In-vitro dissolution rate enhancement of poorly water soluble non-steroidal antiandrogen agent, bicalutamide, with hydrophilic carriers

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This study presents dissolution rate enhancement of poorly water soluble antiandrogen agent, bicalutamide, using different solubilizing enhancers (Povidone K 30 and Poloxamer 407). Poloxamer 407 based dispersions exhibited higher dissolution rate than Povidone K 30. Powder X-ray diffraction (PXRD) showed that degree of crystallinity decreased by increasing concentration of Povidone K 30 carrier. FTIR studies showed that drug used was compatible with carriers. Solid dispersions prepared with povidone K30 changed crystalline form of drug to amorphous form.

Keywords: Bicalutamide, Dissolution rate, Poloxamer 407, Povidone K 30, Solid dispersion

Introduction

Poorly water-soluble drugs are associated with slow drug absorption leading to inadequate and variable bioavailability. Bicalutamide (BC), N- [4-cyano-3-( trifluoromethyl) phenyl]-3-[(4-fluorophenyl) sulfonyl]-2-hydroxy-2-methyl- propanamide, is a poorly water soluble drug, which is a non-steroidal antiandrogen (pKa, 12). It inhibits action of androgens by binding to cytosol androgen receptors in target tissue. Aqueous in vitro solubility of BC (5 µg/ml) is low at pH 7 and 37°C. Solubility and dissolution rate of BC can be altered by modification of drug crystal forms, addition of co solvents, addition of surfactants, complexation with cyclodextrins (CD) etc. In addition, formation of solid dispersions (SDs) with hydrophilic carriers [povidone K 30 (PVP K 30), poloxamer 407 (POL), polyethylene glycol (PEG), gelucire etc.] can be applied to increase dissolution rate. SDs are generally prepared by solvent evaporation or co precipitation technique, whereby both guest solute and solid carrier solvent are dissolved in a common solvent such as ethanol. Liquid solvent is removed by evaporation under reduced pressure or by freeze-drying, which results in an amorphous precipitation of guest in a carrier. Thus, drug is precipitated out in an amorphous form in the former as opposed to crystalline form in the latter. Amorphous form of drug exists only when suitable concentration of carrier is used. Solvent evaporation can be preceded by rotary evaporation, spray drying, and spray granulation. Under fusion technique, dispersion is a binary system comprising of a solid solute molecularly dispersed in a solid solvent, thereby two components are crystalline together in a homogeneous one phase system. In solid solution process, particle size of drug is reduced to molecular level, thus giving more aqueous solubility and faster dissolution than other preparations.

This study developed an economical and simple manufacturing steps formulation, wherein SDs of bicalutamide were prepared by solvent evaporation technique using PVP K 30 and by fusion technique using POL at stoichiometric ratios. Out of these techniques, best carrier was selected depending upon their efficiency to enhance dissolution rate of drug.

Experimental Section

Materials

BC was a generous gift sample from Dr Reddy’s Laboratories Ltd (Hyderabad, India). Povidone K 30 and Sodium lauryl sulphate (SDS) were obtained as gift samples from Unichem Laboratories Ltd (Goa, India). Poloxamer 407 was purchased from Sigma Chemical Co (St Louis, MO). All other reagents and chemicals were of analytical grade.

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Preparation of Solid Dispersions

Preparation of Solid Dispersions with PVP K 30

SDs of BC were prepared with PVP K30 in carrier ratios of 1:3, 1:4 and 1:5 by conventional solvent evaporation technique. PVP K 30 solution (20% w/v) was prepared by dissolving it in ethanol in a round bottom flask with continuous stirring. An appropriate weight of BC powder was dissolved in acetone so as to obtain 15% w/v of drug solution. Both solutions were mixed and stirred until formation of a clear solution. If any precipitation is observed, volume is adjusted with either ethanol or acetone depending upon precipitated substance. Solvents were evaporated at 50°C under reduced pressure in Rota evaporator and further dried in a desiccator for 24 h to remove residual solvents. Dried mass was collected, sifted through 60 # and packed in a closed container. Physical mixtures (PM) were prepared by simple geometric mixing of two pure solid components with a spatula, followed by sieving mixture three times through 60 #.

Preparation of Solid Dispersions with POL

SDs of BC with POL were prepared in 1:1 and 1:2 ratios by fusion technique. Required amount of POL was taken in a glass beaker and melted by heating on a water bath. To this, molten mass drug was added with continuous stirring for 5-10 min, or until drug was completely dispersed in molten mass. After mixing, dispersion was solidified by cooling on an ice bath. Resultant product was further dried in a desiccator for 24 h, collected, sifted through 60 # and packed in a closed container.

Evaluation of Dispersions

Content Uniformity

Uniformity of BC in SDs was evaluated by content uniformity test, wherein dispersions were collected (equivalent to 50 mg of BC) in four different positions [top \(T_1\), middle \(M_1\), bottom \(B_1\), and composite \(C_1\)]. and were evaluated for drug content by measuring absorbance at 272 nm.

Dissolution Rate Studies

Dissolution rate studied separately in 1% SLS (900 ml) maintained at 37±0.5°C using USP XXII type II dissolution rate test apparatus at a stirring speed of 50 rpm. Samples (BC, 50 mg) were taken for dissolution studies. Aliquots (5 ml) were withdrawn at different time intervals up to 1 h and replaced same volume with fresh dissolution medium. Samples were filtered and estimated for BC dissolved by measuring absorbance at 272nm. Dissolution experiments were done in triplicate.

