, 2006) because formulation of nanopar-

ticles can provide a way of sustained, controlled and targeted drug delivery to improve the therapeutic effect especially for water-insoluble drug (Praetorius and Mandal, 2007; Medina et al., 2007; Zhang and Feng, 2006). However, the properties of nanoparticles always make them difficult to process into dry powders (Tam et al., 2008; Sepassi et al., 2007; Young et al., 2007; Lindfors et al., 2006). The major challenges faced in the formulation of poorly soluble drug nanoparticles are the solid state stability.

Bicalutamide (BIC) is a pharmaceutically active compound (Fig. 1) that possesses antiandrogenic activity, which is approved by FDA in 1995, thought to prevent the growth of prostate cancer by blocking the action of androgens on the cancer cells. BIC presents two crystalline polymorphs (form I and form II) (Vega et al., 2007), which have the same chemical composition but different internal crystal structures due to different molecular conformation and, therefore, possess different physico-chemical properties (Vippagunta and Brittain, 2001). Form I is more stable than form II, and is already applied for medical use, such as Caxodex, produced by AstraZeneca, has been the most widely used commercial formula. Classified as a BCS class compound (low solubility, high permeability) (Kanfer, 2000), BIC features a low dissolution rate in the gastrointestinal tract, which limits its effective absorption and bioavailability (Shekunov et al., 2006). We have already reported the fabrication of BIC nanoparticles by anti-solvent precipitation (Le et al., 2009). However, the fine pure drug particles have a high tendency to agglomerate and grow because of their higher surface energy, which leads to decrease in the dissolution rate or bioavailability (Swanepoel et al., 2000; Ticehurst et al., 2000; De Villiers, 1996). In order to overcome this issue, it is necessary to keep

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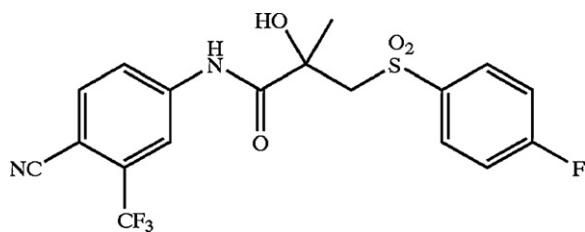


Fig. 1. Molecular structure of bicalutamide.

drug nanoparticles dispersed in a matrix during product formation. Loading of hydrophobic drug nanoparticles on hydrophilic materials has some advantages, one is an improvements in the flowability of the drug powder, which leads to effective formulation, the other is effective wetting (due to hydrophilicity of excipients) and prevention of reagglomeration of drug particles during dissolution (Sanganwar and Gupta, 2008).

Solid dispersion typically involves incorporation of the poor soluble API with polymeric excipients, such as polyethylene glycol (Tran et al., 2008), polyvinylpyrrolidone (Lakshman et al., 2008), and hydrogels (Zahedi and Lee, 2007). More recently, several inorganic materials such as mesoporous silica (Sanganwar and Gupta, 2008; Wang et al., 2010) have been employed. However, to the best of our knowledge, there are few published articles reported on nanoscaled solid dispersion, only Zhang et al. (2008) presented nanodispersion of amorphous form triclosan loaded on PVA by freeze-drying emulsions. However, Amorphous form of API presents numerous formulation stability challenges since the high energy amorphous form tends to undergo molecular reordering to the more thermodynamically stable crystalline form (Newman et al., 2008; Pan et al., 2008; Zhu et al., 2008). Environmental factors play a critical role in determining the amorphous-crystalline transformation rate, in particular temperature and humidity, which may lead to the solid state recrystallization process.

In this study, we report on the preparation of a nano-dimension solid dispersion of BIC crystal form I by combined anti-solvent precipitation and spray-dry process. Conventional water-soluble pharmaceutical excipients were screened as a solid support to stabilize the poorly soluble BIC, which dissolve rapidly on addition of water to disperse the nanoparticles. The as-prepared products were characterized by SEM, FT-IR, XRD, DSC, BET surface area test and contact angle measurement. Dissolution performance of BIC solid nanodispersions are evaluated and compared to the commercially available formula.

