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Solubility And Dissolution Enhancement Of Bosentan Monohydrate By Solid Dispersion Technique

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Abstract: ***Solid dispersions (SDs) are one of the most promising strategies used to improve the solubility of poorly water soluble drugs. This technology is mainly applied to improve the solubility of Class II and Class IV drugs. Bosentan monohydrate is an anti-hypertensive agent used in the treatment of pulmonary arterial hypertension, which has oral bioavailability of 40-50% and it belongs to the BCS class-II. Many attempts are made in the past to increase its solubility by preparing its solid dispersions. However, very few literature reports are available wherein polymers are used for preparation of solid dispersions. In the present work, an attempt is made to increase the solubility of bosentan by preparing its solid dispersions using polymer i.e. gelucire44/14 and poloxamer407 various techniques used for preparing Solid dispersions are by physical mixture, of solvent evaporation methods using different drug-polymer ratio. Thus prepared solid dispersions were evaluated for percentage yield, drug content, saturation solubility and in-vitro dissolution studies. The result obtained from above studies indicated that, the solubility and dissolution of bosentan monohydrate of solid dispersions was improved as compared to pure drug by all the methods employed. Among various methods employed, solvent evaporation method produced good results compared to physical mixture, solvent method. Hence, Solid dispersion technology can be used to improve the solubility of bosentan monohydrate.***

Keywords: ***Solid Dispersions, bosentan monohydrate, solvent evaporation method, in-vitro dissolution study***

I. INTRODUCTION

The solubility processes in human body is very important. The 60% of human body is water; the biological and chemical reactions are taken place in this medium in soluble form. The active agent of drug has to dissolve and be absorb in the body to reach adequate concentration in the near of receptor. In drug development there is an increasing importance of solubility measurements. Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Various formulation parameters that play a vital role for successful formulation includes, aqueous solubility, stability at ambient temperature and humidity, photo stability, compatibility with different solvents & excipients etc. Out of these parameters solubility is the most important for developing the formulation. Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems associated with these drugs was its very low solubility in biological fluids, which results into poor bioavailability after oral administration. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption[1,2] Therefore, pharmaceutical researchers focuses on two areas for improving the oral bioavailability of drugs include:

- ✓ Enhancing solubility and dissolution rate of poorly water-soluble drugs.
- ✓ Enhancing permeability of poorly permeable drugs.[3]

The therapeutic efficacy of a drug product intended to be administered by the oral route mainly depends on its absorption by the gastrointestinal tract. However, for a drug

substance to be absorbed, it needs to be solubilised. Solubility is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and low permeability. By improving the dissolution profile of these drugs, it is possible to enhance their bioavailability and reduce side effects. Solid dispersions are one of the most successful strategies to improve dissolution rate of poorly soluble drugs. SDs can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties Solid dispersion is a unique approach which was introduced by Sekiguchi and Obi. In this method, the drug is dispersed in extremely fine state in an inert water soluble carrier in solid state. Bosentan is a competitive antagonist of endothelin-1 at the endothelin-A (ET-A) and endothelin-B (ET-B) receptors. Under normal conditions, endothelin-1 binding of ET-A or ET-B receptors causes constriction of the pulmonary blood vessels. By blocking this interaction, bosentan decreases pulmonary vascular resistance. Bosentan has a slightly higher affinity for ET-A than ET-B.[4,5] One of the pharmaceutical strategies to improve the oral bioavailability is formation of solid dispersions. Solid dispersion can able to improve their dissolution by increasing drug-polymer solubility, amorphous fraction, particle wettability and particle porosity. In this present study, the solubility of pure bosentan monohydrate was enhanced, with increasing the dissolution rate of pure bosentan monohydrate. Based on these facts, dissolution rate of pure bosentan increased, with increasing the various Polymers content and with increasing the various 1% sodium lauryl sulphate content The solubility of pure bosentan was observed in pH 7.2 ± 0.2 buffer solution, with increasing the polymer ratio as 1:1:0.25, 1:2:0.50, 1:1.5:0.75. The SD of bosentan monohydrate with Poloxamer407 and gelucire44/14 was prepared successfully by solvent evaporation method in different ratio. In-Vitro dissolution showed that, there were increased in dissolution rate in case of SD of bosentan monohydrate with Poloxamer and gelucire. It was observed that complex formed between bosentan monohydrate with Poloxamer and gelucire (1:1.5:0.75) ratios had change the structure of the drug. Solid Dispersion of bosentan monohydrate poloxamer and gelucire improved the dissolution rate of bosentan which helps to enhancing solubility of bosentan monohydrate.

