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FORMULATION AND CHARACTERIZATION OF SOLID DISPERSIONS OF BICALUTAMIDE BY FREEZE DRYING

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Abstract-

The aim of this research is to prepare and characterize solid dispersion of Bicalutamide–polyvinylpyrrolidone (PVP) K-30 by freeze drying to increase its solubility. Solid dispersion of Bicalutamide – PVP K-30 was prepared by Freeze drying method with ratio 1:1, 1:2 and 1:3 and dried using a freeze dryer. Characterizations were done by scanning electron microscopy (SEM), powder X-ray diffraction analysis, and Fourier transform infrared (FT-IR) spectroscopy. Solubility test was carried out by Shake flask Method. Powder X-ray diffractogram showed a decrease in the peak intensity, which indicated the crystalline altered to amorphous phase. SEM results indicated the changes in the morphology of the crystal into an amorphous form compared to pure components. FT-IR spectroscopy analysis showed a shift wavenumber of the spectrum Bicalutamide and PVP K-30. The solubility of solid dispersion at ratio 1:1, 1:2 and 1:3 was 28.12µg/mL, 36.12 µg/mL, and 63.25µg/mL, respectively, whereas the solubility of intact Bicalutamide was 8.12µg/mL. In conclusion, the solubility of solid dispersion increased significantly ($P < 0.05$).

Keywords- Bicalutamide, Freeze Drying, PVP K-30, Solubility, *In-vitro* drug release

Introduction-

The oral bioavailability of active pharmaceutical ingredients (APIs) may be hampered by their low water solubility, which results in poor gastrointestinal dissolution.1. Low aqueous solubility is thus a problem that formulation scientists must solve, particularly when designing oral dosage forms. More specifically, drugs with poor solubility but high permeability in class II of the Biopharmaceutical Classification System (BCS) are commonly candidates for solubility or dissolution rate improvement. These drugs experience dissolution rate-limited absorption.

Pharmaceutical firms and researchers have used several strategies to create formulations or drug delivery systems for this family of drugs. The methods encompass a variety of techniques, such as API micronization, solid dispersion (SD), inclusion complexes, self-emulsifying delivery systems, nanoemulsions, and inclusion complexes. One of the most efficient and user-friendly methods for increasing the apparent solubility of the API is solid dispersion, dispersion of the API in a completely or partially amorphous form, or solid solution in an appropriate carrier matrix of the API.

There are numerous methods for creating solid dispersions, including melt mixing, hot-melt extrusion, and solvent evaporation using a rotary evaporator, spray dryer, or freeze dryer. Deciding which approach is the best is silly because each has advantages and disadvantages. For example, melt extrusion is a solvent-free, industrially scalable process, but it requires a low-melting-point polymeric carrier and heat-stable API at the carrier's melting temperature.8 Conversely, spray drying may be used at low temperatures, but one of the

main obstacles is its inherent complexity with regard to process optimization and the characteristics of the finished product. Making solid dispersions can also be done by freeze-drying or lyophilization.It functions mostly without the need of heat by prefreezing and sublimating under low pressure. As a result, it works well for dispersing heat-sensitive APIs into solid form. In this study, we have created a solid dispersion system for bicalutamide using the lyophilization approach.

In order to explore the potential therapeutic benefit of beliceutamide (BLT), a nonsteroidal antiandrogen, Bicalutamide was chosen as the model drug in this study to be incorporated into Solid dispersion and studied for prostate cancer treatment. Prostate cancer is the main indication for BLT, an FDA-approved antineoplastic hormonal medication . It is frequently used, either alone or in conjunction with other anticancer medications, to treat locally advanced and metastatic prostate cancer. It mainly works by preventing androgen from attaching to androgen receptors. Furthermore, BLT is a class II medication under the biopharmaceutics classification system (BCS) with high permeability and low aqueous solubility. Bicalutamide encorporated into solid dispersion enhance its bioavailability and water solubility.

Material and Method-

Material-

Bicalutamide was kindly gifted by Sun Phramceutical Pvt LTD, Deu-Daman, India. Ethanol was procured from Vikash Drug Pvt Ltd, All the chemicals mention are analytical grade only.