2. Experiments

2.1. Materials

Raw BIC (Form I, purity is 99.6%) was purchased from Beijing Guo lian Chenghui Pharmaceutical Technology Co., Ltd. Lactose (>98%), hydroxypropyl methylcellulose (HPMC, CP) and arabia gum (AG, CP) were supplied by Beijing Chemical Reagents Company. Microcrystalline cellulose (MCC, CP) was obtained from FMC Corporation. Deionized water was prepared with Hitech-K Flow Water Purification System (Hitech Instruments Co. Ltd., Shanghai, China). Casodex tablets by AstraZeneca (50 mg dose) and bicalutamide tablets by Shanghai Zhaohui Company, China (50 mg dose) were purchased for the contrast test. All other solvents were analytical grade. High purity water was used throughout the study.

2.2. Preparation of bicalutamide nanodispersions

In the typical experiment, 2 g raw BIC was dissolved in 20 mL N,N-dimethyl acetamide to get the organic solution. Afterwards,

20 mL organic solution was poured into 400 mL deionized water rapidly under stirring conditions. 30 min later, the suspension was filtered. Various excipients were selected for the formulation of nanodispersions including lactose, HPMC, AG and MCC, which was dissolved in water. Next, the prepared BIC filter cake was put into aqueous excipients solution (1 wt%). After mechanically stirring for 10 min at speed of 5000 rpm, the suspension was dried by spray drying process, which was carried out using laboratory scale spray dryer (SD-Basic, Labplant, UK) under the following conditions: inlet temperature, 170 °C; outlet temperature, 60–90 °C; spray flow rate, 20 ml/min; atomization air pressure, 0.65 MPa. Finally, BIC solid nanodispersion was obtained.

2.3. Characterization

Particle morphology was observed using SEM JSM-6360LV (JEOL Inc., Japan). The samples, an appropriate amount of BIC powder or a glass slide with a small drop of the suspension, were fixed on an SEM stub using double-sided adhesive tape and coated with Au at 50 mA for 6 min through a sputter-coater (KYKY SBC-12, Beijing, China). A scanning electron microscope with a secondary electron detector was used to obtain digital images of the samples at an accelerating voltage of 10 kV.

The particle size and zeta potential were analyzed using laser diffractometer (Malvern; ZETASIZER-3000HS). The sample was diluted by deionized water and sonicated to create a homogenous suspension. All the samples were analyzed in triplicate.

X-ray diffraction analysis was employed to detect the crystallinity of BIC, which was conducted using a XRD-6000 diffractometer (Shimadzu, Japan). The powder was placed in a glass sample holder. Cu K α radiation was generated at 30 mA and 40 kV. Samples were scanned from 5° to 45° with a step size of 0.05°.

FT-IR spectra of samples were recorded with a Nicolet model 8700 spectrometer (Nicolet Instrument Corporation, USA) in the wavenumber range of 500–4000 cm⁻¹ to evaluate the molecular states of samples. Samples were diluted with KBr mixing powder at 1% and pressed into self-supporting disks.

The phase transition of samples was analyzed by differential scanning calorimeter (DSC) (Pyris 1, Perkin-Elmer, USA) at a heating rate of 10 °C/min. A dry nitrogen purge of 20 mL/min was employed in the process. Calibration of the instrument with respect to temperature and enthalpy was achieved using high purity standard of indium.

BET surface area was measured using N₂ adsorption method. In this method, calculation was implemented by Surface Area Analyzer ASAP 2010-M (Micromeritics Instrument Corporation, USA) based on the BET equation. Before measuring, sample powder was degassed for at least 4 h.

Contact angle was measured by the sessile drop technique using a goniometer (OCA20, Dataphysics, Germany). Compressed discs of the powders were made at a 30 MPa compression force using a laboratory powder press (model 769YP-15A, Tianjin, China). A droplet of purified water was placed onto the surface of the compressed disc and observed through a low-powder microscope. The contact angle was determined by measuring the tangent of the droplet on the disc surface.

