COMPARATIVE EVALUATION OF SOLUBILITY AND DISSOLUTION ENHANCEMENT OF BICALUTAMIDE SOLID BY DISPERSION TECHNIQUE

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Abstract

Bicalutamide is poorly water soluble Anti- Cancer drug used in prostate cancer. Due to poor solubility of drug, its bioavailability rate is limited by drug dissolution. In the present study, an attempt has been made to increase solubility and dissolution of Bicalutamide by solid dispersion technique using Solvent Evaporation and Hot Melt method with PEG- 6000 (Poly ethylene glycol), PVP K-90 (Poly vinyl pyrrolidone), and Poloxamer F-68. Effects of various parameters such as type of carrier system used, drug: carrier ratio were studied. The evaluation of solid dispersion was done by IR spectroscopy, solubility and dissolution studies. Improvement in dissolution of drug was observed in all solid dispersions as compared to pure drug. The dissolution rate of Bicalutamide was directly proportional to increment in proportion of the carrier Pure Bicalutamide showed only 48% drug release in 1 hour whereas the Solid dispersion prepared by Solvent Evaporation method, using PEG 6000 showed faster in vitro drug release.

Keywords: Bicalutamide, Solid dispersion, PEG- 6000, Poloxamer, PVP K- 90, Solvent evaporation, Hot- melt

Introduction

Poorly water soluble compounds have solubility and dissolution related bioavailability problems. The dissolution rate is directly proportional to solubility of drug. Drugs with low aqueous solubility have low dissolution rates and hence suffer from poor oral bioavailability. The solid dispersion approach has been widely used to improve the solubility, dissolution rate, and consequently the bioavailability of poorly water soluble drugs[1-3]. Solid dispersion is defined as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting, solvent, or melting solvent method. The release mechanism of drug from variety of solid dispersions depends upon the physical properties of carriers as well as drug substance and preparation method. There are number of carriers used in the preparation of solid dispersion like acids, sugars, polymeric materials, surfactants[4]. Bicalutamide *N*-[4-cyano-3-(trifluoromethyl) phenyl]-3-[(4-fluorophenyl) sulfonyl]-2-hydroxy-2- methylpropanamide) [5] is an oral non steroidal anti-androgen used in the treatment of prostate cancer and hirsutism. It was first launched in the 1995 as combination treatment for advanced prostate cancer and subsequently launched as monotherapy for the treatment of earlier stages of diseases[6]. The present investigation was an attempt to improve the dissolution rate of Bicalutamide by solid dispersion using PEG- 6000, PVP K-90, and Poloxamer F-68 as carriers. Solid dispersion of Bicalutamide was prepared by Solvent Evaporation and Hot Melt method using three different proportions of drug: carrier. All the solid dispersions were characterized for IR spectroscopy, solubility study and dissolution study.

Experimental

Bicalutamide was obtained as gift sample from Jubilliant Organosys LTD Noida, PEG-6000, PVP K-90, and Poloxamer F-68, Methanol, Ethanol, Acetone Qualigens Mumbai (India)

Methods

Preparation of solid dispersion [8]

In Solvent evaporation method, polymers (PEG, Poloxamer and PVP) were dissolved completely in Ethanol in different ratio in a beaker. Bicalutamide was dispersed in the solution in Drug: polymer ratio of 1:1, 1:3, 1:5. The resulting solution was kept on the thermostatically controlled water bath (at 60 ± 0.5^{o}C) to remove the solvent from resulting mixture. The obtained mass was dried in the desiccator for 24hrs. The resultant mass was pulverized using a glass mortar and pestle. The pulverized mass was sifted through # 60, weighed and transferred to the glass vials.

In Hot Melt method, carriers were heated at a temperature of 55 ± 0.5^{o}C and 150 ± 0.5^{o}C using a thermostatically controlled water bath. Bicalutamide in a 1:1, 1:3 and 1:5 Drugs: carrier ratio was dispersed in the melted polymer. The resultant mixture was immediately cooled using ice-water bath and was maintained for a specific period of 2 hrs. The solidified mass was then removed from the ice water mixture and allowed attaining the room temperature for 24 hrs and then pulverized using a glass mortar and pestle. The pulverized mass was sifted through # 60, weighed and transferred to the glass vials.

Drug content estimation

Solid dispersion equivalent to 50 mg. of Bicalutamide was weighed accurately and dissolved in suitable quantity of ethanol. The solutions were filtered through nylon disc filter. The drug content was determined at 269 nm using UV double beam spectrophotometer (Shimadzu Japan) after suitable dilution. Analysis of data was done using graph pad prism instate 3.01 software. The percentage yields were also calculated for each formulation.