Method-

Using a magnetic stirrer, the mixture of Bicalutamide and PVP K-30 was mixed in ratios of 1:1, 1:2, and 1:3. Bicalutamide was dissolved in 5 mL of 96% ethanol, while PVP K-30 was dissolved in 20 mL of distilled water. The mixture was homogenized and then dried using a freeze dryer (Tarun Scientific, Chennai). The freeze-dried solid dispersions were then stored in a sealed container.

Table 1 – Formulation Table

Sr. No.	Formulation	Drug (gm)	PVPK-30 (gm)	Ratio
1	F1	0.5	0.5	1:1
2	F2	0.5	1	1:2
3	F3	0.5	1.5	1:3

Evaluation of solid dispersion-

FTIR-

Compatibility studies of the drug (Bicalutamide) with PVP K- 30 were carried out using FTIR spectroscopy. Sample from the drug alone, carrier alone, and physical mixture of drug and polymer was examined by ATR sampling technique and the spectrum was scanned over the frequency range between 4000 and 400 cm^{-1} and at 4 cm resolution. The appearance, disappearance, or broadening of absorption band(s) on the spectra of the solid dispersions and the polymeric carriers in comparison with the spectrum of the drug were used to determine possible interactions between pure drug and polymers.

Solubility Analysis-

Prepared 5 mg of solid dispersion in the ratios of1:1, 1:2 and 1:3 were added to 10 ml of phosphate buffer 6.8 in a conical flask. After being sealed, a conical flask was put in a mechanical shaker for a full day. After a day, the material was filtered, and a UV spectrophotometer (Systonic 2201) was used to determine the absorbance at 272 nm.

Drug Content-

The homogeneity of the drug content in solid dispersions was examined. A precisely weighed portion of the material was dissolved in 10 ml of methanol and agitated for ten minutes using a magnetic stirrer. After the solution was diluted appropriately and filtered through a membrane filter (0.45 μm), its Bicalutamide content was measured using spectrophotometry.

% Yield-

The percent yield of Bicalutamide solid dispersions was determined according to the method described using the following expression:

% yield =weight of prepared SD / Wt. of drug + carrier× 100

Powder X-ray diffraction -

Powder X-ray diffraction studies were performed to check for any crystallinity in the formulation after it was made and after the stability studies were performed. Avoiding recrystallization of the drug in the formulation was one of the goals of the present study. PAN analytical X-Pert Pro V1.6 with X Pert Data Collector V2.1 software was used equipped with a CuKa2 anode tube and diffractometer of radius 240 mm. The X-ray powder diffraction scan was performed using a BB004 flat stage. The powdered sample was placed in an aluminum sample holder that had a 2.5 cm square with a depth of 0.5 mm. The data were collected by scanning the sample at 45 kV and 40 mA. Samples were scanned from 5 to 50°C 2θ at a step size of 0.0170 and scan rate of 1.0°C/min.

Scanning electron microscopy -

The surface morphology of the raw materials and the formulated product were studied using a scanning electron microscope equipped with a JEOL JSM 7500. Snappy 4 software was used to obtain the digital picture. Samples were placed on brass stubs using double-sided adhesive tape. The samples were coated with a layer of gold using a gold sputter technique to improve the conductivity of the surface of the sample to obtain good images. A Denton Vacuum Desk II was used for the gold sputter technique. Pictures were taken at magnifications whereby they could be compared with each other, showing best the surface features of the various materials.

In-vitro Drug Release -

The drug dissolution profiles of the drug alone and the SD powder 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 0.1% 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, 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 was plotted versus time.

Result and Discussion –

FTIR-

Using IR spectra of pure BL, PVP K30, and BLSD (1:1), interactions between the polymer and the BL were investigated. Fig. 1 displays these findings. A stretching vibration was observed by the hydroxyl group in compounds as a wide band centered at 3400–3650 cm. 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}.Hence Drug and bicalutamide solid dispersion showed similar absorption peak which indicate its good compatibility with polymer.