Dissolution studies were carried out following the USP Apparatus 2 (paddle) method using a dissolution apparatus (D-800LS, Tianjin, China). The paddle speed and bath temperature were set at 50 rpm and 37.0 ± 0.5 °C, respectively. Sodium dodecyl sulfate (SDS) (1 wt%) was employed as the dissolution medium. Approximately, 50 mg bicalutamide was added into vessels containing 1000 mL of the dissolution medium. The samples (5 mL) were taken each time at specific intervals and filtered using a 0.45 μm filter, then the concentrations of samples were measured by a spec-

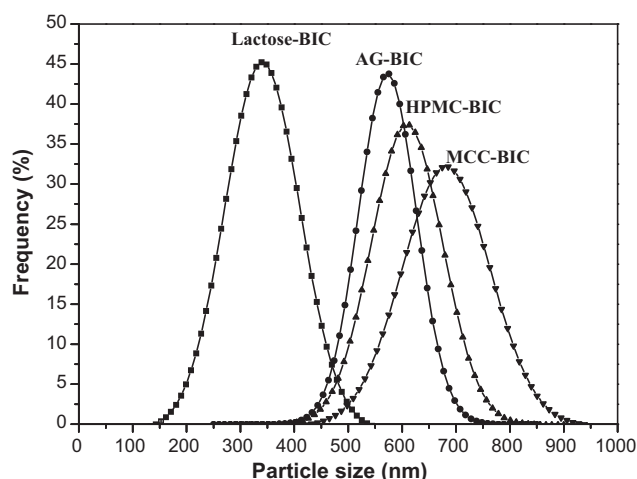


Fig. 2. Particle size distribution of BIC nanodispersions.

trophotometer at 270 nm (UV-3000, Shimadzu, Japan). Each sample was analyzed in triplicate.

3. Results and discussion

3.1. Formulation of BIC nanodispersions

Liquid precipitation methods are able to create nanoparticles of poor water soluble drugs. Precipitation from solution can offer greater flexibility for controlling the crystalline form of the API as well for achieving high drug loadings (Young et al., 2000; Sarkari et al., 2002; Rogers et al., 2004; Matteucci et al., 2006). The API in organic solution may be mixed with an aqueous anti-solvent solution in the presence of stabilizing surfactants to form

ultrafine particles. Hydrophilic groups in the surfactants lead to rapid wetting of the high-surface-area particles in aqueous media. Using this technique, nanoparticle suspensions were designed with different types and concentrations of surfactants, individually or in combination, as a means to control the particle size and surface charge of the prepared nanoparticles (El-Gendy and Berklund, 2009). Surfactants were chosen from a selection of excipients proven to be safe for human use in certain concentrations (Chougule et al., 2007).

The prepared BIC dispersions composed of 50 wt% BIC and 50 wt% excipients. Based on particle size, the most successful combination and ratios for generating BIC nanodispersion turned out to be the formulations. These excipients combinations yielded small particle size (330–680 nm) and played narrow size distribution, as shown in Fig. 2. Combination with lactose was chosen as it showed smaller particle size and narrow size distribution compared to the others.

Particle size and morphology of raw BIC and BIC nanodispersions are compared in Fig. 3. Raw BIC performed irregular shape, with a mean particle diameter of 30 μm . The anti-solvent precipitated particles without excipient show a rod-like shape, with length from some hundred nanometers up to several micrometers. In comparison, lactose–BIC particles exhibit regular morphology, they are rectangular in shape, and the average size was approximately 330 nm in length.

Surface area can significantly influence the drug release characteristics of the system through both kinetic and thermodynamic factors. It is generally recognized that increased surface area can provide enhanced mass transfer during the dissolution process. In all cases, the BIC dispersions exhibited a highly increased surface area compared to the precipitated BIC without excipient, providing an order of magnitude increase in surface area, as shown in Table 1. Among them, lactose–BIC presented the highest BET surface area, which was 10.35 m^2/g , 7 times larger than that of precipitated BIC of 1.43 m^2/g .

