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Development and characterization of bicalutamide-poloxamer F68 solid dispersion systems

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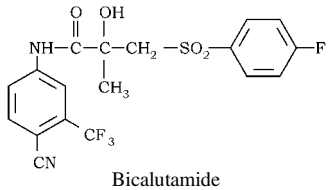
The objective of the present work was to improve the dissolution rate of a poorly water-soluble drug, bicalutamide, by a solid dispersion technique. The solid dispersion systems of bicalutamide were prepared with poloxamer F68 in 1 : 1, 1 : 3, and 1 : 5 ratios using the melting method. The interaction of drug with polymer was evaluated by TLC, FTIR, and powder XRD. The results of powder XRD showed a significant decrease in the crystallinity of drug in the binary systems of bicalutamide. All binary systems of bicalutamide showed faster dissolution than pure drug alone ($p < 0.001$). However, among all binary systems studied, 1 : 1 proportion of bicalutamide : poloxamer was found to be excellent for dissolution enhancement (DP_{30}: 99.98% $\pm$ 3.9) of bicalutamide. The higher ratios of poloxamer F68 (1 : 3 and 1 : 5) had retarded the release of drug from their corresponding binary systems which might be due to its gelling property in higher concentration.

1. Introduction

Poor aqueous solubility is, unfortunately, a frequent problem for drug delivery. Many molecules that are therapeutically active *in vitro* show poor activity *in vivo* as a result of a variety of possible problems such as low aqueous solubility or stability and limited transport across cell membranes. It is generally considered that compounds with very low aqueous solubility will show dissolution rate-limited absorption (Proudfoot 1991). The dissolution of drugs is a prime determinant in the absorption of poorly water-soluble drugs and also serves as a rate-limiting step (Horter and Dressman 1997). Improvements in the apparent solubility and/or dissolution rate of a poorly water-soluble drug through the formation of a solid dispersion may lead to an enhancement of its bioavailability. An enhancement in oral bioavailability would be expected to result in the reduction in dosage frequency as well as dose of the drug which ultimately improves patient compliance. In continuation of our previous work on solubility enhancement of bicalutamide using cyclodextrin, in this article increasing the solubility of bicalutamide has been addressed via solid dispersion technique.

Bicalutamide, chemically (2*RS*)-4′-cyano-3-(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3′-(trifluoromethyl)-propionanilide is an orally active, nonsteroidal antiandrogen (Fradet 2004). It is mainly used in the treatment of prostate cancer (Cockshot et al. 1997, 2004). The antiandrogenic activity resides almost exclusively in (*R*)-bicalutamide with little activity in (*S*)-bicalutamide (Tucker and Chesterton 1988; Furr et al. 1996; Mukherjee et al. 1996). Though bicalutamide has gained widespread acceptance in the treatment of prostate cancer, it is a highly lipophilic drug (log P 2.92) having very low aqueous solubility (5 mg/L). The low aqueous solubility of bicalutamide may be due to polymorphism and hence the drug has been classified as BCS class II drug according to the biopharmaceutical classification system (Vega et al. 2006).



Bicalutamide

Various techniques have been used to enhance the solubility of poorly water-soluble drugs, including the use of surfactants (Schott et al. 1982), inclusion complexation (Veiga et al. 1996), use of polymorph (Henck et al. 1997), and amorphous form of drug micronisation (Hancock and Zografi 1997) and solid dispersion (Chiou and Riegelman 1971; Christian and Dressman et al. 2000; Serajuddin 1999). The solubilization of a drug from solid dispersion systems is mainly caused by a reduction in particle size, increase in the surface area and reduction in the crystallinity that improves dissolution rate. Also, no energy is required to break up the crystal lattice of a drug during dissolution process and drug solubility and wettability may be increased by surrounding hydrophilic carriers (Craig 2002). The various methods used to prepare solid dispersions are the hot melt method (Zajc 2005; Wang and Cui 2006), solvent evaporation (Tantishaiyakul et al 1999), spray drying (Weuts et al. 2005), hot melt extrusion (Adel El-Egakey et al. 1971), solvent deposition technique (Dastmalchi et al. 2005) and solvent wetting method (Kim et al. 2006).