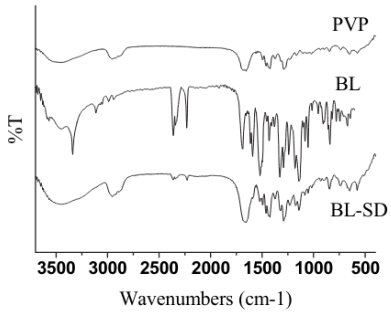

Fig. 1 – IR Spectra of PVP k-30, Bicalutamide and Solid dispersion

Solubility Analysis –

Solubility of all formulations of nanosponges in distilled water and 1% SLS was determined by using flask shaking method. Prepared Bicalutamide loaded nanosponges showed increased solubility than the pure drug in 1% SLS and water. The increase in solubility is due to the reduction of particle size. The result of the solubility is represented in table 2.

Table 2 – Solubility Analysis

Sr. No	Batches	Water (µg/ml)	1% SLS (µg/ml)
1	Pure Drug	8.12	20.12
2	F1	28.12	41.23
3	F2	36.12	49.12
4	F3	63.25	76.12

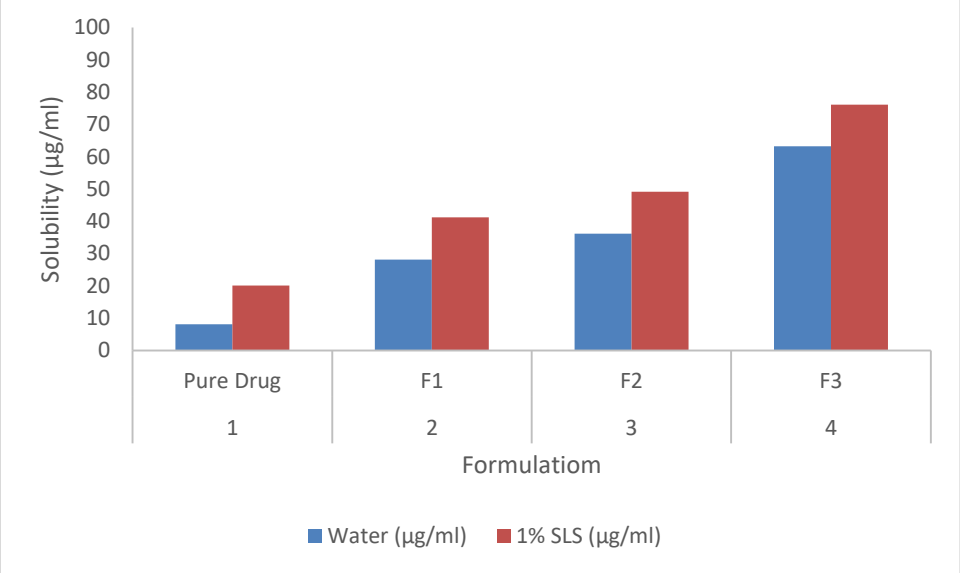

Fig. 2 – Solubility Analysis

% Drug Content –

The examination of the drug content (%) for solid dispersion formulations, taking into account the number of powders equivalent to 50 mg of Bicalutamide, revealed findings within the permissible range of (98.7±0.82)−(101.2±0.72) (Table 3). All of the solid-dispersion formulations exhibit uniform drug distribution, as indicated by low standard deviation (SD) values for drug content.

Table 3 - % Drug Content and Percentage Yield

Sr. No.	Formulation	% Drug Content	Percentage Yield (%)
1	F1	99.1±0.92	90.23
2	F2	101.2±0.72	92.56
3	F3	98.7±0.82	95.17

Percentage Yield

Percentage yield of all formulations of solid dispersion were calculated taking theoretical and practical yield, shown in table 11. Percentage yield of nanosponges was in the range of 90.23% to 95.17%.

XRD-

The results of XRD clearly demonstrated that crystals were present in BL at room temperature. In the BL-SD (1:3), X-ray patterns (Fig. 3) did not display any distinct peaks attributed to BL, suggesting that BL crystals underwent an amorphous state transformation throughout the co-solvent process. Little peaks were seen in the BL-SD (1:3, 1:4), indicating the presence of a crystalline fraction in that dataset. They appeared to be able to demonstrate the transition of crystalline BL to the amorphous form. The physical state of BL was not affected by the presence of PVP K30 in the physical mixture, as indicated by the X-ray diffraction data of BL in a physical mixture with PVP K30 still displaying crystallinity.

