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FORMULATION, EVALUATION AND SOLUBILITY ENHANCEMENT OF BOSENTAN MONOHYDRATE BY DIFFERENT TECHNIQUES

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Abstract:
Oral route still remains the convenient route of drug administration in many diseases. But the major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility of certain drugs. Incase of poorly water soluble drugs, dissolution is the rate limiting step in the process of drug absorption. So, bioavailability problems are prevalent with extremely hydrophobic drugs (aqueous solubility < 3.4 mg / ml at 37^0 C). The enhancement of oral bioavailability of poorly water soluble drugs like Bosantan could be improved by enhancing aqueous solubility. Among numerous ways of enhancing drug dissolution, solid dispersions and inclusion complexation are promising techniques to enhance the dissolution of poorly water soluble drugs.
Increasing the in vitro dissolution of poorly soluble drugs such as bosentan using different technology and we expect a good correlation between the in vitro and in vivo performance of the formulations. Of the different techniques lipid solid dispersion has been concluded as the best in increasing the solubility of bosentan when compared to the other techniques like solid didpersion and liquisolid compacts. The technique being simple and effective can also be extended to other poorly soluble drugs. The in vivo performance of the lipid solid dispersion has further concluded the ability of enhancing the solubility of the drug.
Keywords: *Lipophilicity, Solid dispersions, Bosantan, ICH guidelines, Dissolution ,Disentigration*

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INTRODUCTION:

The advent of combinatorial chemistry and high throughput screening has resulted in the rapid identification of many highly potent new chemical entities[1]. Coincident with the increasing use of these technologies, however, has been a developing trend towards the identification of lead compounds with higher molecular weights and lower aqueous solubilities. Whilst these attributes conspire to provide optimised drug-receptor binding characteristics, the high lipophilicity is advantageous in terms of compound permeability. It intrinsically translates into poor aqueous solubility. Since the first step in the oral absorption process is dissolution of the drug compound in the gastrointestinal lumen contents, poor aqueous solubility is rapidly becoming the leading hurdle for formulation scientists working on oral delivery of drug compounds. They also tend to result in poor drug solubility and poor membrane permeability characteristics. As solubility and permeability are considered prerequisites to oral absorption many of these drugs exhibit poor and variable bioavailability [2]. Several recent publications reviewed the formulation development aspects of drug candidates at discovery stage. Amidon et al[3] developed a system that groups drug molecules on the basis of their different solubility and/or permeability, known as the biopharmaceutical classification system (BCS). The molecular parameters, such as H-bond donors, H-bond acceptors, molecular weight, and calculated logP (Clog P) can also serve as a guide to understand the challenge in formulation development[4]. Lee et al[5] presented a high-throughput formulation decision scheme to support early discovery injectable formulation development to address the formulation development challenge presented at the discovery stage. Strickley [6] summarized the solubilizing excipients used in commercially available solubilized oral and injectable formulations, providing a great reference in excipient selection. To overcome biopharmaceutical challenges, versatile formulation approaches are designed which will accommodate the physicochemical properties of the individual drug while simultaneously improving the aqueous solubility and oral bioavailability. These approaches include co-solvents [7], solid dispersions[8], cyclodextrin inclusion complexes[9] nanosuspensions [10], colloidal delivery systems[11] and lipid based delivery systems[12-16].

MATERIALS AND METHODS:

Preparation and evaluation of bosentan monohydrate loaded liquid solid dispersions

Materials:

Gelucire 44/14 (Stearoyl macrogoglycerides) and Compritol 888 ATO (Glyceryl dibehenate) are generous gifts from Gateefosse; india.Bosentan monohydrate is obtained from Chandra Labs, Hyderabad, India. All HPLC and analytical grade chemicals are purchased from Standard Reagents, India

Preparation of Bosentan monohydrate (BM) loaded lipid-solid dispersions

In the selection of lipid mixture for the preparation of BM loaded lipid-solid dispersions, different lipid composition lipid dispersions were selected. The lipid mixture used is gelucire 44/14 and compritol at a weight ratio **of 1:3.** Different formulations are prepared by varying the drug concentrations in the lipid matrix **(**BMLS1 to BMLS6). From the prepared formulations the optimum drug to excipients ratio, BMLS3 is selected based on the drug content, drug solubility (saturation solubility) and physical form. The preparation method includes the dispersion of BM in the lipid matrix consisting of gelucire and compritol at a weight ratio of 1:1. The drug dispersed lipid matrix is dissolved in the dichloromethane (DCM) to obtain a clear solution. The ratio of lipids in the lipid mixture is maintained at a final concentration of **1:3** of gelucire and compritol. The drug and lipid mixture solution is spray dried (Labultima, Mumbai) using a co-axial nozzle with co-current flow. The total solid contents concentration is maintained at 5 w/v%. The conditions that are maintained during spray drying are as follows

Inlet temperature 50^{o}c
Outlet temperature 40^{o}c
Feed rate 3ml/min
Atomization pressure 2.5kg/cm^{2}
Aspiration 25m3/h.

The dried BM loaded lipid-solid dispersions (BMLS3) are collected from the spray drier and stored in desiccated environment until further study. Plain BM is dispersed in DCM and spray dried using similar conditions to prepare the spray dried bosentan monohydrate (BMS1).

A) Characterizations

I. Drug content estimation

The amount drug incorporated in the lipid-solid dispersions is determined by using a HPLC method after completely extracting the drug by using non aqueous solvent. The extraction method includes dispersion of 10 mg sample in 10 mL of acetonitrile and vortexed well. The solutions are filtered through a membrane filter (0.45 mm) and suitably diluted with mobile phase before injecting to the HPLC.

II. Saturation Solubility

The efficacy of the formulations in improving the dissolution is preliminarily evaluated by measuring

the saturation solubility of the drug from the formulations. The saturation solubility is determined for the plain drug (BM), spray dried drug (BMS) and the formulations (BMLS1 to BMLS6).
The impact of spray drying on the solubility enhancement is studied by taking plain drug as a control (BM). The known excess amount of bosentan monohydrate is added to 10 mL of pH 1.2 acetate buffer. Samples are rotated at 20 rpm in a water bath (37± 0.5ºC) for 48 hours. The samples are then filtered, suitably diluted, and analyzed by HPLC. The saturation solubility values represented in µg/ml

III. Differential Scanning Calorimetry (DSC):
The enhanced solubility of the bosentan monohydrate from the developed formulations can be attributed to the morphological conversion of the drug upon spray drying. To validate the morphological conversion of the bosentan monohydrate, DSC studies are performed for the formulations using a TA instrument, Model Q200 equipped with a RCS-90(-90°C to 450°C) cooling unit. DSC is performed with 2mg sample in Tzero pan-Aluminium, encapsulated with Tzero lid-Aluminium by T zero press. Inert atmosphere is maintained by purging nitrogen gas at a flow rate of 50 mL/min. Samples are heated at a temperature range of 0 to 300°C with ramping at 10°C/min. The DSC spectra of the bosentan monohydrate and formulation (BMLS3).

IV. Infrared Spectroscopy (IR):
Infrared spectra are obtained for plain bosentan monohydrate, gelucire, compritol and spray dried formulation (BMLS3) for evaluating the chemical compatibility of BM with the excipients used in the formulation development. Spectra are taken after preparing the pellet with 2-3 mg of sample with potassium bromide and the samples are scanned from 4000-400cm^{-1}.

V. *In vitro* dissolution:
The dissolution rate of BM from the prepared dispersion (BMLS3) is measured in a Disso-2000 model dissolution test system (Labindia, India) using simulated gastric fluid (SGF) without pepsin at pH 1.2 and USP apparatus II (paddle) method. The drug dispersed dispersions are filled into hard gelatin capsule equivalent to 62.5mg of BM. And also compared with bosentan mixed with mannitol as excipient in 1:1 ratio. In each dissolution vessel, drug filled capsules are added to 900 mL dissolution medium. Bath temperature and paddle rotation speed are maintained at 37°C and stirred at 100 rpm. Samples are collected periodically and replaced with a fresh dissolution medium. After collection of 90min sample, recovery study is conducted by stirring the paddle at 200rpm for 5min and sample is collected. Samples are filtered through filters (10µm) and analyzed using HPLC (Sec. 2.2.5).