II. MATERIALS AND METHODS

Materials Bosentan Monohydrate was gifted by Mylan Laboratories, Hyderabad, Gelucire44/14, poloxomer407 was gattefosse, Mumbai, and crosscarmellose sodium, microcrystalline cellulose, magnesium stearate, aerosol-200, lactose and talc were purchased by Research-Lab Fine Chem.

IN PREPARATION OF SOLID DISPERSION

Solvent evaporation method was used for the preparation of SDs. three different drug: carrier ratios (1:1:0.25, 1:2:0.50 and 1:1.5:0.75) were used in poloxamer and gelucire were weighed according to these weighed ratios.

SOLVENT EVAPORATION METHOD

For preparation of solid dispersions, firstly drug was dissolved in solvent (methanol). Then gelucire and poloxamer was dissolved in that solvent with continuous stirring using magnetic stirrer. The solvent was allowed to evaporate on hot plate with stirring at 45±5°C to get a clear solution and solvent removed at room temperature, obtained mass is dried. [6]

III. EVALUATION OF PREPARED SOLID DISPERSIONS

Production Yield
Drug content
Saturation solubility studies
In vitro Dissolution studies

A. PRODUCTION YIELD

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation as [7]

$$\text{Percentage yield} = \frac{\text{Practical mass (Solid dispersion)}}{\text{Theoretical mass (Drug + carrier)}} \times 100$$

B. DRUG CONTENT

The Physical mixture and solid dispersion equivalent to 10 mg of drug were taken and dissolved separately in100 ml of sodium lauryl sulphate. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbances of solutions were determined at 270 nm by UV-visible spectrophotometer. The actual drug content was calculated using the following equation as [8]

$$\% \text{ drug content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

C. SATURATION SOLUBILITY

Saturation solubility was determined by using shake flask method. Excess quantities of drug and prepared SDs were added in 10 ml distilled water in 100 ml flasks which were then incubated in orbital shaker at 37°C and at 100 rpm for 72 hrs. Absorbance of resulting solution was measured on UV spectrophotometer at 270 nm. [9]

D. IN- VITRO DISSOLUTION STUDIES

In- vitro dissolution studies were done in USP Dissolution apparatus containing dissolution medium sodium lauryl sulphate. Pure drug and SDs powder was put in 900 ml of the dissolution media, temperature maintained at 37 ± 2C and speed was set at 50 rpm (USP XXVI). The samples (5.0 ml) were withdrawn at various time intervals, filtered through

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Whatman filter paper and analyzed by UV spectrophotometer at 270nm. The dissolution was evaluated as dissolution efficiency at 60 min. [10-11]

IV. CHARACTERIZATION OF SOLID DISPERSION

Solid dispersion of bosentan monohydrate were characterized using following analytical techniques

Ultraviolet spectrophotometric study
FT-IR spectral analysis
Differential Scanning Calorimetry
X-Ray Powder Diffraction

A. ULTRAVIOLET SPECTROPHOTOMETRIC STUDY

For determination of in the spectrophotometric estimation of Bosentan Monohydrate, the absorbance of the standard solutions of Bosentan were determined in distilled water alone and in the presence of the hydrotropic blend employed for formulation purpose. The absorbance were recorded at appropriate wavelengths. A UV-visible recording spectrophotometer (JASCO V-630) with 1 cm matched silica cells were employed for spectrophotometric determinations. [12]

B. FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

The infrared (IR) spectra were recorded using an FTIR spectrophotometer (Shimadzu IR) and spectra were recorded in the wavelength region between 4000 and 400cm–1 by using Kbr. The FTIR spectra obtained for pure drug (bosentan), polymers (gelucire, poloxamer) and physical mixtures of drug with excipients are compared.

C. DIFFERENTIAL SCANNING CALORIMETRY (DSC)

DSC studies of pure drug, pure polymer and solid dispersions were performed to access what changes had actually occurred when SD were prepared. Analysis of samples was carried out on Differential Scanning Calorimeters (DSC 60, Shimadzu, Japan) instruments at heating rate of 10oC /min. The measurements were performed at a heating range of 0 to 300^{0C} under nitrogen atmosphere.