Solubility studies [09]

To evaluate the increase in solubility of Bicalutamide saturation solubility measurements were carried out. The known excess of Bicalutamide (approximately 10 mg.) was added to 10 ml. of 0.1N HCl. Samples were shaken on electrical shaker for 48 hours. The samples were filtered, suitably diluted and analyzed by UV double beam spectrophotometer at 269 nm (Shimadzu Japan). (Table 1 & 2)

Infrared Spectroscopy[10]

Infrared Spectroscopy was recorded on a Fourier transform infrared (FTIR) spectrophotometer using KBr disc method. All the samples were recorded in range of 4000 - 400 cm.$^{-1}$ IR spectra of Bicalutamide, carrier and solid dispersion (1:5) are illustrated in Figure 1.

In Vitro Dissolution studies[11]

Solid Dispersion equivalent to 50mg of Bicalutamide was used for the dissolution Studies. The study was performed using USP type II apparatus (Veego, Mumbai) at 37 ± 0.5^{o}C at 100 rpm, using 0.1N HCl (900 ml). A 10-ml amount of aliquot was withdrawn at an interval of 10, 20, 30, 45 and 60 min. An equal amount of the fresh dissolution

medium was replaced immediately after withdrawal of test sample. Test samples were filtered through a 0.45µm nylon filter and suitably diluted. The absorbance of each diluted sample was measured at 269 nm using UV double beam spectrophotometer (Shimadzu Japan) (Fig. 2 & 3). T_{50} values of Bicalutamide in Solid dispersion were calculated from dissolution data[12].

Result and discussion

Solubility of Bicalutamide was found to be 0.00005 gm/100 ml, while improvement in solubility was observed in all solid dispersions. Maximum solubility enhancement was found in 1:5 ratio of drug: PEG 6000 Solid dispersion prepared by solvent evaporation method. (Table 1 & 2)

Enhancement in saturation solubility was found to be in order PVP K-90 > Poloxamer F-68 > PEG 6000. All the solid dispersion system prepared were fine, free flowing and white in color. The low standard deviation values in case of % drug content showed that the drug distribution was uniform in all the solid dispersions. (Table 1 & 2)

Characteristic peak of Bicalutamide at 3115.14, 3580 and 1504.3 $cm.^{-1}$ due to stretching of O-H, C-H stretch and C-H asymmetric stretch. This characteristic stretching band of Bicalutamide was absent in IR of solid dispersion of PEG 6000, Poloxamer F-68 and PVP K-90. This peak may be shifted to lower frequency in solid dispersion. The lowering of shift could be attributed to the physical interaction of Van-der Waals forces of drug with polymer moiety, which may result in dissolution enhancement of Bicalutamide (Fig.1)

Time for 50% drug dissolution (T_{50}) was calculated from the percent cumulative release versus time plot. As the amount of carriers increased in the formulations, T_{50} (time for 50% dissolution of drug) values decreased. T_{50} values indicated that there was enhancement in dissolution rate of Bicalutamide (Table 1 & 2).

The dissolution studies showed faster release of drug from solid dispersion. The dissolution rate was found to increase with increase in carrier proportions in case of PEG- 6000, PVP K- 90, and Poloxamer F- 68 Solid dispersion system. The decreasing order of dissolution profiles given by polymers is PEG > Poloxamer > PVP. Among the polymer ratios the decreasing order of dissolution is given as 1:5 < 1:3 < 1:1. It has been found that among the two methods of solid dispersion preparation, solid dispersion prepared by solvent evaporation method had comparatively better in vitro drug release. The distribution of drug in this solid dispersion are more uniform than the solid dispersion prepared by other method, however the polymer which have high melting point (as in case of PVP) can not be used for solid dispersion preparation. The increased dissolution rate in the system containing PEG- 6000 was probably the result of increased wettability and dispensability of Bicalutamide and PVP K- 90, and Poloxamer F- 68 may be due to surface lowering effect to medium resulting in wetting of hydrophobic. Thus, it can be concluded from the present investigation that PEG can be used as hydrophilic carriers to enhance the in vitro dissolution of Bicalutamide.