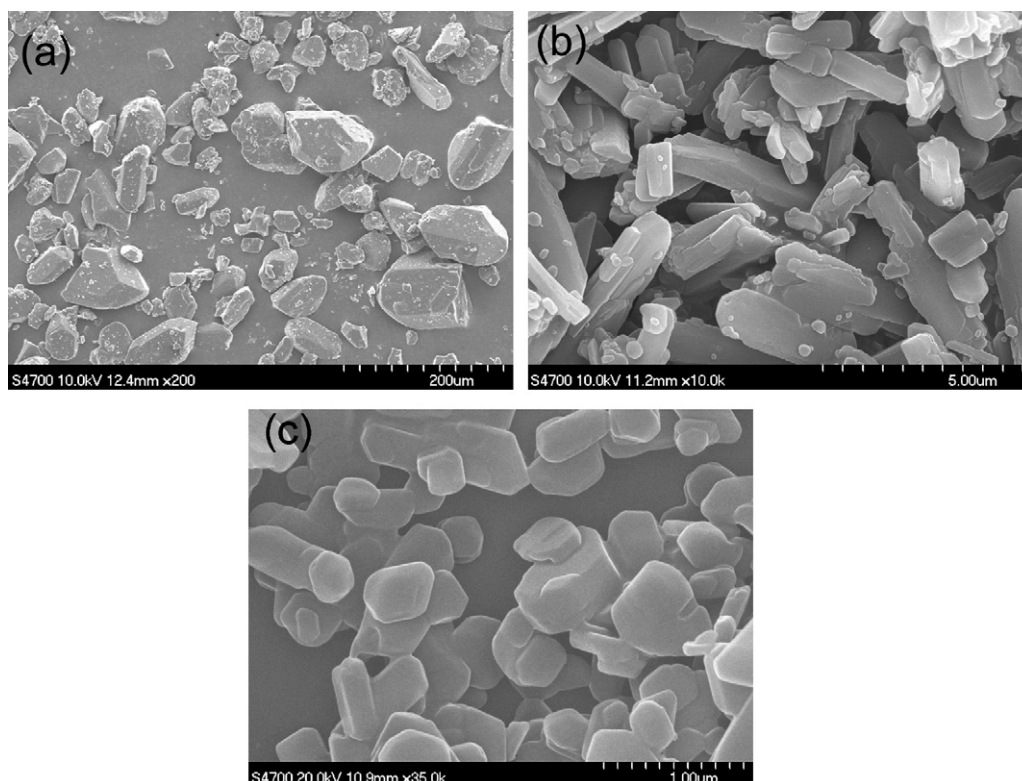


Fig. 3. SEM images of (a) raw BIC, (b) precipitated BIC without excipients, and (c) lactose–BIC nanodispersion.

Table 1
Physical properties of BIC nanodispersions.

Sample	Lactose-BIC	AG-BIC	HPMC-BIC	MCC-BIC	Precipitated BIC
Particle size (nm)	330 ± 4	572 ± 6	609 ± 5	680 ± 8	3000–5000
BET (m ² /g)	10.35	8.56	7.12	6.89	1.43
Contact angle (°)	40.8	53.2	63.4	65.2	71.7
Zeta-potential (mV)	-28.9 ± 1.3	-38.7 ± 1.5	-30.5 ± 1.5	-19.1 ± 1.2	-5.3 ± 0.8

After loading BIC with excipients, a large and hydrophilic surface can be formed, which could result in lower contact angle. Table 1 showed the contact angles of BIC dispersions. They evidently turned down compared to that of the precipitated BIC without excipient. Lactose-BIC presented the smallest contact angle, which was 40.8°, reducing 44% of that of the precipitated BIC. In addition, zeta potential (ξ) of BIC dispersions obviously increased in contrast to the precipitated BIC without excipient. It could be observed from Table 1 that ξ of BIC dispersions with different excipients ranged from -19.1 to 38.7 mV, while ξ of the precipitated BIC without excipient valued only -5.3 mV.