Poloxamers or pluronic block copolymers have been widely used in pharmaceutical formulations for enhancing

the solubility of poorly water-soluble drugs. Poloxamer consists of hydrophilic corona EO (ethylene oxide) and hydrophobic core PO (polypropylene oxide) blocks arranged in a triblock structure which results in an amphiphilic copolymer. Their low melting point renders them suitable for melt granulation technique. Further, their ability to self aggregate thereby forming micelles and liquid crystalline phases is the added advantage for solubility enhancement of poorly water-soluble drugs via solid dispersion technique. For drug delivery purposes, hydrophobic drugs may be solubilized within the core of micelle or conjugated to the micelle-forming polymer (Singhare et al. 2005).

This work was aimed to enhance the dissolution rate of bicalutamide via solid dispersion technique using poloxamer F68 as a hydrophilic carrier. The solid dispersion systems of bicalutamide were prepared with poloxamer F68 in 1 : 1, 1 : 3 and 1 : 5 ratios using melting technique. The selection of different ratios of polymer was purely on a random basis. Thin layer chromatography (TLC), Fourier transformation-infrared spectroscopy (FTIR) and Powder X-Ray diffractometry (XRD) were used to characterize the solid state properties of pure bicalutamide and its solid dispersion systems. The dissolution behavior of bicalutamide and all its binary systems were further evaluated.

2. Investigations, results and discussion

2.1. Percentage drug content study

Percentage drug content was found to be in the range of 96.28 ± 0.15 to 98.63 ± 0.08 (Table 1).

2.2. Thin layer chromatography (TLC)

TLC study showed Rf values from $0.47 - 0.51$ for all solid dispersions, which was almost identical with Rf value of pure drug (Table 1). It indicates that there was no interaction between drug and carrier.

2.3. Fourier transformation infrared spectroscopy (FTIR)

Fig. 1 illustrates the FTIR spectra of bicalutamide, poloxamer F68 and solid dispersion systems. IR spectrum of bicalutamide (A) is characterized by principal absorption peaks at 3051 cm^{-1} (C-H aromatic), 2943 cm^{-1} (C-H aliphatic asymmetric), 2229 cm^{-1} (C≡N), 1689 cm^{-1} (C=O), 3580 cm^{-1} (O−H), 3339 cm^{-1} (N−H), 1327 cm^{-1} (S=O), 1612 cm^{-1} (C=C aromatic), 1014 cm^{-1} (C−O), 839 cm^{-1} (p substituted benzene), 1242 cm^{-1} (monofluorinated benzene) and 1140 cm^{-1} (C−F of CF_3). The intense peaks appearing in the spectrum of bicalutamide are due to symmetric or asymmetric stretching vibrations of the functional groups. Bicalutamide shows strong absorption peaks at 2229 cm^{-1}, 1689 cm^{-1} and 3339 cm^{-1} indicating the presence of cyanide and amide carbonyl group respectively while, peaks at 709 and 839 cm^{-1} may be assigned to aromatic stretching of the phenyl group in the molecule which is substituted.

Table 1: Rf values and % drug content of pure bicalutamide and solid dispersions

System	Rf Values	% Drug content* ± S.D.
Pure drug Bicalutamide	0.47	–
Bicalutamide: poloxamer (1 : 1) SD	0.51	96.28 ± 0.15
Bicalutamide: poloxamer (1 : 3) SD	0.49	97.57 ± 0.46
Bicalutamide: poloxamer (1 : 5) SD	0.48	98.63 ± 0.08

* Indicates mean of three readings (n = 3); S.D.: Standard deviation; SD: Solid dispersion