VI. *In-vivo* bioavailability study
The efficacy of the formulations in improving the oral absorption of bosentan monohydrate is tested in rats by oral administration of the formulations to rats. Male wistar rats (SICRA, Hyderabad, India) weighing 220-250gm are used for the study. The rats are housed in stainless steel cages and kept on a 12 hr light/dark cycle. On the day of experiment, animals are randomized and divided into two groups and kept for fasting for 12hrs. All animal studies conducted are approved by local animal ethical committee.
The formulations are prepared for administration by dispersing the BM solid-lipid dispersion (BMLS3) in potassium dihydrogen phosphate buffer solution (pH 7.4; 0.16M) and administered orally at a dose of 15mg/kg body weight. The plain BM is administered as a suspension (BM2) in phosphate buffer solution (pH 7.4; 0.16M) and at a dose of 15mg/kg body weight. Blood samples are withdrawn from the animals after a period of 15, 30, 60, 90, 120min post administration of the dose. The blood samples are collected into glass tubes containing disodium-EDTA. Plasma is separated by centrifugation at 1500 rpm and 4ºc. The plasma samples are transferred into plastic tubes and stored at -80ºc until further analysis is done. The drug levels in plasma are estimated by HPLC after extracting the drug from plasma. (Sec 2.2.6.)

Preparation and evaluation of bosentan monohydrate Liquid solid Compacts
Bosentan was initially dispersed in the non-volatile solvent systems (Tween 80) termed as liquid vehicles with different drug vehicle ratio.Then a mixture of carrier(AvicelpH102)was added to the above liquid by continuous mixing for a period of 10 to 20 minutes in a mortar. Then to the above mixture coating material (silica gel powder) was added and mixed thoroughly. The amount of carrier and coating materials added were based on the R value.
To the above binary mixture disintegrant and other remaining additives such as Glidant (magnesium stearate) are added according to their application and mixed in a mortar.Then the final blend was compressed using tablet compression machine.

Table no 1. Formulation Design Of Bosentan Liquisolid Compacts

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bosentan	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Tween 80	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Carrier:coating material (R)	20	20	20	20	20	20	20	20	20
Liquid load factor (L_f)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
SSG	11.25	22.5	33.75	-	-	-	-	-	-
CP	-	-	-	11.25	22.5	33.75	-	-	-
CCS	-	-	-	-	-	-	11.25	22.5	33.75
Micro crystalline Cellulose (mg)	120	120	120	120	120	120	120	120	120
Aerosil(mg)	6	6	6	6	6	6	6	6	6
Lactose Monohydrate	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Mg.stearate(mg)	2	2	2	2	2	2	2	2	2
Total weight	450	450	450	450	450	450	450	450	450

Evaluation parameters:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

1. Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

II. Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

III. Weight variation test:

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets of a sample of tablets with an upper and lower percentage limit of the observed sample average. The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

IV.Thickness and diameter: The thickness and diameter of 10 tablets were recorded during the process of compression using vernier calipers.

V. Friability:

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

VI. *In-Vitro* disintegration time

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

Preparatio\n and evaluation of Bosentan monohydrate loaded solid dispersions

I. Materials:

Kolliphor SLS and kleptose HPB are generous gifts from Gateefosse; india.Bosentan monohydrate is obtained from Chandra Labs, Hyderabad, India. All HPLC and analytical grade chemicals are purchased from Standard Reagents, India.

II. Preparation of Bosentan monohydrate (BM) loaded solid dispersions

Solid dispersions were prepared by fusion method. Fusion Method: Each of water soluble carrier Kolliphor SLS and kleptose HPB were weighed accurately in various ratios (1:1, 1:2, 1:3, 1:4) and melted in a porcelain dish at 80-85ºC and to this calculated amount of Bosentan was added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was then pulverized by passing through sieve no.85 and stored in a dessicator until used for further studies

Table.2: Composition of Bosentan solid dispersions

Solid dispersion composition	Method	Drug-Polymer ratio	Formulation code
Bosentan: Kolliphor SLS	**Fusion method**	1:1	SD1
		1:2	SD2
		1:3	SD3
		1:4	SD4
Bosentan: kleptose HPB	**Fusion method**	1:1	SD5
		1:2	SD6
		1:3	SD7
		1:4	SD8

A) Characterization

I. Drug content estimation

The amount drug incorporated in the lipid-solid dispersions is determined by using a HPLC method after completely extracting the drug by using non aqueous solvent. The extraction method includes dispersion of 10 mg sample in 10 mL of acetonitrile and vortexed well. The solutions are filtered through a membrane filter (0.45 mm) and suitably diluted with mobile phase before injecting to the HPLC. The drug content values expressed.

II. **Saturation Solubility**

The efficacy of the formulations in improving the dissolution is preliminarily evaluated by measuring the saturation solubility of the drug from the formulations. The saturation solubility is determined for the plain drug (BM), spray dried drug (BMS) and the formulations (SD1 to SD8).

The impact of fusion method on the solubility enhancement is studied by taking plain drug as a control (BM). The known excess amount of bosentan monohydrate is added to 10 mL of pH 1.2 acetate buffer. Samples are rotated at 20 rpm in a water bath (37± 0.5ºC) for 48 hours. The samples are then filtered, suitably diluted, and analyzed by HPLC. The saturation solubility values represented in µg/ml

III. Differential Scanning Calorimetry (DSC):

The enhanced solubility of the bosentan monohydrate from the developed formulations can be attributed to the morphological conversion of the drug upon spray drying. To validate the morphological conversion of the bosentan monohydrate, DSC studies are performed for the formulations using a TA instrument, Model Q200 equipped with a RCS-90(-90°C to 450°C) cooling unit. DSC is performed with 2mg sample in Tzero pan-Aluminium, encapsulated with Tzero lid-Aluminium by T zero press. Inert atmosphere is maintained by purging nitrogen gas at a flow rate of 50 mL/min. Samples are heated at a temperature range of 0 to 300°C with ramping at 10°C/min. The DSC spectra of the bosentan monohydrate and formulation (SD4)

IV. Infrared Spectroscopy (IR):

Infrared spectra are obtained for plain bosentan monohydrate, and melt fusioned formulation (SD4) for evaluating the chemical compatibility of BM with the excipients used in the formulation development. Spectra are taken after preparing the pellet with 2-3 mg of sample with potassium bromide and the samples are scanned from 4000-400cm^{-1}.

V. *In Vitro* dissolution:

The dissolution rate of BM from the prepared solid dispersion (SD4) is measured in a Disso-2000 model dissolution test system (Labindia, India) using simulated gastric fluid (SGF) without pepsin at pH 1.2 and USP apparatus II (paddle) method. The drug dispersed dispersions are filled into hard gelatin capsule equivalent to 62.5mg of BM. And also compared with bosentan mixed with mannitol as excipient in 1:1 ratio. In each dissolution vessel, drug filled capsules are added to 900 mL dissolution medium. Bath temperature and paddle rotation speed are maintained at 37°C and stirred at 100 rpm. Samples are collected periodically and replaced with a fresh dissolution medium. After collection of 90min sample, recovery study is conducted by stirring the paddle at 200rpm for 5min and sample is collected. Samples are filtered through filters (10µm) and analyzed using HPLC (Sec. 2.2.5).

VI. *In-vivo* bioavailability study

The efficacy of the formulations in improving the oral absorption of bosentan monohydrate is tested in rats by oral administration of the formulations to rats. Male wistar rats (SICRA, Hyderabad, India) weighing 220-250gm are used for the study. The rats are housed in stainless steel cages and kept on a 12 hr light/dark cycle. On the day of experiment, animals are randomized and divided into two groups and kept for fasting for 12 hrs. All animal studies conducted are approved by local animal ethical committee.