During the preparation process, the hydrophobic portion of an amphiphilic excipient may be adsorbed on the precipitating hydrophobic drug surface, while the hydrophilic portion provides static and/or electrostatic stabilization in the aqueous medium. The excipients diffuse to and adsorb on the drug surface to arrest growth. In all cases, the particles exhibited smaller particle size providing significantly increased surface area compared to micronized powder, these increased surface areas offered the potential for increased dissolution rates in vitro.

Hydrogen bonding and steric hindrance have been traditionally used to explain the stabilizing performance of excipients in dispersions (Dinunzio et al., 2008). Examination of molecular structure of BIC revealed numerous hydrogen bond acceptor sites that are capable of interacting with the hydrogen bond donor sites of the enteric polymers, including the C=O group which functions as a hydrogen bond acceptor. Lactose has more hydrogen bond donor sites, so carbonyl group of BIC is willing to bond to lactose and the bonds present the steric hindrance which is preventing BIC nanoparticles from aggregating. The potential interactions between BIC and lactose were investigated using FTIR, as shown in Fig. 4. BIC indicated an intense C=O stretch located at 1700 cm⁻¹. Lactose-BIC processed particles showed a decrease in C=O bond intensity and a decrease intensity with a broadening of the C-H stretch compared to raw BIC and after washed lactose-BIC, which suggesting possible hydrogen bonding between lactose and BIC.

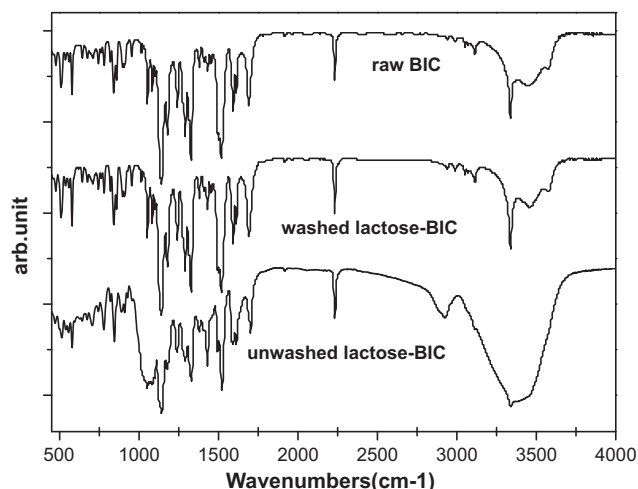


Fig. 4. FT-IR spectra of raw BIC, unwashed and after washed lactose-BIC.

To evaluate the performance of BIC nanodispersions, in vitro dissolution tests were operated. Fig. 5 showed the dissolution profiles of BIC in different excipients systems. All of BIC dispersions exhibited rapid dissolution, above 50% dissolved in the first 10 min. Lactose-BIC performed the highest dissolution rate, which reached nearly 94% of drug released within 10 min and 99% in the 120 min. MCC-BIC released slowly, it dissolved less than 50% in the first 10 min and did not reach 85% within 120 min. In contrast, we observed an obviously reduced dissolution rate of the BIC without excipient, with less than 30% dissolved in the first 10 min and did not reach 78 wt% for the whole 120 min. This study highlights that BIC loading with excipients can be an effective way to improve the dissolution rate, in particular, lactose is found to be remarkably effective with respect to the improvement of apparent solubility and dissolution of BIC.

3.2. Influence of precipitated temperature on particle size

Temperature has a significant effect on the particle size. It is evident that there is a notable increase in particle size when the temperature rises. As shown in Fig. 6, when the temperature is 3 °C, the average particle size of lactose-BIC was about 330 nm with narrow distribution. While the temperature increasing to 30 °C, the average particle size increases to 1.15 μm with a wide distribution. Increasing the temperature to 60 °C, the particle size is dramatically increased to 3–7 μm accompanied with irregular shape. It can be concluded that the higher the precipitation temperature, the larger the particle size. The following reasons may be responsible for this phenomenon. First, solubility of BIC in the DMA-water mixture decrease with the temperature decrease, the lower temperature is beneficial to a high degree of supersaturation in a solvent-antisolvent system. Second, temperature influences the crystal growth rate. The crystal growth rate can be expressed as follows (Praetorius and Mandal, 2007):

$$\frac{dl}{dt} = K_g(C_i - C^*)^b$$

where K_g is crystal growth rate constant, b is usually in the range of 1–3, C_i and C^* are the solute concentration on the crystal surface and saturation concentration, respectively. The value b decreases with reductions in the temperature. As a result, smaller particles could be gotten at lower temperature.