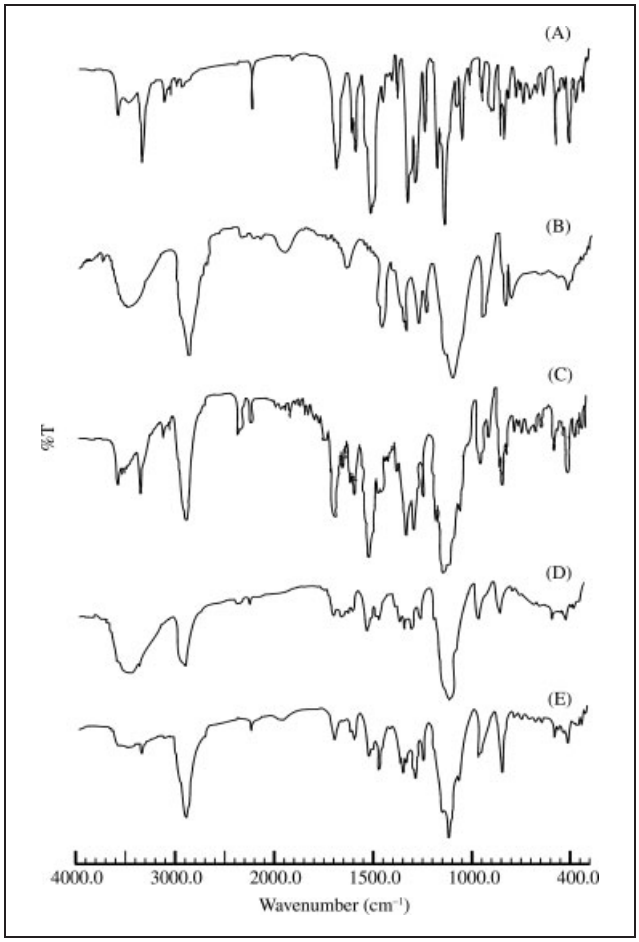


Fig. 1: FTIR spectra of single components and binary systems of bicalutamide and poloxamer F68: (A) Bicalutamide; (B) Poloxamer F68; (C) Bicalutamide-Poloxamer F68 1 : 1 SD; (D) Bicalutamide-Poloxamer F68 1 : 3 SD; (E) Bicalutamide-Poloxamer F68 1 : 5 SD. SD: Solid dispersion

The IR spectra of all solid dispersions show disappearance of some peaks of bicalutamide. The 1 : 1 solid dispersion shows almost all peaks of bicalutamide with decreased peak intensity. However, the peaks at 3580 cm^{-1}, 1689 cm^{-1}, 1612 cm^{-1} and 1014 cm^{-1} have been completely disappeared in 1 : 3 and 1 : 5 bicalutamide-poloxamer F68 binary systems. (Fig. 1C, 1D and 1E). The peak at 3339 cm^{-1} of NH was shifted to 3337 cm^{-1} in 1 : 5 due to hydrogen bonding and disappeared completely in 1 : 3 solid dispersions. All other peaks of bicalutamide were smoothened indicating strong physical interaction of bicalutamide with polymer. However, no additional peak was observed in all binary systems indicating the absence of any chemical interaction between bicalutamide and polymer (Ford 1986).

2.4. X-ray powder diffractometry (XRD)

The XRD pattern of bicalutamide showed (Fig. 2) intense and sharp peaks, indicating its crystalline nature. The peak intensities of pure bicalutamide and its corresponding binary systems are presented in Table 2. Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with those of a reference (pure bicalutamide) (Ryan 1986). Bicalutamide (Fig. 2A) showed sharp peaks at 16.97° and 23.85° (2θ)