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References

1. Serajuddin ATM. Solid dispersion of poorly water soluble drugs: Early promises, subsequent problems, and Recent Breakthrough. J Pharma Sci. 1999; (10): 1058-1066.
2. Leuncer C, Dressman J. improving drug solubility for oral delivery using solid dispersion. Eur J Pharma Biopharm. 2000; 47-60.
3. Chiou WL, Riegelmann S. Preparation and dissolution characteristics of several fast – release solid dispersion of griseofulvin. J Pharm Sci, 1969; 58: 1505-1509.
4. Moustafa MA, Khalil SA, Ebion AR, J Pharm Sci.1974; 63-1103.
5. Tucher H, Furr BJ. The preclinical development of Bicalutamide pharmaco-dynamics and mechanism of action. Urology 1996; 47- 2532.
6. Eri LM, Haug E, Tveter, KJ. Effects on endocrine system of long term treatment with non steroidal anti- androgen Casodex in patients with benign prostatic hyperplasia. Br. J. Urol.1995; 75-335.
7. Finholt. Dissolution Technology Academy of pharmaceutical science, American Pharmaceutical Association, Washington D.C.1974; 106-146.
8. Ford J, Rubinstein MA, Pharm Acta Helv. 1978; 53-32.
9. Higuchi T. Connors KA. Phase solubility techniques. Adv Anal Chem Instr. 1965; 4: 117-212.
10. V. Szejtli "topics in inclusion science" cyclodextrin technology" kluwer Academic publisher's dordreht, 1988.
11. British Pharmacopoeia**,** international Edn., vol. 2, Her Majesty's Stationary Office, Cambridge, 2002, p: 2193.
12. Khan, K.A., J Pharm. Pharmacol., 1975, 27, 48.

Table 1: Data Obtained from Evaluation of Solid Dispersion of Bicalutamide (Solvent Evaporation method)

System	% Drug Content*	Solubility gm/100ml	T_{50} (Min)
Pure Drug	99.24±0.012	0.00005	> 60
SD (PEG 1:1)	95.35±0.45	0.00448	17.0
SD (PEG 1:3)	97.72±0.35	0.00522	15.0
SD (PEG 1:5)	98.60±0.28	0.00622	12.0
SD (Poloxamer 1:1)	79.87±1.24	0.00442	18.0
SD (Poloxamer 1:3)	82.41±1.05	0.00518	16.0
SD (Poloxamer 1:5)	86.12±1.46	0.00553	15.0
SD (PVP 1:1)	55.05±0.24	0.00153	28.0
SD (PVP 1:3)	74.72±0.98	0.00308	22.0
SD (PVP 1:5)	76.78±1.05	0.00396	21.5

* indicates mean of three readings, SD – Solid dispersion, PEG – Poly ethylene glycol, PVP- Poly vinyl pyrrolidone

Table 2: Data Obtained from Evaluation of Solid Dispersion of Bicalutamide (Hot Melt method)

System	% Drug Content*	Solubility gm/100ml	T_{50} (Min)
Pure Drug	99.24±0.24	0.00005	> 60
SD (PEG 1:1)	90.24±0.36	0.00224	21.0
SD (PEG 1:3)	93.72±0.42	0.00288	17.5
SD (PEG 1:5)	96.60±0.28	0.00464	15.0
SD (Poloxamer 1:1)	72.87±1.00	0.00192	32.0
SD (Poloxamer 1:3)	84.41±1.00	0.00254	29.0
SD (Poloxamer 1:5)	85.12±1.84	0.00372	27.0
SD (PVP 1:1)	65.05±0.20	0.00102	34.0
SD (PVP 1:3)	76.72±0.92	0.00208	32.5
SD (PVP 1:5)	78.78±1.39	0.00296	28.0

* indicates mean of three readings, SD – Solid dispersion, PEG – Poly ethylene glycol, PVP- Poly vinyl pyrrolidone

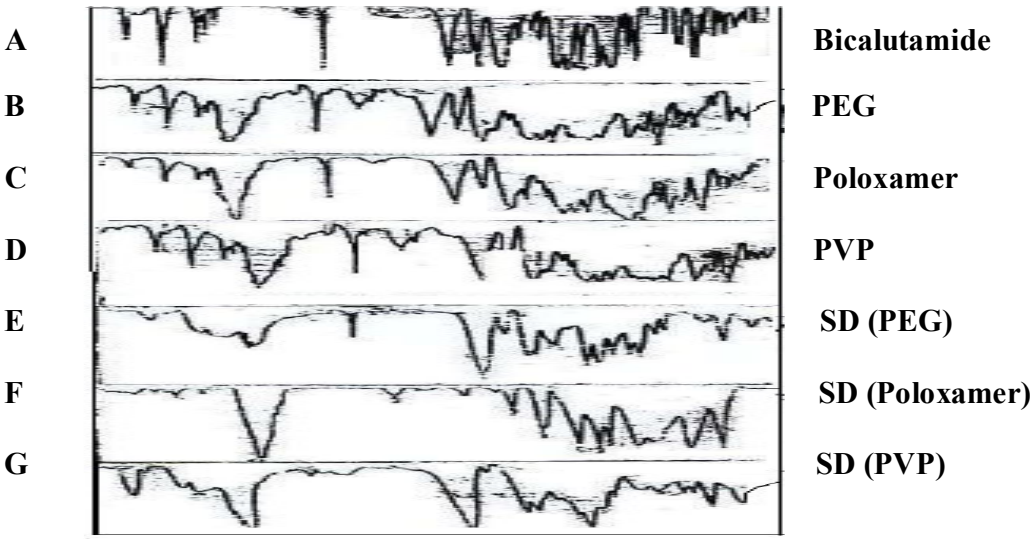

Fig. 1. IR spectrum of Bicalutamide, pure carriers and solid dispersion system A) Bicalutamide; B) PEG 6000; C) Poloxamer F-68; D)PVP K-90; E) Solid dispersion

with PEG 6000; F) Solid dispersion with Poloxamer F-68; G) Solid dispersion with PVP K-90