The formulations are prepared for administration by dispersing the BM solid dispersion (SD4) in potassium dihydrogen phosphate buffer solution (pH 7.4; 0.16M) and administered orally at a dose of 15mg/kg body weight. The plain BM is administered as a suspension (BM2) in phosphate buffer solution (pH 7.4; 0.16M) and at a dose of 15mg/kg body weight. Blood samples are withdrawn from the animals after a period of 15, 30, 60, 90, 120min post administration of the dose. The blood samples are collected into glass tubes containing disodium-EDTA. Plasma is separated by centrifugation at 1500 rpm and 4°c. The plasma samples are transferred into plastic tubes and stored at -80°c until further analysis is done. The drug levels in plasma are estimated by HPLC after extracting the drug from plasma. (Sec 2.2.6.)

RESULTS:

Bosentan monohydrate lipid solid dispersiontechnique

1. Drug content and Saturation solubility

HPLC analysis is used to estimate the drug content in the formulations after the complete extraction of the drug from the formulations. The obtained values for the formulation (BMLS1-6) are between 80% and 95% (w/w) of the theoretical values.

The saturation solubility study is conducted for the plain drug, spray dried drug and spray dried formulation (**BMLS-3)** in phosphate buffer pH 7.4. After 48hrs of incubation the solubilized drug is evaluated by HPLC and values were represented in the table.3. The saturation solubility of plain BM is 17.15 µg/ml, whereas the spray dried drug and lipid dispersion formulations have shown improved solubility. The saturation solubility of the spray dried drug is improved by two times compared to the plain drug. The formulated dispersions also have shown improved solubility and is highest in BMLS3. The enhancement is 4 times higher to the BMLS3 (64.5 µg/ml) when compared to the plain drug (BM1). The higher solubility in the formulation can be attributed to the morphological conversion of the drug and also to the improvement in the wetting of the drug, reduced particle size and localized solubilization by lipid carriers[3].

Table 3: Table showing formulations with different drug/ excipient ratios and their assay value and saturation solubility values

S.No.	Formulation	Drug/lipid mixture ratio	Assay (%)	Saturation Solubility (µg/ml)
1	BMLS1	0.25:1	90	32±2.1
2	BMLS2	0.5:1	92	42±1.7
3	BMLS3	1:1	93	54.5±1.5
4	BMLS4	1.5:1	90	87±6.2
5	BMLS5	1.75:1	92	62.3±2.2
6	BMLS6	2:1	95	60.5±1.2
7	ISD1	Spray dried drug	--	34.2±0.8
8	ICZ	Plain drug	--	17.15±1.3
9	ICZ1	Bosentan monohydrate +Mannitol	--	--
10	ICZ2	Bosentan monohydrate suspension	--	--

Zeta sizer Particle Size Analysis

The reason for the enhancement of solubility from the lipid solid dispersion formulations can be attributed to the reduced particle size of the drug. The particle size and distribution of the formulations are measured by zeta sizer and are represented in table 4. and Fig.1,2,3. From the results it is observed that by spray drying the size of drug particles is reduced and in turn enhances the dissolution of the drug. The spray drying of drug alone results in the higher size of the particles compared to the formulation because of the aggregation of the reduced particles due to the static charge development.

The plain bosentan monohydrate has mean volume diameter (VMD) of 42.6 µm. The VMD of the spray dried drug particles (BMS) and formulations (BMLS3) is found to be 30µm and 17.6µm respectively. However the plain drug has larger particle size and distribution compared to spray dried drug and formulation.

Table 4: Particle size analysis data of the solid-lipid dispersions BMLS3), Spray dried bosentan monohydrate and plain bosentan monohydrate

F.Code	Particle size in µm
BM Pure	42.6
BMS	30
BMSL3	17.6

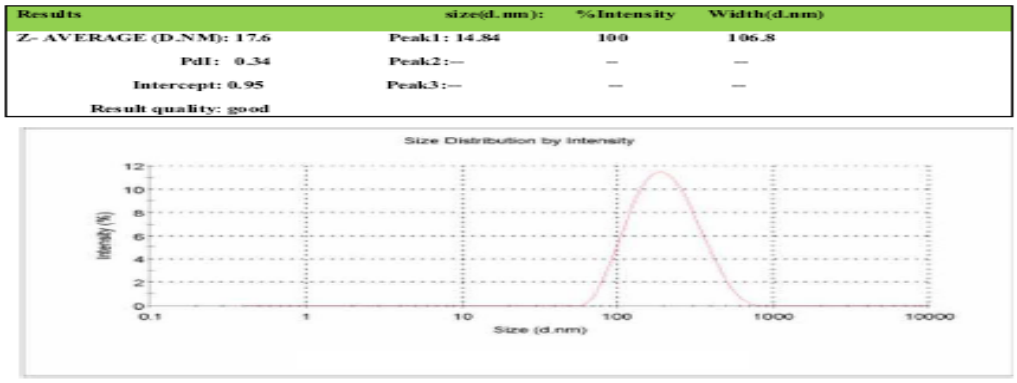


Fig.1 Histograms of Particle size distribution of Solid-lipid dispersion (BMLS3)

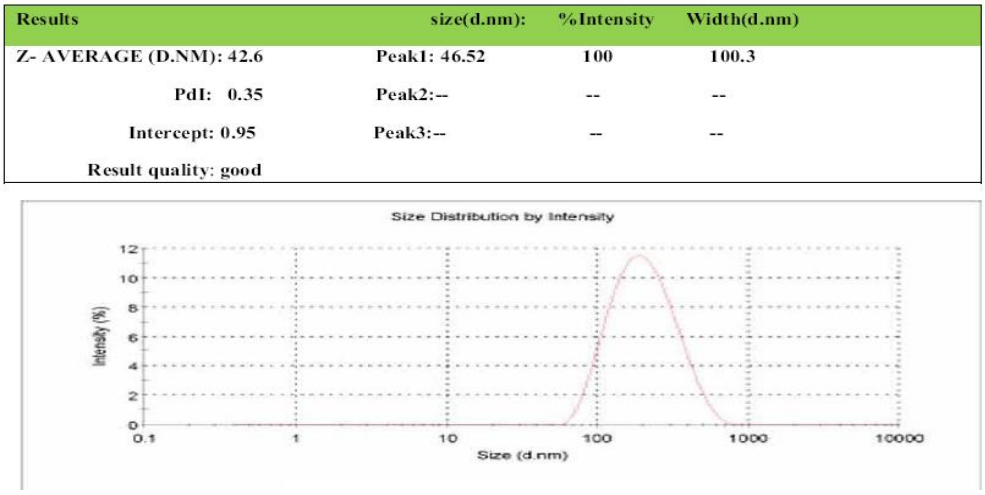


Fig 2 Histograms of Particle size distribution of Spray dried drug (BMS)

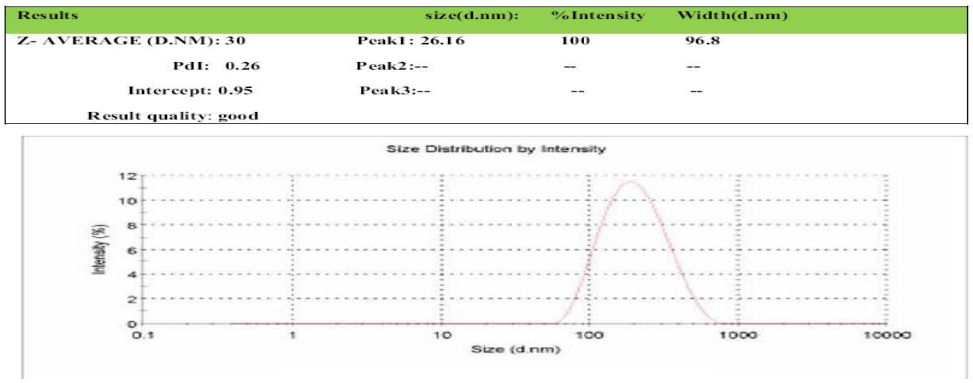
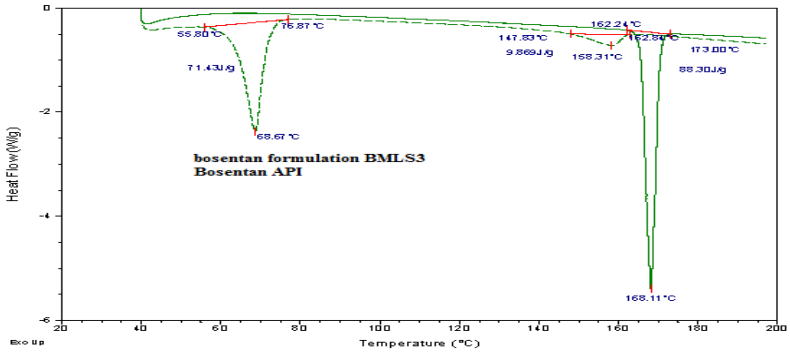