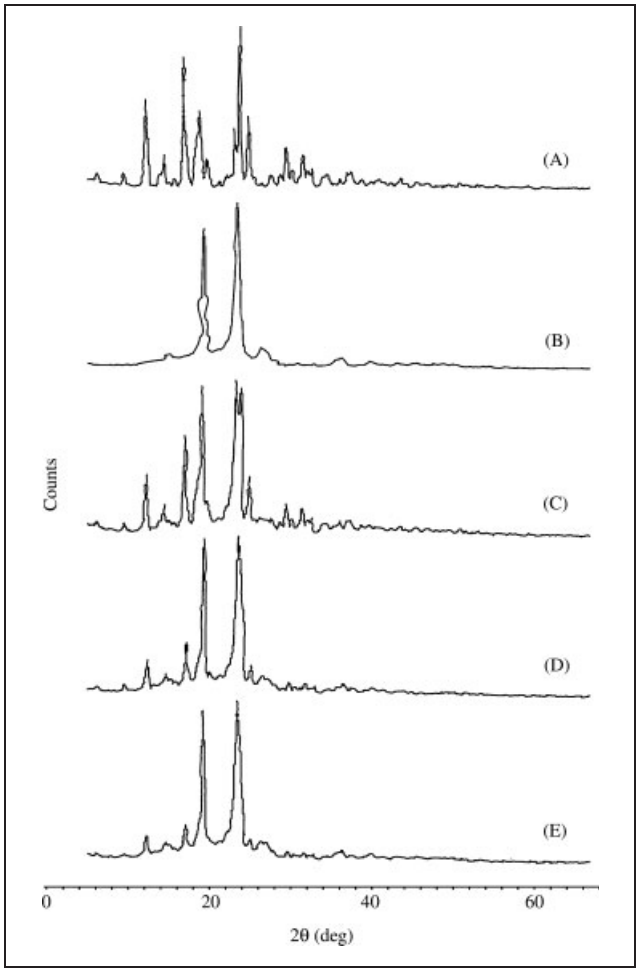


Fig. 2: XRD patterns of single components and binary systems of bicalutamide and poloxamer F68: (A) Bicalutamide; (B) Poloxamer F68; (C) Bicalutamide-Poloxamer F68 1 : 1 SD; (D) Bicalutamide-Poloxamer F68 1 : 3 SD; (E) Bicalutamide-Poloxamer F68 1 : 5 SD. SD: Solid dispersion

Table 2: Peak intensities of bicalutamide in the XRD patterns of bicalutamide-poloxamer F68 solid dispersions

2θ	Bicalutamide	1 : 1 SD	1 : 3 SD	1 : 5 SD
23.85	734	458	424	–
16.97	538	416	–	–
12.31	372	216	169	–
24.98	303	213	164	71

SD: Solid dispersion

with peak intensities of 538 and 734 respectively. The peak height at 23.85° (2θ) was used for calculating the relative decrease in crystallinity (RDC) of bicalutamide in solid dispersion systems (Fig. 2C, 2D and 2E). The RDC values of 1 : 1 and 1 : 3 binary systems were 0.6239 and 0.5776 respectively. However, the RDC values of 1 : 5 binary systems cannot be calculated as all intense peaks of bicalutamide have been completely disappeared. The disappearance of intense peaks of bicalutamide in 1 : 5 solid dispersion indicated that the drug was no longer present in the crystalline state but was converted to amorphous form.

2.5. Dissolution rate studies

The dissolution curves of pure bicalutamide and solid dispersions in 1% SLS at 37 ± 0.5 °C are shown in Fig. 3.

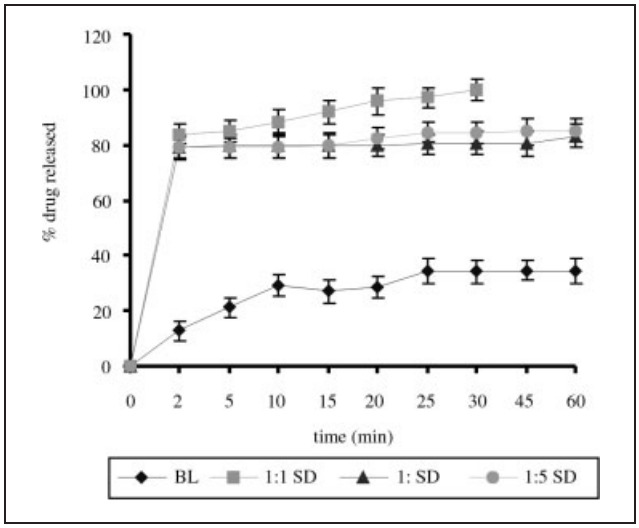


Fig. 3: Dissolution curves of bicalutamide alone and from binary systems of bicalutamide with poloxamer F68. SD: Solid dispersion