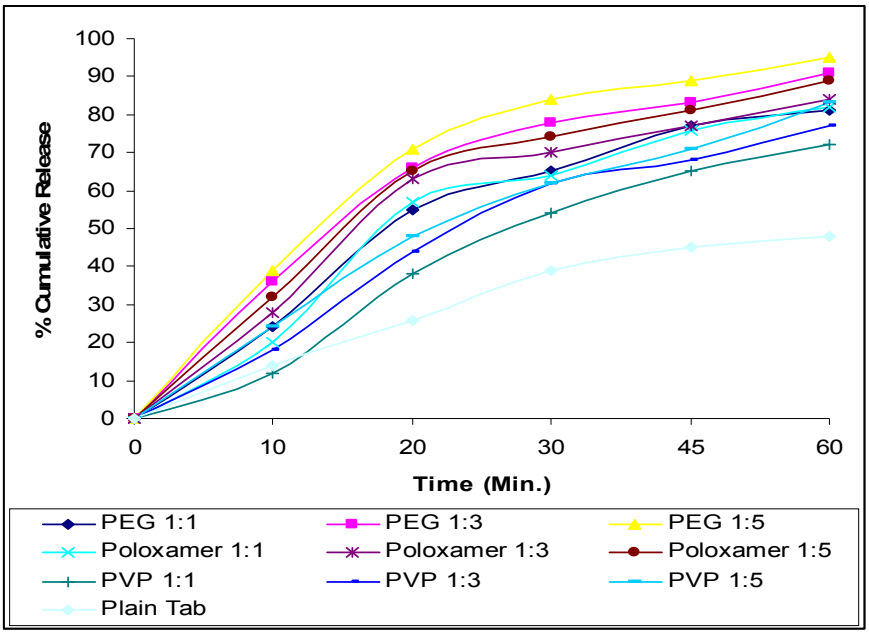

Fig. 2: Comparative Dissolution profile of Bicalutamide from Solid dispersions prepared by Solvent evaporation method using PEG 6000, Poloxamer F-68, and PVP K-90 using USP type II apparatus (Veego, Mumbai) at 37 ± 0.5°C at 100 rpm

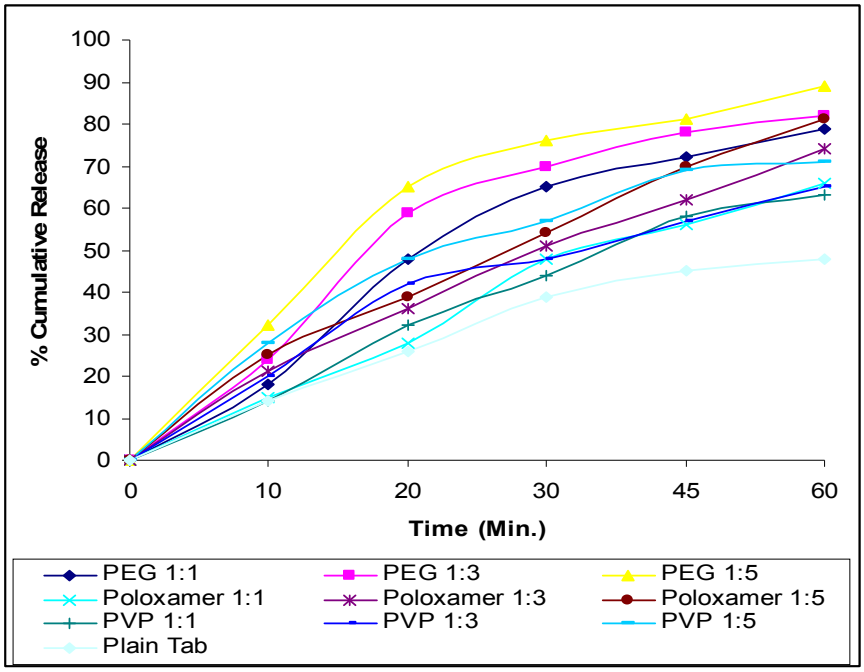

Fig. 3: Comparative Dissolution profile of Bicalutamide from Solid dispersions prepared by Hot Melt method using PEG 6000, Poloxamer F-68, and PVP K-90 using USP type II apparatus (Veego, Mumbai) at 37 ± 0.5°C at 100 rpm