Fig 3 Histograms of Particle size distribution of Plain bosentan monohydrate(BM)

Differential Scanning Calorimetry (DSC)

DSC thermograms obtained for BM, gelucire, compritol and for solid-lipid dispersion (BMLS3) are shown in Fig.4 (A and B,). Pure BM has shown well defined endothermic peak at 168.11ºc corresponding to the melting point of crystalline drug. Likewise the lipid excipients have shown endothermic peaks at 43.42ºc and 71.82ºc for gelucire and compritol, respectively, representing the melting points. However in the thermogram of the spray dried lipid-solid dispersion, the endotherm peak of drug disappeared and instead new peak is observed at 158.3ºc. However the endothermic peaks of gelucire and compritol remained same. The significant reduction in the melting point of the BM can be attributed to the morphological conversion of BM from crystalline to amorphous form.

A



B)

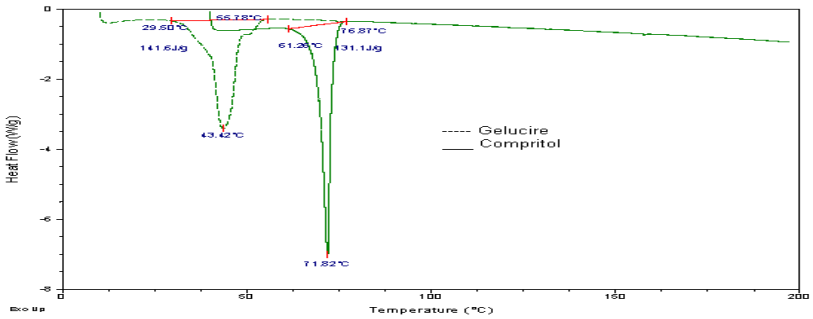
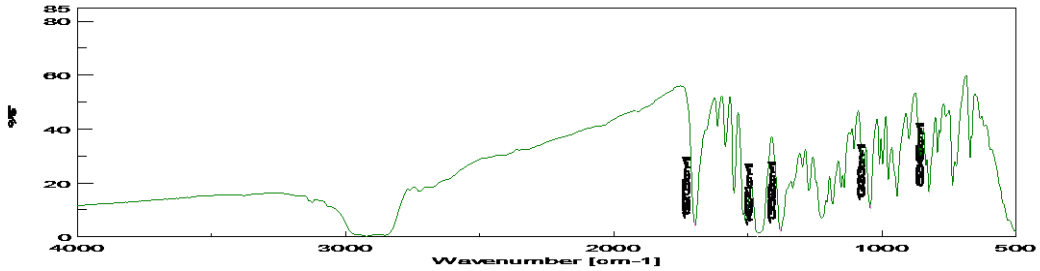


Fig. 4: Differential Scanning Calorimetry (DSC) thermograms of Bosentan monohydrate, gelucire, compritol and Bosentan monohydrate loaded solid-lipid dispersion. A) Thermgrams of Bosentan monohydrate API and ILSD3 B) Thermograms of Gelucire and Compritol

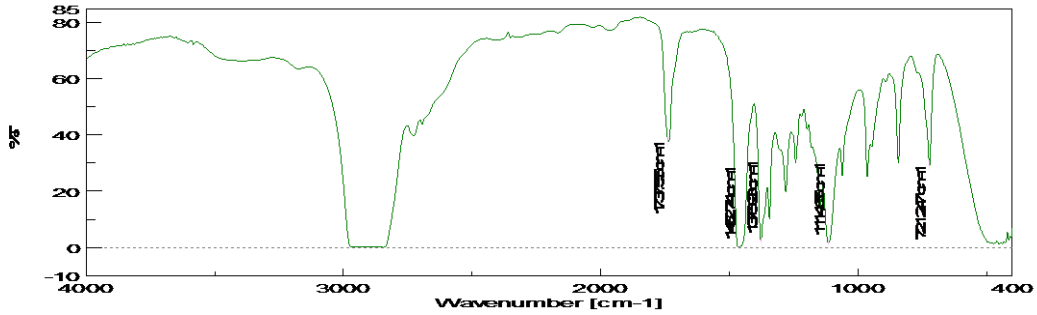
Infrared Spectroscopy:

To evaluate the chemical compatibility between the Bosentan monohydrate and excipients, IR analysis is performed and are shown in Fig.5(A,B,Cand D). The IR spectra's of plain Bosentan monohydrate showed characteristic peaks at 400-1800cm^{-1}. They might have arisen from the stretching and vibrations of functional groups such as –C=C- of aromatic groups. A peak observed at 1600-1800 cm^{-1} can be attributed to –C=O stretching and vibration, whereas peaks for alkane and amine groups are noticed at 2800-3200 cm$^{-1.}$ Peaks of lipid carriers, gelucire and compritol, have shown significant broadening O-H stretching vibrations peaks between 2800—3200 cm^{-1} representing the characteristic peaks of lipids. The same peaks are seen in the spectra of the formulation also. The major peaks observed for Bosentan monohydrate before and after the preparation of solid dispersion formulation at 400-1800cm^{-1} are almost superimposable. This suggests the absence of any significant interactions between Bosentan monohydrate and excipients used to preparing the lipid-solid dispersion formulation.

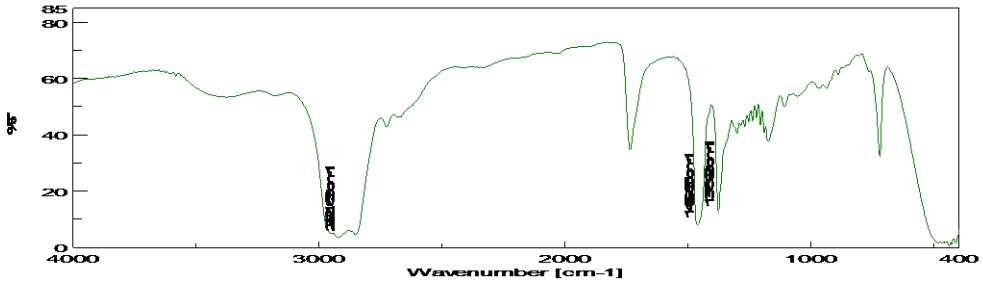
A) Bosentan monohydrate



B) Gelucire



B) Compritol



C) Formulation BMLS3

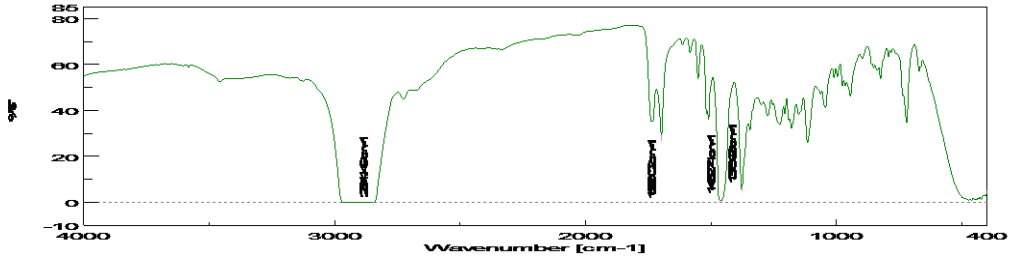


Fig. 5:Infrared spectra's of Bosentan monohydrate (A), Gelucire (B), Compritol (C) and formulation-BMLS3 (D)

***In-vitro* dissolution:**

In order to assess the performance of the solid-lipid dispersions prepared prior to the *in vivo* testing, *in vitro* dissolution testing is conducted under sink conditions. The dissolution profiles of the BMLS3 and BM are shown in the Fig.7.6 The release of BM from the BMLS3 is steepest initial slope and the dissolution rate is higher compared to BM in all time points. The enhancement of dissolution is approximately 3-4 times higher until 60 mins compared to BM1. The percent drug release in BMLS3 formulation in 60 mins is 95% whereas it is only 19% in the plain drug formulation. It is assumed that there are two mechanisms responsible for dissolution of BM. They are drug controlled and carrier controlled dissolution. As BM in solid-lipid dispersion is in amorphous form the dissolution is more compared to plain drug. And by means of spray drying more precise particles are prepared and the produced smaller particles enhanced the dissolution by increased surface area. The spray dried particles improved the wettability of the drug and localized solubilization in the diffusion layer more efficiently. .