PREPARATION OF TABLETS BY DIRECT COMPRESSION TECHNIQUE

Preparation of tablets by direct compression technique Three batches of tablets was prepared as shown in Table 1. All the ingredients were passed through 60 mesh sieve separately. Solid dispersion equivalent to 62.5 mg of Bosentan and microcrystalline cellulose and crosscarmellose sodium were mixed in geometric proportion to get a uniform mixture. Then the other ingredients were weighed and mixed in geometrical order and tablets were compressed using flat round punch of 8 mm sizes on a karnatvati mini Compression Machine.

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredient	Mg								
SD (≈62.5 mg Bosentan Monohydrate)	203	203	203	203	203	203	203	203	203
Crosscarmellose Sodium	15	20	25	15	20	25	15	20	25
Microcrystalline Cellulose	60	60	60	75	75	75	90	90	90
Aerosil-200	05	05	05	05	05	05	05	05	05
Lactose	64	59	54	49	44	39	34	29	24
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1

Table 1: Composition of Formulations as Per 3^2 Full Factorial Design

V. EVALUATION OF TABLETS

A. POST COMPRESSION PARAMETERS

a. HARDNESS TEST

The hardness of the tablets was determined using Monsanto Hardness tester. Its unit is expressed in kg/cm2. Three tablets were randomly picked from each formulation and hardness was determined, the mean and standard deviation value was calculated. [13]

b. FRIABILITY

The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (W final). The percentage friability was then calculated by,

F = W initial-W final/W initial × 100

(% Friability of tablets <1% is considered acceptable) [14]

c. DRUG CONTENT UNIFORMITY

Twenty tablets were weighed and crushed in a mortar then powder containing equivalent to 203 mg of Bosentan was dissolved in 100 ml of methanol to achieve a solution that has a concentration of 1000 µg/ml. 10 ml from this stock solution was taken and diluted to 100 ml using methanol, to get concentration 100 µg/ml. Further, 20 µg/ml solution was prepared by taking 2 ml from the stock solution and diluting to 10 ml. Absorbance was measured at 270 nm.[15]

d. IN VITRO DISSOLUTION STUDIES

Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test apparatus at 50 rpm) using 900 ml of 1% SLS in water as dissolution medium. Temperature of the dissolution medium was maintained at 37°C ± 0.5°C, 10 ml aliquot of dissolution medium was

withdrawn at every 2 min interval and filtered and the absorbance of filtered solution was measured by UV spectrophotometric method at 270 nm and concentration of the drug was determined from standard calibration curve.

VI. RESULTS AND DISCUSSION

✓ PRODUCTION YIELD

Sr. no.	Batch	% Yield
1	1:1:0.25	84.26
2	1:1.5:0.75	88.67
3	1:2:0.50	86.67

Table 2: Production Yield of All Batches in Percentage

✓ PER CENT DRUG CONTENT

Sr. no.	Batch	Drug content (%)
1	1:1:0.25	67.78
2	1:1.5:0.75	84.73
3	1:2:0.5	75.75

Table 3: Per Cent Drug Content in Complexes

✓ SATURATION SOLUBILITY STUDY

Sr. no	Bosentan monohydrate : carrier combination	Saturated Solubility (mg/ml)
1.	1:1:0.25	3.8446
2.	1:1.5:0.75	6.6401
3.	1:2:0.05	8.7840

Table 4: Saturation solubility data for Bosentan monohydrate and carrier combinations in distilled water

✓ SOLUBILITY STUDY

Sr. No.	Formulation	Solubility (mg/ml) ± S.D.
1.	**Pure Drug : Polymers**	0.0210
2.	BM:P:G (1:1:0.25)	0.0623
3.	BM:P:G (1:1.5:0.75)	0.1274
4.	BM:P:G (1:2:0.50)	0.0923

Table 5: Result of Solubility Study of Various Solid Dispersion

FOURIER-TRANSFORM INFRARED STUDY

Fourier-transform infrared was employed to characterize the possible interaction of bosentan and solid dispersion was found at 1348 cm^{-1} (S=O) shows strong absorption peak at 1377 cm-1 (N-H) and ester (C-O) 1242 stretch, these characteristics peaks also found in the drug-polymer mixture, which indicates no drug-excipients interaction.