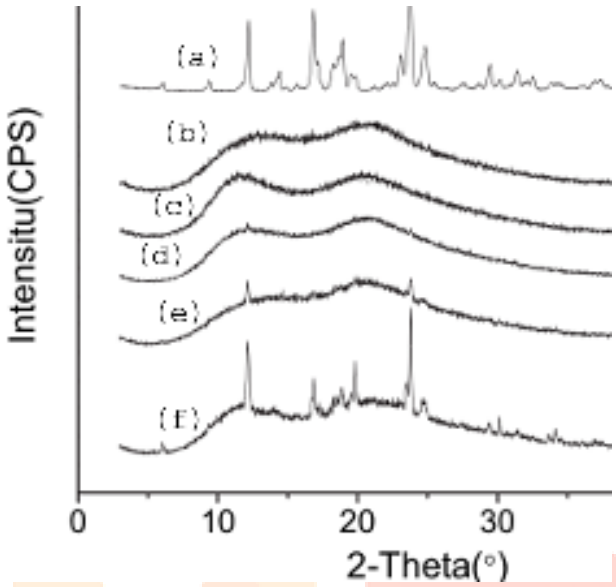

Fig. 3 – XRD of- (a)- pure Bicalutamide, (b)- Physical mixture of Bicalutamide and PVP K-30, (c)- Solid dispersion(1:1), (d)- Solid dispersion(1:2), (e)- Solid dispersion(1:3), (f)- PVP K-30

Scanning electron microscopy-

SEM analyses of the formulated Bicalutamide solid dispersion were performed to evaluate the surface morphology of formulaton. The SEM images of formulation F3 are shown in Figure 4. The surface morphology studies revealed that the solid dispersion was closely compacted into small spherical form.

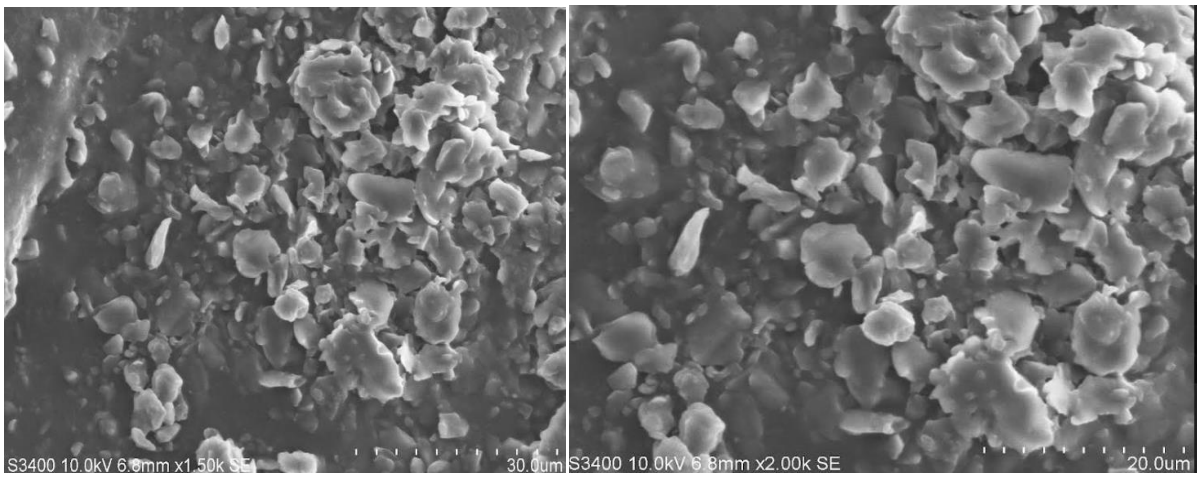

Fig.4 – SEM images of Solid Dispersion

In-vitro Drug Release –

The *in-vitro* drug release profile of pure Bicalutamide and Bicalutamide solid dispersion was shown in the Table 4. Pure drug Bicalutamide drug release was found to be 42.7% in 150 min. The *in-vitro* drug release of Bicalutamide solid dispersion was found in the range of 80.2% to 86.9% in 150 min. Drug release of Bicalutamide solid dispersion was found to be increased than the pure Bicalutamide. Highest drug release was found to be 97.6% in 150 min. Increase in the drug release was due to the increase in polymer concentration.