The release rate profiles were expressed as the percentage of drug released (vs.) time. It is evident that the solid dispersion (SD) technique has improved the dissolution rate of bicalutamide to a greater extent. Table 3 shows % drug dissolved in 2 min (DP_2), 15 min (DP_{15}), and 30 min (DP_{30}) for bicalutamide and its binary systems with hydrophilic carrier. The dissolution efficiency values (DE_{30}) at 30 min have been also reported and compared statistically. All binary systems of bicalutamide showed faster dissolution (DE_{30}: $p < 0.001$) than pure drug alone. The % release of bicalutamide was 83.75 ± 3.6, 79.19 ± 3.8 and 78.82 ± 4.2 from 1 : 1, 1 : 3 and 1 : 5 solid dispersion systems respectively within 2 min (DP_2). Thus solid dispersion systems of bicalutamide with poloxamer F68 have significantly improved the dissolution rate of pure drug. However, the release of bicalutamide from pure drug was incomplete even in 60 min. The 1 : 1 ratio of bicalutamide : poloxamer solid dispersion has shown superior performance to its corresponding other ratios in enhancing the dissolution rate of pure drug (DE_{30}: $88.80\% \pm 4.01$ ($p < 0.05$)), indicating complete release of drug from solid dispersion (DP_{30}: 99.98 ± 3.9). However, no significant differences have been found in the dissolution rate of 1 : 3 and 1 : 5 when compared statistically ($p > 0.05$). It was noticed that the higher ratios of poloxamer F68 (1 : 3 and 1 : 5) had retarded the release of drug from their corresponding binary systems even though the crystallinity of drug was reduced to greater extent in these binary systems than 1 : 1 solid dispersion. This might be because of the gelling property of poloxamer in higher concentration (Park et al. 2003).

The rapid dissolution of bicalutamide from solid dispersions may be attributed to decrease in the crystallinity of drug and its molecular and colloidal dispersion in hydrophilic carrier matrix. As soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution. (Geneidi et al. 1978; Save et al. 1992).

The other factors that might contribute to enhancing the dissolution rate are greater hydrophilicity and surfactant property of polymer, increased wettability and dispersibility and particle size reduction of drug (Ford 1986). The greater hydrophilicity and surfactant property of poloxamer F68 result in greater wetting and increases surface available for dissolution by reducing interfacial tension be-

Table 3: Dissolution time of pure bicalutamide and from solid dispersions in 1% SLS in water at 37 ± 0.5 °C

System	DP_2^* ± S.D.	DP_{15}^* ± S.D.	DP_{30}^* ± S.D.	DE_{30}^* ± S.D.
Bicalutamide	12.9 ± 3.5	26.99 ± 4.2	34.08 ± 4.3	26.55 ± 3.90
1 : 1 SD	83.75 ± 3.6	91.89 ± 4.2	99.98 ± 3.9	88.80 ± 4.01†‡
1 : 3 SD	79.19 ± 3.8	79.59 ± 4.1	80.51 ± 4.2	76.84 ± 3.51$^{\dagger\#}$
1 : 5 SD	78.82 ± 4.2	79.86 ± 4.6	84.38 ± 3.9	78.38 ± 3.86†

* Indicates mean of three readings (n = 3); S.D.: Standard deviation; SD: Solid dispersion; DP: % drug dissolved; DE: dissolution efficiency; † indicates p value compared to pure bicalutamide ($p < 0.001$) i.e. all significant. ‡ indicates p value compared to 1 : 3 SD and 1 : 5 SD ($p < 0.05$); i.e. significant. $^\#$ indicates p value compared to 1 : 5 ($p > 0.05$) i.e. not significant

tween hydrophobic drug and dissolution media. During dissolution experiments, it was noticed that drug carrier systems sank immediately, whereas pure drug floated on the surface of dissolution medium for a longer period of time.