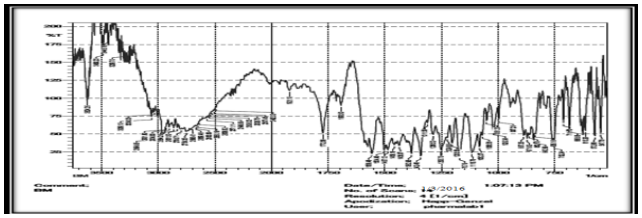

Figure 1: FTIR spectrum of bosentan monohydrate

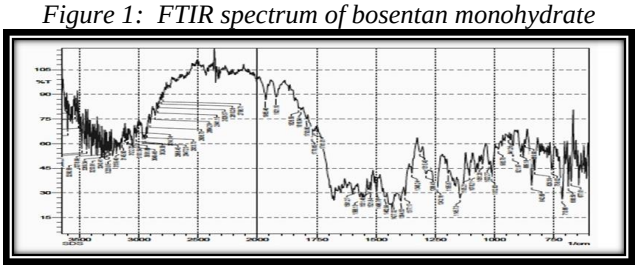

Figure 2: FTIR spectrum of Solid Dispersion

SOLID DISPERSIONS OF BOSENTAN MONOHYDRATE DIFFERENTIAL SCANNING CALORIMETRY ANALYSIS

The DSC thermogram of Bosentan is shown in Figure 3. The onset temperature was reported in the graph. The melting point of Bosentan monohydrate was 196-198°C and DSC thermogram of Bosentan shows endothermic melting peak at 200.00 °C. DSC thermogram of Bosentan solid dispersion is shown in Figure 4.

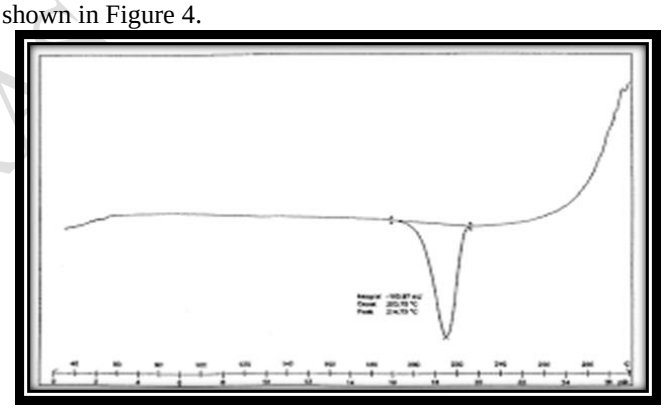

Figure: 3. Differential scanning Calorimetry thermogram of Bosentan monohydrate

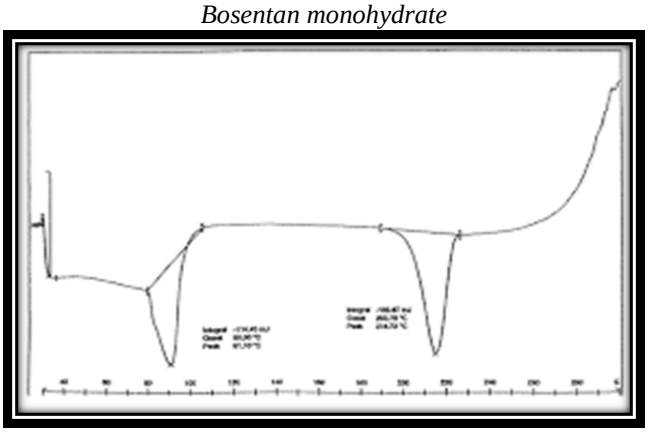

Figure 4: DSC of Solid Dispersion

VII. EVALUATION OF TABLETS

All the tablet preparations were evaluated for various physical parameters before proceeding further. Table 6

includes the values of thickness, hardness, Friability and weight variation of 9 batches tablet prepared using different combinations of functional excipients. Tablet weights in all batches varied between 346-350 thickness between 4.37-4.53 and tablet hardness between 4-4.7. Thus all the physical parameters of the manually compressed tablets were quite within control.