***In-Vivo* bioavailability study**

The efficacy of the BMLS3 in the improvement of oral bioavailability of BM is evaluated after administering the dose to the rats. The plain drug suspension is prepared (BM2) and administered to the rats for comparative evaluation. The tested formulations (BMLS3 & BM2) are dispersed in pH 7.4 phosphate buffer and administered orally. All the dosage forms are well tolerated and no obvious side effects are observed. After dosing, plasma samples are analyzed by HPLC for BM levels and drug plasma concentrations as a function of time are shown in Fig.7 The plasma profiles are analyzed by non-compartmental analysis for extra-vasucular administration to determine the appropriate pharmacokinetic parameters of administered formulations and represented in Table 5 . Statistically significant differences are observed for $AUC_{(0\text{-inf})}$ values indicating that developed solid dispersion formulation has improved the oral bioavailability of BM and suggested that large concentrations of drug is available for absorption in the formulation.

The BMLS3 has shown increased C_{max} value compared to BM2. The C_{max} values of BMLS 3 and BM2 are found to be 39.12ng/ml and 13.72ng/ml, respectively. The enhancement in the C_{max} from the ILSD3 is 3 times higher compared to BM2. The $AUC_{(0\text{-inf})}$ values are 2.5 times higher in formulation BMLS3 compared to BM2 (7821 vs 2152 ng/h/ml). However in the BMLS3 administered formulations the T_{max} of the BMLS3 is found to be below 60min compared to below 30min in the case of BM2**.** However, the T_{max} from the BM2 is below 30min since the immediate availability of the solubilized drug at the absorption site. This allows the extent of drug absorption is higher. The increase in the C_{max} and $AUC_{(0\text{-inf})}$ in the BMLS3 compared to BM can be mainly attributed to the enhancement of aqueous solubility and dissolution properties. Also the drug absorption through lymphatic system can also be assumed to enhance the oral bioavailability of bosentan monohydrate from the formulation.

Table 5:Mean Pharmacokinetic parameters for Bosentan monohydrate formulations in plasma after oral administrations to the rats

Parameter	ILSD3	BM2
Cmax (ng/ml)	39.12	13.72
Tmax (min)	<60	<30
AUC (0-t) (ng.hr/ml)	5421	1814
AUC (0-inf) (ng.hr/ml)	7821	2152

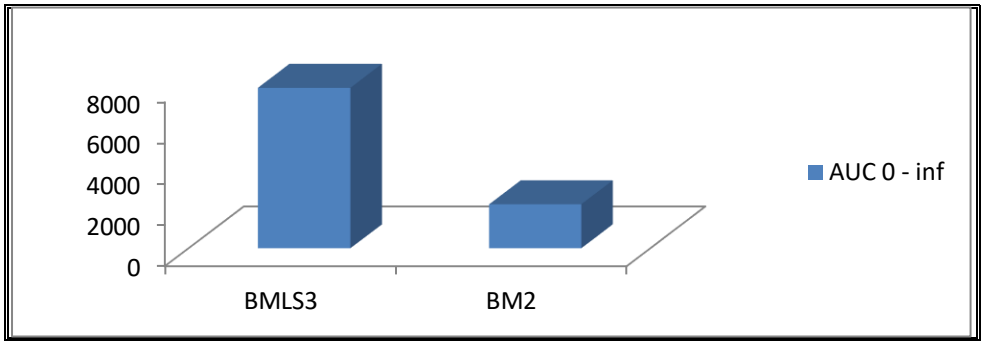


Fig.7 Bosentan monohydrate plasma concentrations in rats after oral administration of formulations (BMLS3) and plain drug suspension (BM2).

Bosentan mono hydrateliquisolid compacts

1.Compatability Studies

The spectrum of the standard and the samples were then super imposed to findout any possible interactions between the drug and the polymers. All the characteristic peaks of bosentan mentioned in table no:were also found in the spectrum formulations. The results suggest that the drug is intact in the formulations and there is no interaction found between the drug and the excipients.

2. Application of New Mathematical Modelfor Design of LiquisolidSystem

The liquid solid technique as suggested by Spireasetal[12],states that the drug dissolved in a liquid vehicle is incorporated into carrier and coating materials having porous structure and closely matted fibres in its interior, is a phenomenon of both adsorption and absorption. Coating materials like A vicel PH102 have high adsorptive capacity and greater surface are and thus gives the liquid solid systems the desirable flow and compaction properties. The quantity of carrier material(Q) required, the quantity of coating material (q),Liquid load factor (Lf) and excipients ratio (R) was calculated by using the following equations;

Amount of carrier material required (Q) = $W/L_f eq$……...(11)

Amount of coating material required (q) = Q/Req...…....(12)

Liquid load factor (L_f) = W/Qeq……...(13)

Excipient Ratio (R) = Q/qeq…….. (14)

Where W is the weight of liquid medication, Lf is the Liquid load factor, R is the carrier and coating material ratio.

Table 6 : Evaluation tests for Bosentan Liquisolid Compacts tablets

S.no	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F9
1	**Weight variation**	451	458	456	445	448	457	451	452	449
2	**Hardness(kg/cm^2)**	5.8	5.6	5.3	5.5	5.52	5.25	5.31	4.42	5.1
3	**Thickness(mm)**	5.32	5.48	5.26	5.41	5.21	5.32	5.41	5.26	5.32
4	**Friability %**	0.45	0.52	0.21	0.18	0.12	0.14	0.11	0.14	0.16
5	**Disintegration time**	3min	2min 52sec	2min 32sec	1min 22sec	44sec	28sec	1min 10sec	1min	1min

3. *In Vitro* Dissolution Study

Table 7 below shows the dissolution profile of 8 formulations. Among all, F6 showed higher release rate (98%) at the end of the 60thmin. Since the liquid solid compacts contain a solution of the drug in non volatile vehicle used for the preparation of the liquid solid compacts,the drug surface available for the dissolution is tremendously increased. Inessence, after disintegration, the Liquisolid primary particles suspended in the dissolving medium contain the drug in a molecularly dispersed state, where as the directly encapsulated compacts are merely exposed micronized drug particles. Therefore, in the case of liquid solid compacts, the surface area of drug available for dissolution is much greater than that of the directly encapsulated compacts.