3.3. Influence of stirring speed on particle size

Stirring speed also has a significant effect on the particle size and size distribution. As shown in Fig. 7, the mean particle size under different stirring speed were 1.07 μm (1000 rpm), 0.85 μm (4000 rpm), 0.55 μm (7000 rpm) and 0.33 μm (10,000 rpm) in length. The particle size is decreased with the increase of the stirring speed in some range. Moreover, with the increase in stirring speed, the particle size distribution becomes narrower, from 0.4 to 1.50 μm at 1000 rpm to 0.17–0.43 μm at 10,000 rpm. Within the as shown range of the speed, the mechanism of the particle size decrease can be analyzed by the increasing in stirring speed. High intense stirring reduces the mass-transfer resistance and enhances the rate of diffusion between the multiphase, which induced high

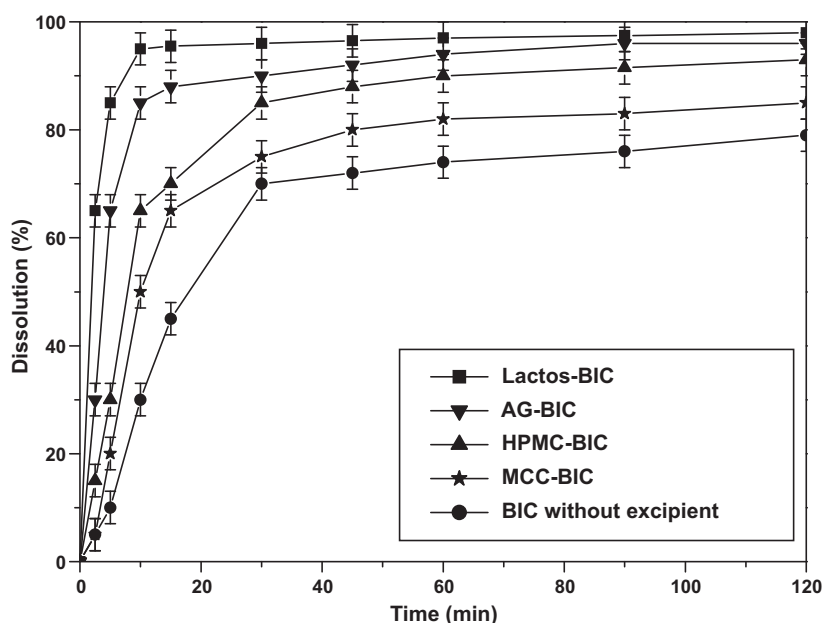


Fig. 5. Dissolution profiles of BIC nanodispersions.

homogeneous supersaturation in a short time and, thus, rapid nucleation to produce smaller drug particles in a narrower size distribution. Therefore, high stirring speed generates small particles with narrow size distribution. However, when the stirring speed goes high up to 15,000 rpm, the particles increase obviously, because of the high intense speed producing large amount of heat energy to enhance the temperature, which leads to the nanoparticle size increasing.

3.4. Solid state characterization

In order to verify the chemical structure and crystalline of BIC in nanodispersion, lactose–BIC was washed by DI water several times to get rid of lactose and the pure BIC was characterized.

The FT-IR spectra of both processed BIC and raw BIC were shown in Fig. 4. The spectrum of processed BIC matched that of raw materials very well. The identical FT-IR spectra suggested that the addition of stabilizers and employment of the liquid precipitation process did not affect the chemical structure of BIC.