Powder X-ray Diffractometry (PXRD)

Powder X-ray diffractometry (PXRD) was performed for pure drug, placebo and for final dispersions of both carriers to identify nature of dispersions (Philips PW 1729).

Fourier Transformation-Infrared Spectroscopy (FTIR)

Fourier transform infrared spectroscopy (FTIR) was used to identify any drug excipient interaction. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (Shimadzu, FTIR 8700) in the region between 3500-500 cm\(^{-1}\).

Results and Discussion

Content Uniformity

Content uniformity (Table 1) of BC in SDs of both carriers was within limits (98-101%).

Drug Dissolution from Povidone K 30 Solid Dispersions

SDs with Povidone K 30 (drug: carrier ratios of 1:3, 1:4 and 1:5) were evaluated for dissolution studies. It was observed (Fig. 1) that dissolution rate was enhanced by increased concentration of PVP K 30. Pure drug released its active content (< 60%) at the end of 1 h, whereas PM with higher concentration (1: 5) of carrier released drug
Drug Dissolution from POL Solid Dispersions

SDs of POL with drug: carrier ratios of 1:1 and 1:2 were evaluated for dissolution rate study. Dissolution rate was found (Fig. 2) dramatically enhanced by using POL when compared to other dispersions. PM with 1:2 ratio exhibited 80% of drug release at the end of 1 h, whereas SDs with 1:1 & 1:2 ratio exhibited 99.9% & 99.7% drug release respectively. No significant difference was observed in dissolution profiles of 1:1 and 1:2 ratios of drug: carrier dispersions. So to avoid large quantities of carrier in dispersion and for economical reasons, 1:1 ratio dispersion was considered as an optimized ratio and further characterized.

Powder X-Ray Diffractometry (PXRD)

PXRD studies (Fig. 3) shows that BC exhibits sharp peaks at 12.25°, 17.05°, 23.90° and 24.30° (2θ), which indicates drugs of crystalline nature. PVP K 30 exhibited smooth curves with no sharp peaks observed,
whereas dispersion with PVP K 30 (1:5) exhibited no sharp peaks and diffraction pattern were similar to that of PVP K 30, indicating that crystalline form of BC was transformed to amorphous during dispersion process\textsuperscript{15}. Drug release properties were altered with polymorphic changes. Amorphous substances have more solubility than crystalline substances. Dispersion with PVP K 30 at 1:5 ratio exhibited highest dissolution rate, may be due to conversion of drug from crystalline to amorphous form. Diffraction patterns of POL dispersions exhibited similar peaks to that of pure BC indicating that crystallinity of drug was unaffected by the use of POL (Fig 4). In case of POL dispersion, dissolution rate was enhanced dramatically without any change in crystallinity of drug. POL dispersion is better than PVP K 30 dispersion as there is enhancement in dissolution rate without any polymorphic change.

**Fourier Transform-Infrared Spectroscopy (FTIR)**

IR spectrum of BC (Fig. 5) was identified by absorption peaks at 3345 cm\(^{-1}\) (secondary amine N-H stretch), 3065 cm\(^{-1}\) (=C-H aromatic ring), 2947 cm\(^{-1}\) (C-H stretch), 2242 cm\(^{-1}\) (C=N stretch), 1699 cm\(^{-1}\) (C=O stretch) and 1595 cm\(^{-1}\) (C=C stretch, aromatic ring), whereas IR spectrum of PVP K 30 was identified by absorption peaks at 1645cm\(^{-1}\) (C=O stretch), and 1475 cm\(^{-1}\) (N-H band). IR spectrum of SD exhibited less intensity of bands compared to drug alone. IR spectrum of POL (Fig 6) is identified by 3450 cm\(^{-1}\) (H-bonded O-H Stretch), 2885 cm\(^{-1}\) (C-H stretch),
1455 cm\(^{-1}\) (aromatic ring) and another three peaks within the range 1000-1300 cm\(^{-1}\) indicating (C-O stretch) whereas in case of dispersion there was no significant change in spectrum, indicating no significant interaction between POL and drug in SD. Thus there was no significant interaction between drug and carriers.

**Conclusions**

A dissolution characteristic of poorly soluble BC was greatly enhanced by SD process with hydrophilic carriers (PVP K 30 and Poloxamer 407). Poloxamer 407 and BC (1:1) enhanced drug release to a maximum extent when compared to all other formulations. PXRD showed that drug exists in an amorphous form. But in case of Poloxamer 407 dispersion, it enhanced dissolution rate more significantly when compared to PVP K 30; at the same time there was no interaction between drug and carrier, which was concluded from characterization of complex by using PXRD and FTIR studies. High proportion of carrier was required to enhance dissolution rate in case of PVP K 30, which leads to practical problems like increase of bulkiness and increase in tablet weight during formulation development; this can be avoided by using Poloxamer 407, which was required in small concentrations and is more economical. Major advantage of Poloxamer 407 dispersion is that it avoids usage of organic solvents, which are major constituents in preparation of PVP K 30 SDs. Hence prepared Poloxamer 407 dispersions are more economical and safe than PVP K 30 dispersions. Therefore, bicalutamide-poloxamer 407 (1:1) ratio was considered as optimum ratio for dispersion.

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References