According to the Noyesandwhitey, the drug dissolution rate (DR) is directly proportional not only to the concentration ngradient(Cs) of the drug in the stagnant diffusion layer,but also to its surface area(S)available for dissolution.More over ,since all dissolution tests for both bosentan preparations were carried out at a constant speed (50RPM) and identical dissolving media, it is assumed that the thickness (h) of the stagnant diffusion layer and the diffusion co efficient(D) of the drug molecules transported through it remain almost identical

Table 7: Dissolution profiles for liquisolid compact tablets

Time(mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	25	37	42	40	63	**52**	49	52	53
20	46	48	53	51	77	**72**	73	74	65
30	52	59	64	68	82	**82**	78	81	75
40	60	63	70	72	84	**87**	80	85	81
50	69	69	76	79	87	**89**	86	89	86
60	81	83	85	84	89	**98**	85	94	92

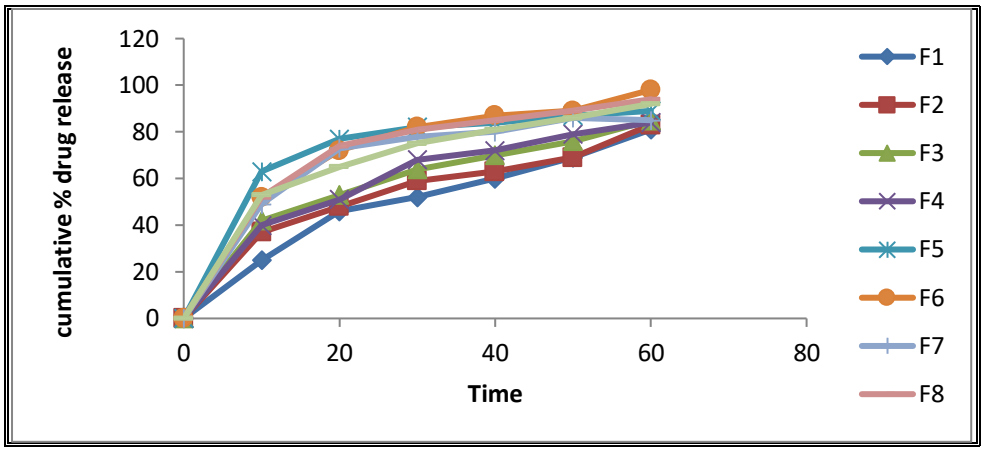


Fig 8: Graph showing dissolution profile for formulations F1-F9

Table 8: Percentage drug release in formulation-F6

Time(mins)	F6	Bosentas
10	52	16
20	72	24
30	82	38
40	87	46
50	89	54
60	98	61

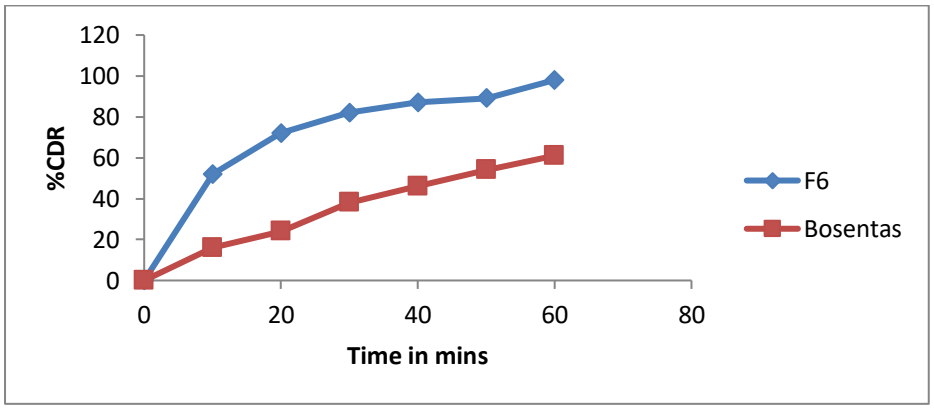


Fig 9: Graph showing dissolution profile for formulations F6 Vs Marketed formulation

Bosentan monohydrate loaded solid dispersions

Each of water soluble carrier Kolliphor SLS and kleptose HPB were weighed accurately in various ratios (1:1, 1:2, 1:3, 1:4) and melted in a porcelain dish at 80-85ºC and to this calculated amount of Bosentan was added with thorough mixing for 1-2 minutes followed by quick cooling. By preparing the bosentan monohydrate incorporated solid dispersion particles it is assumed to have a higher aqueous dissolution of drug due to morphological conversion of the drug and reduced particle size[1]. After morphological conversion to amorphous form the bosentan monohydrate is stabilized by carriers and additionally by the melt fusion process the particle size can be precisely controlled to lower range.

The melt fusion process conditions are chosen so that the molten carrier rapidly solidify entrapping the drug, trapping the drug in the carrier matrix in the amorphous form[2]. In the present study, kolliphor SLS and kleptose HPB are taken as lipid matrix. In the optimized composition of lipid mixture, the drug is incorporated in different concentrations and lipid solid particles were prepared by melt fusion method. The prepared dispersion particles are evaluated for saturation solubility and drug content. Based on the saturation solubility and drug content one

composition (SD4) is identified and processed further complete characterization.

1 Drug content and Saturation solubility

HPLC analysis is used to estimate the drug content in the formulations after the complete extraction of the drug from the formulations. The obtained values for the formulation (SD1-8) are between 90% and 97% (w/w) of the theoretical values.

The saturation solubility study is conducted for the plain drug, solid dispersion (**SD4)** in phosphate buffer pH 7.4. After 48hrs of incubation the solubilized drug is evaluated by HPLC and values were represented in the Table.9 The saturation solubility of plain BM is 17.15 µg/ml, whereas the solid dispersion formulations have shown improved solubility. The saturation solubility of the solid dispersion drug is improved by three times compared to the plain drug. The formulated dispersions also have shown improved solubility and is highest in SD4. The enhancement is 4 times higher to the SD4 (63.9 µg/ml) when compared to the plain drug (BM1). The higher solubility in the formulation can be attributed to the morphological conversion of the drug and also to the improvement in the wetting of the drug, reduced particle size and localized solubilization by carriers[3].

Table 9: Table showing formulations with different drug/ excipient ratios and their assay value and saturation solubility values

S.No.	Formulation	Drug/Carrier ratio	Assay (%)	Saturation Solubility (µg/ml)
1	SD1	1:1	92	41±2.1
2	SD2	1:2	93	49±1.7
3	SD3	1:3	96	63.9±1.5
4	SD4	1:4	97	97±3.1
5	SD5	1:1	90	32.3±2.2
6	SD6	1:2	91	40.5±1.2
7	SD7	1:3	93	54.2±0.8
8	SD8	1:4	94	74.2±0.8
9	PD	Plain drug	90	17.15±1.3
10	PMSD8	PHYSICAL MIXTURE OF SD8 (1:4)	91	26.21±1.6

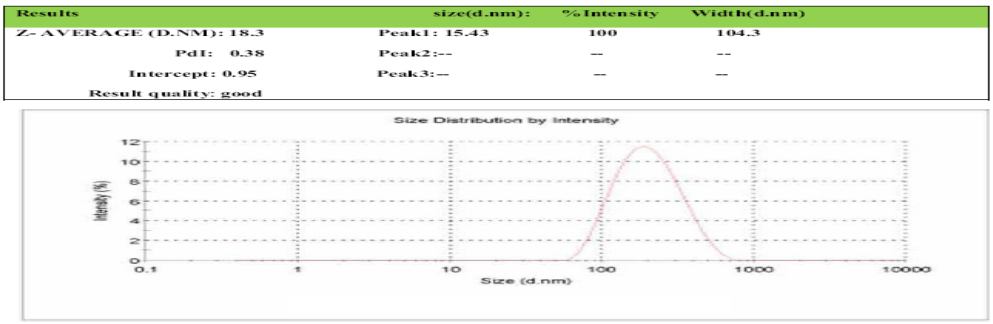
2. Zeta sizer Particle Size Analysis

The reason for the enhancement of solubility from the lipid solid dispersion formulations can be attributed to the reduced particle size of the drug. The particle size and distribution of the formulations are measured by zeta sizer and are represented in table 10. and Fig.10 (A and B) From the results it is observed that by solid dispersions(melt fusion method) the size of drug particles is reduced and in turn enhances the dissolution of the drug.

The plain bosentan monohydrate has mean volume diameter (VMD) of 42.6 µm. The VMD of the spray dried drug particles (BMS) and formulations (BMLS3) is found to be 30µm and 17.6µm respectively However the plain drug has larger particle size and distribution compared to spray dried drug and formulation.