Batch No.	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	% Drug Release
F1	4.437 ± 0.05	4.70 ± 0.08	0.331± 0.045	348.6 ± 0.4	54.03 ±0.5
F2	4.394 ± 0.03	4.50 ± 0.08	0.319± 0.040	348.2 ± 0.51	61.40 ±0.04
F3	4.454 ± 0.02	4.08 ± 0.01	0.293 ±0.023	349.9 ± 0.52	63.10 ±0.01
F4	4.533 ± 0.02	4.63 ± 0.120	0.345± 0.023	347.85 ± 0.44	66.53 ±0.3
F5	4.529 ± 0.03	4.04 ± 0.10	0.265± 0.046	347.05 ± 0.56	64.45 ±0.5
F6	4.48 ± 0.01	4.31 ± 0.091	0.292± 0.046	348.2 ± 0.14	73.08 ±0.4
F7	4.37 ± 0.06	4.37 ± 0.08	0.266 ± 0.061	348.1 ± 0.43	66.22 ±0.2
F8	4.37 ± 0.03	4.7 ± 0.09	0.279 ± 0.040	346.5 ± 0.25	69.51 ±0.1
F9	4.40 ± 0.02	4.7 ± 0.84	0.476± 2.074	347.2 ± 0.079	67.52 ±0.5

Table 6: Evaluation of Tablets Characteristic

The percentage friability, as depicted in Table 6 was in the range of 0.265-0.476 to be well within approved range (<1%) which indicates the tablet had good mechanical resistance.

IN VITRO DISSOLUTION STUDIES

The F6 batch showed good dissolution profile shown in Figure 5. 73.08 % of the drug release takes place within 60 min. When the tablet enters into dissolution medium tablet disintegrates, further due to solid dispersion, soluble carrier releases the drug in molecular form due to which the dissolution of tablet increased and drug is released quickly from tablets and absorb rapidly by oral route resulting in increased bioavailability.

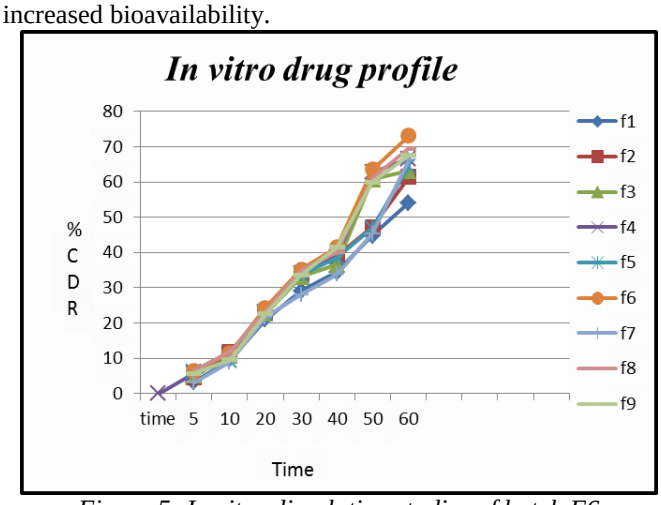

Figure 5: In vitro dissolution studies of batch F6

VIII. CONCLUSION

Bosentan monohydrate, an anti-hypertensive drug has poor water solubility there by posing problems in their formulations in absorption leads to poor bioavailability. As it is anti-hypertensive drug it has to be absorbed rapidly. So enhancement of the solubility of drug is important. Solid dispersions of bosentan monohydrate were prepared with polymers (MCC, CCS) in different ratios by solvent evaporation method. From the studies it is concluded that the formulation with drug: polymer ratio 1:1.5:0.75 showed better dissolution rate in comparison with bosentan API and marketed drug. Solid dispersion of drug: polymer showed faster release than other dispersions in ratio of 1:1.5:0.75 it was noticed from the study that increases in the polymer concentration increases the drug release from solid dispersions. The formulation was successful converted to tablet dosage form. The characterizations of the powder blend were in favourable range. The tablets formulated were in acceptable hardness, disintegration time and in vitro release. The tablet of bosentan from optimized formulation shows almost 30percent increase in the dissolution from the marketed tablet. Thus this can be concluded from the work that such combination can further be used for the development of bosentan monohydrate tablet for enhanced dissolution.

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