XRD patterns of raw BIC and the processed BIC were presented in Fig. 8. The processed BIC is obviously crystalline. The peak positions of the processed BIC were the same as those of raw materials, indicating that there were no changes in crystal structure after the precipitation process. It could also be seen that the peaks of BIC nanoparticles exhibited lower intensities than those of raw BIC, suggesting smaller particle size of the processed BIC according to Scherrer equation (Torrado et al., 1998).

DSC was performed on raw BIC and processed BIC, and the results were illustrated in Fig. 9. Both raw BIC and the processed BIC showed a sharp endothermic peak at 195 °C, which corresponds to melting point of crystalline form I of BIC. DSC analysis further confirmed that the crystal type of the processed BIC is unchanged.

3.5. In vitro dissolution

Dissolution profiles of lactose–BIC nanodispersion, current marketed product Casodex (produced by AstraZeneca), and commercial BIC tablets (produced by Shanghai Zhaohui Company, China), as

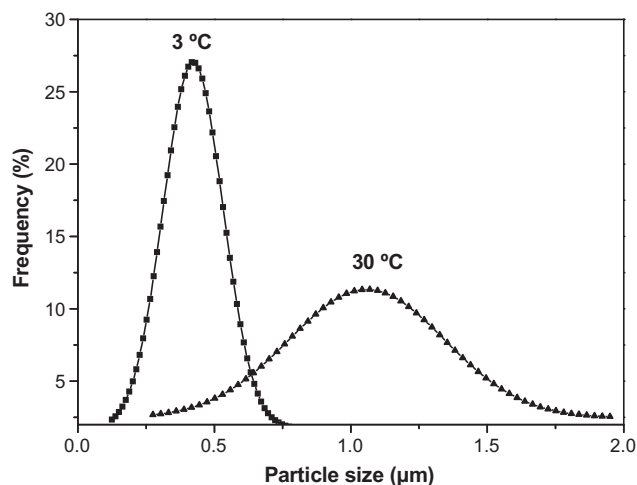


Fig. 6. Particle size distributions of lactose–BIC at different temperature.

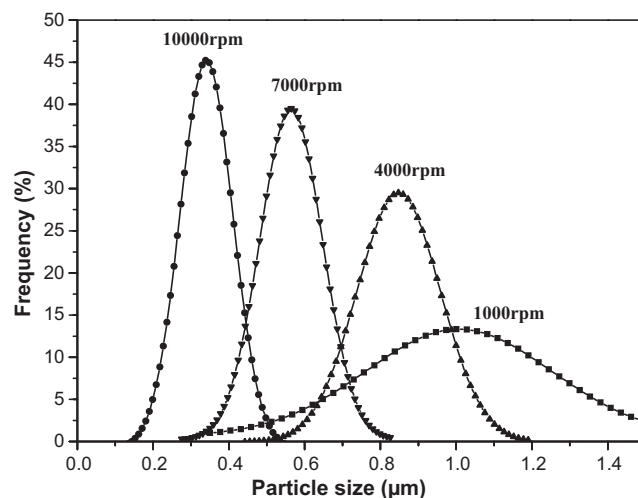


Fig. 7. Particle size distributions of lactose–BIC at different stirring speeds.

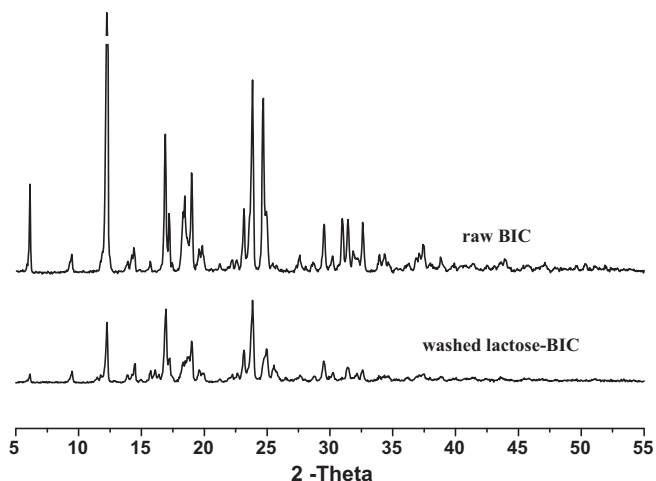


Fig. 8. XRD patterns of raw BIC and after washed lactose-BIC.