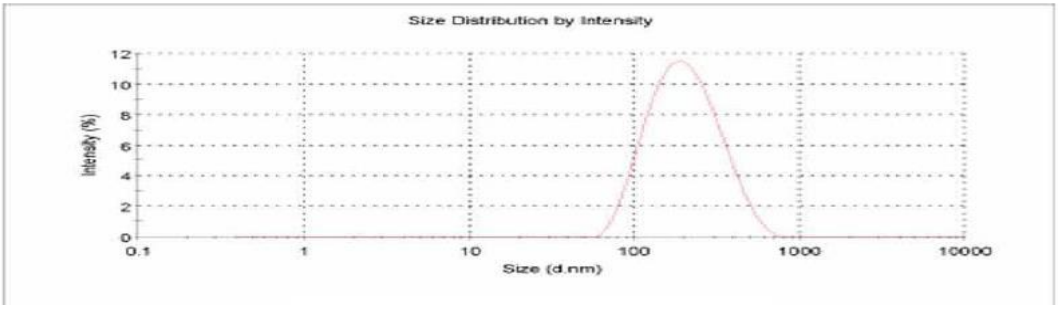
Table 10:Particle size analysis data of the solid-lipid dispersions (SD4) and plain bosentan monohydrate

F.Code	Particle size in (micrometre)
BM Pure	42.6
SD4	18.3



A) Solid dispersion (SD4)

Results	size(d.nm):	%Intensity	Width(d.nm)
Z- AVERAGE (D.NM): 42.6	Peak1: 46.52	100	100.3
PdI: 0.35	Peak2:--	--	--
Intercept: 0.95	Peak3:--	--	--
Result quality: good			

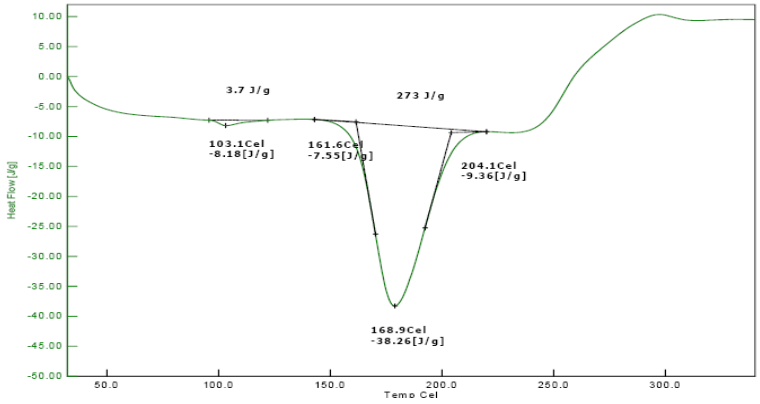


B) Plain bosentan monohydrate(BM)

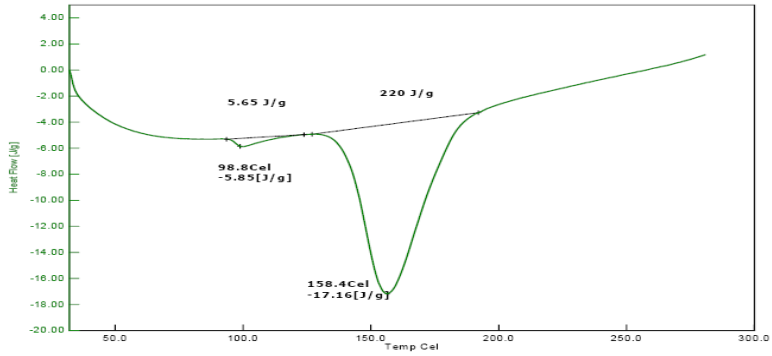
Fig.10 Histograms of Particle size distribution A) Solid dispersion (SD4) B) Plain bosentan monohydrate(BM)

3. Differential Scanning Calorimetry (DSC)

DSC thermograms obtained for plain Bosentan Monohydrate, and for solid dispersion (SD4) are shown in Fig.2.2. Pure BM has shown well defined endothermic peak at 168.9ºc corresponding to the melting point of crystalline drug. However in the thermogram of the solid dispersion, the endotherm peak of drug disappeared and instead new peak is observed at 158.4ºc. The significant reduction in the melting point of the BM can be attributed to the morphological conversion of BM from crystalline to amorphous form.



A) Bosentan monohydrate

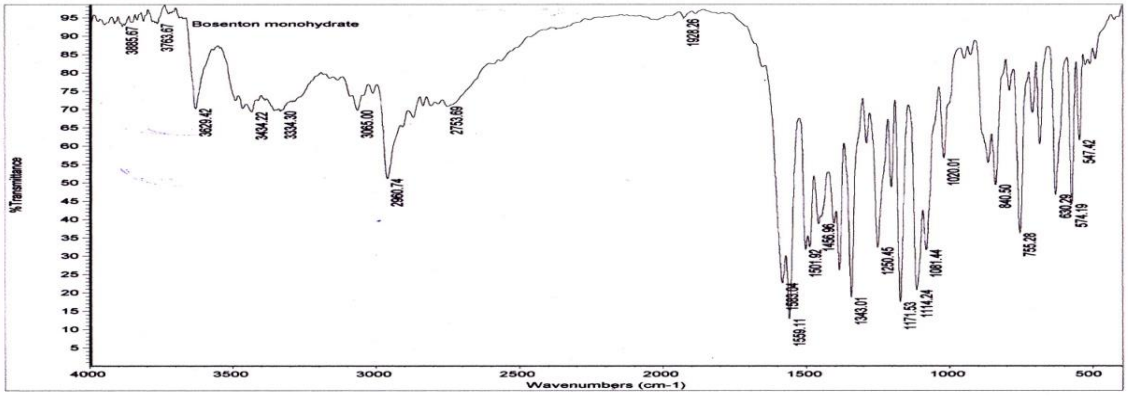


B)Bosentan monohydrate loaded solid- dispersion (SD4).

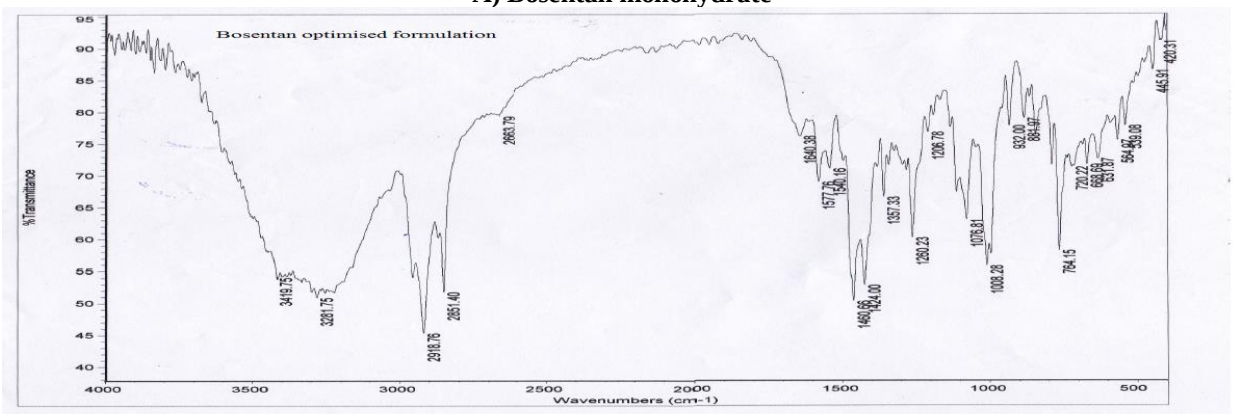
Fig11: Differential Scanning Calorimetry (DSC) thermograms of A) Bosentan monohydrate, B) Bosentan monohydrate loaded solid- dispersion (SD4).