Table 4- In-vitro Drug Release

Time (min)	Pure drug	F1 (%)	F2 (%)	F3 (%)
0	0	0	0	0
5	5.6	6.9	5.9	5.9
10	7.2	11.9	7.3	8.9
15	8.7	13.9	13.2	16.9
30	13.8	20.9	22.5	25.1
45	14.8	39.3	34	44
60	31	49.2	49	54.2
90	35.6	62	68.6	64.6
120	41	76.3	74	82.5
150	42.7	80.2	81	86.9

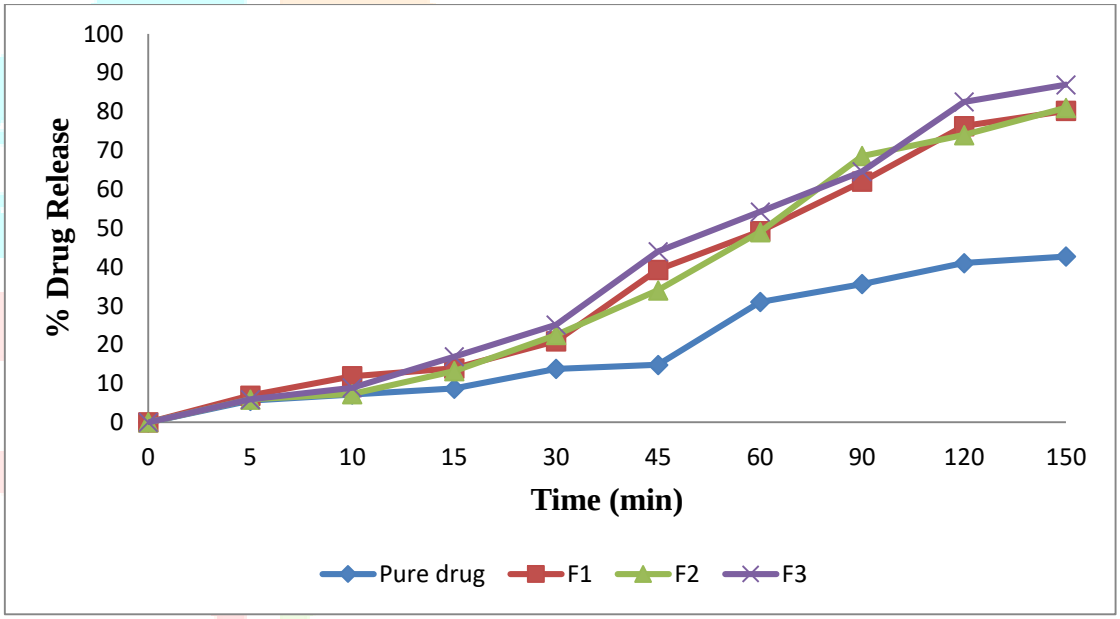

Fig. 5 – In-vitro Drug Release

Conclusion –

In the present study it was clearly demonstrated that Bicalutamide solid dispersion formulation can be effectively produced by processing via Freeze Drying with enhanced solubility and dissolution rates. *In vitro* drug release studies of optimized formulation F3 exhibited a cumulative release of 86.9 after 150 min. The FTIR spectrum revealed that no chemical interaction occurred between the drug and excipients used in the formulation. Analysis by DSC and powder X-ray diffraction showed that Bicalutamide existed in amorphous form within the solid dispersion formulation fabricated using the Freeze Drying process. Additionally, scanning electron microscopy studies suggested the conversion of crystalline Bicalutamide to an amorphous form. The dissolution rate and solubility of Bicalutamide solid dispersions were improved significantly using the PVP K-30 Polymer.

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