2.6. Conclusions

In, the present investigation poloxamer F68 has significantly improved dissolution rate of bicalutamide. The results of FTIR and XRD studies showed a gradual decrease in the crystallinity of bicalutamide in solid dispersions with increase in the proportion of the carrier. However, among the ratios used, 1 : 1 ratio of solid dispersion has shown a performance superior than any other ratios studied. This indicated that increase in the weight fraction of polymer could not offer any advantage for dissolution enhancement. Based on the results, it could be concluded that, solid dosage forms containing bicalutamide for oral administration could be formulated with poloxamer F68 with high dissolution rate, faster onset of action and improved bioavailability. However, *in vivo* bioavailability studies are required to ensure whether, the results obtained in this investigation can be extrapolated to the *in vivo* conditions.

3. Experimental

3.1. Materials

Bicalutamide was supplied by Lupin Ltd., Mumbai, India as a gift sample. Lutrol (poloxamer) F68 was gift sample from Signet Chem Lab, Mumbai, India.All the reagents were of analytical grade. Double distilled water was used throughout the experiment.

3.2. Preparation of solid dispersions by melting method

Solid dispersions of bicalutamide were prepared by the melting method. Poloxamer was melted at 60 °C. Bicalutamide was added to the molten polymer, which was then mixed well and cooled to room temperature to obtain the solid mass. The solidified masses were crushed, pulverized and passed through mesh number 60. The resulting solid dispersions were stored in desiccators until solid dispersion attains constant weight.

3.3. Thin layer chromatography (TLC)

TLC was carried out using silica gel GF 254 (0.2 mm) glass plates with a solvent system of benzene : methanol (90 : 10) as mobile phase, to study any drug carrier interaction. The Rf values of pure drug and solid dispersions were calculated.

3.4. Fourier transformation infrared spectroscopy (FTIR)

Infrared spectra were obtained using a JASCO FTIR-5300 Japan spectrometer using KBr disks. The samples were previously ground and mixed thoroughly with KBr. The KBr disks were prepared by compressing the powder. The scanning range was kept from 4000 to 400 cm^{-1}.

3.5. X-ray powder diffractometry (XRD)

The XRD patterns of bicalutamide, poloxamer F68 and solid dispersions were recorded with a Philips Analytic X-Ray – PW 3710 (Holland) diffractometer with tube anode Cu over the interval 5–70°/2θ. The operation data were as follows: Generator tension (voltage) 40 kV, Generator current 30 mA, and scanning speed 2°/min.

3.6. Percentage drug content study

Drug content was determined by dissolving solid dispersions equivalent to 10 mg of drug in a small quantity of dimethyl formamide and kept in ultrasonicator for 20 min. The volume was adjusted to 100 ml with distilled water. The solution was filtered through Whatman filter paper no. 41, suitably diluted and absorbance was measured at 272 nm using double beam UV spectrophotometer (Shimadzu 1700, Japan).

3.7. Dissolution studies

The dissolution rate studies of bicalutamide alone and solid dispersion systems were performed in triplicate in a dissolution apparatus (Lab India, Model Disso 2000 Tablet dissolution test apparatus, Mumbai, India) using the paddle method (USP Type II). Dissolution studies were carried out using 1000 ml of 1% SLS (Sodium lauryl sulphate) in water at 37 ± 0.5 °C at 50 rpm as per US FDA guidelines (US FDA website, 2006). 50 mg of bicalutamide or its equivalent amount of solid dispersion was added to 1000 ml of 1% SLS in water. Samples (5 ml) were withdrawn at time intervals of 2, 5, 10, 15, 20, 25, 30, 45, and 60 min. The volume of dissolution medium was adjusted to 1000 ml by replacing each 5 ml aliquot withdrawn with 5 ml of fresh 1% SLS in water. The solution was immediately filtered through a 0.45 µm membrane filter, suitably diluted and the concentrations of bicalutamide in samples were determined spectrophotometrically at 272 nm. The results obtained from the dissolution studies were statistically validated using ANOVA (Tukey-Kramer Multiple Comparisons Test).

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