well as the physical mixture of raw BIC and lactose (1:1 weight ratio), were presented in Fig. 10. A significantly high dissolution rate for lactose-BIC was observed, 94% of drug dissolved in 10 min. While 60% and 38% of drug dissolved for Casodex and BIC tablets at that time respectively. After 45 min, almost complete dissolution of the three drugs was observed. In contrast, physical mixing powder showed a slower release, only dissolved 55 wt% until 120 min. The dramatic increase of nanodispersion in drug dissolution rate can be attributed to the enhancement in the surface area upon particle size reduction and the presence of water soluble excipient, which may further lead to higher drug potential in the gastrointestinal tract and finally result in an improvement in oral bioavailability.

4. Conclusion

In this work, bicalutamide nanodispersions were successfully prepared via combination of antisolvent precipitation and spray-dry process. Lactose was chosen as a suitable excipient to inhibit the bicalutamide nanoparticles growth and to improve the drug dissolution rate. The influences of precipitation temperatures and stirring speeds were investigated. The particle size decreased with the decreasing of temperature and increasing of stirring speed. XRD, FT-IR and DSC analysis demonstrated that the composition and crys-

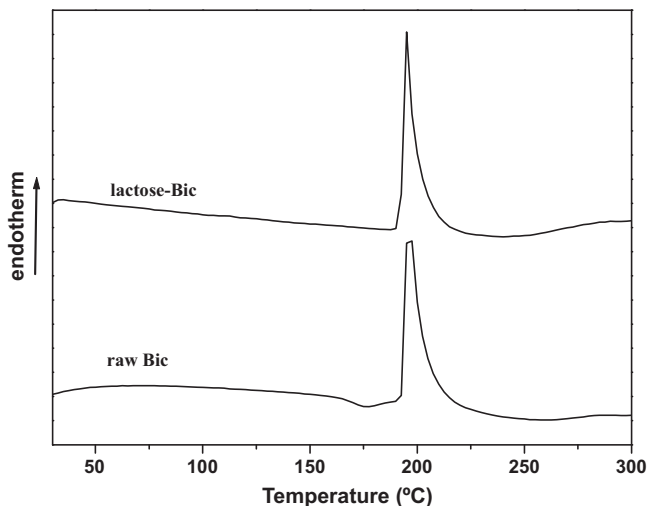


Fig. 9. DSC curves of raw BIC and after washed lactose-BIC.

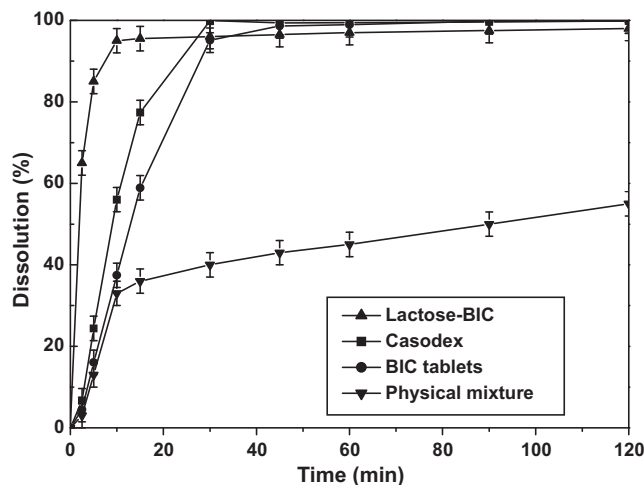


Fig. 10. Comparison of dissolution of BIC nanodispersion with commercial products.

talline of the processed bicalutamide were in agreement with raw material. In vitro dissolution test, lactose-bicalutamide achieved excellent enhancement compared to two commercial medicines. It dissolved 94% in 10 min whereas Casodex and bicalutamide tablets dissolved 60% and 38% respectively at the same period. This work demonstrates the significant potential for the use of nanodispersion as a novel delivery system for poorly soluble drugs.

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