4. Infrared Spectroscopy:

To evaluate the chemical compatibility between the Bosentan monohydrate and excipients, IR analyses is performed and are shown in Fig.8.3. The IR spectra's of plain Bosentan monohydrate showed characteristic peaks at 400-1800cm^{-1}. They might have arisen from the stretching and vibrations of functional groups such as –C=C- of aromatic groups. A peak observed at 1600-1800 cm^{-1} can be attributed to –C=O stretching and vibration, whereas peaks for alkane and amine groups are noticed at 2800-3200 cm$^{-1.}$ Peaks of lipid carriers, kolliphor SLS and Kleptose HPB, have shown significant broadening O-H stretching vibrations peaks between 2800—3200 cm^{-1} representing the characteristic peaks of lipids. The same peaks are seen in the spectra of the formulation also. The major peaks observed for Bosentan monohydrate before and after the preparation of solid dispersion formulation at 400-1800cm^{-1} are almost superimposable. This suggests the absence of any significant interactions between Bosentan monohydrate and excipients used to preparing the lipid-solid dispersion formulation.



A) Bosentan monohydrate



B)Formulation SD4

Fig.12:Infrared spectra's of Bosentan monohydrate (A), formulation-SD4 (B)

5. In-vitro **dissolution:**

In order to asses the performance of the solid dispersions prepared prior to the *in vivo* testing, *in vitro* dissolution testing is conducted under sink conditions. The dissolution profiles of the SD4 and Plain Bosentan Monohydrate are shown in the Fig.2.4. The release of BM from the SD4 is steepest initial slope and the dissolution rate is higher compared to BM in all time points. The enhancement of dissolution is approximately 4 times higher until 60 mins compared to Physical Mixture and Plain Drug. The percent drug release in SD4 formulation in 60 mins is 93.4% whereas it is only 19% in the plain drug formulation. It is assumed that there are two mechanisms responsible for dissolution of BM. They are drug controlled and carrier controlled dissolution. As BM in solid dispersion is in amorphous form the dissolution is more compared to plain drug. And by means of spray drying more precise particles are prepared and the produced smaller particles enhanced the dissolution by increased surface area. The spray dried particles improved the wettability of the drug and localized solubilization in the diffusion layer more efficiently.

Table 11: Dissolution profile of solid dispersion (SD4) and plain Bosentan monohydrate (BM) And Physical mixture of SD4 in acetate buffer pH 1.2.

Time in mins	SD4	Plain Drug	Physical Mixture
0	0	0	0
5	12.4	3.6	6.2
10	21.2	5.5	10.8
15	30.3	6.9	15.4
20	54.2	8.7	24.8
30	60.1	12.6	30.1
40	73.4	14.2	34.6
50	82.4	15.9	40.2
60	93.4	19	48.3

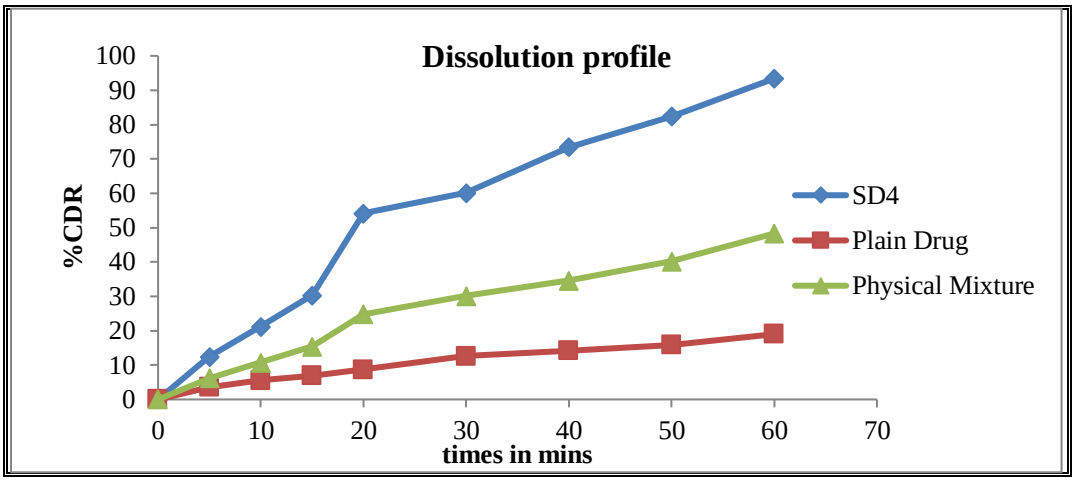


Fig 13: Graph for dissolution profile of solid dispersion (SD4) and plain Bosentan monohydrate (BM) And Physical mixture of SD4 in acetate buffer pH 1.2.

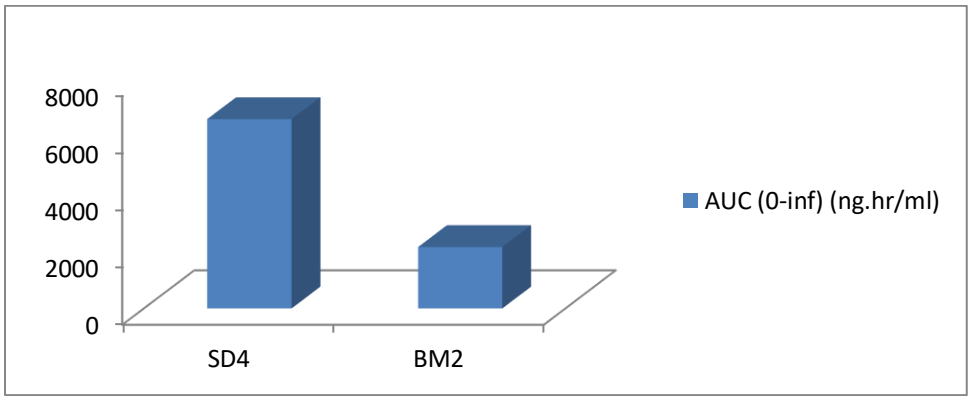
6. *In-Vivo* bioavailability study

The efficacy of the SD4 in the improvement of oral bioavailability of BM is evaluated after administering the dose to the rats. The plain drug suspension is prepared (BM2) and administered to the rats for comparative evaluation. The tested formulations (SD4 & BM2) are dispersed in pH 7.4 phosphate buffer and administered orally. All the dosage forms are well tolerated and no obvious side effects are observed. After dosing, plasma samples are analyzed by HPLC for BM levels and drug plasma concentrations as a function of time are shown in Fig.2.5. The plasma profiles are analyzed by non-compartmental analysis for extra-vasucular administration to determine the appropriate pharmacokinetic parameters of administered formulations and represented in Table 2.3. Statistically significant differences are observed for $AUC_{(0\text{-}inf)}$ values indicating that developed solid dispersion formulation has improved the oral bioavailability of BM and suggested that large concentrations of drug is available for absorption in the formulation.

The SD4 has shown increased C_{max} value compared to BM2. The C_{max} values of SD4 and BM2 are found to be 37.22ng/ml and 12.92ng/ml, respectively. The enhancement in the C_{max} from the SD4 is 3 times higher compared to BM2. The $AUC_{(0\text{-}inf)}$ values are 3 times higher in formulation SD4 compared to BM2 (6624 vs 2152 ng/h/ml). However in the SD4 administered formulations the T_{max} of the SD4 is found to be below 60min compared to below 30min in the case of BM2**.** However, the T_{max} from the BM2 is below 30min since the immediate availability of the solubilized drug at the absorption site. This allows the extent of drug absorption is higher. The increase in the C_{max} and $AUC_{(0\text{-}inf)}$ in the SD4 compared to BM can be mainly attributed to the enhancement of aqueous solubility and dissolution properties. Also the drug absorption through lymphatic system can also be assumed to enhance the oral bioavailability of bosentan monohydrate from the formulation.

Table 12: Mean Pharmacokinetic parameters for Bosentan monohydrate formulations in plasma after oral administrations to the rats

Parameter	SD4	BM2
Cmax (ng/ml)	37.22	12.92
Tmax (min)	<60	<30
AUC (0-inf) (ng.hr/ml)	6624	2152



AUC values of bosentan monohydrate after oral administration of formulations SD4 and BM2.

Fig. 14: Bosentan monohydrate plasma concentrations in rats after oral administration of formulations (SD4) and plain drug suspension (BM2).

DISCUSSION:

Solid lipid dispersions:

\he concept of solid-lipid dispersions for the improvement of aqueous dissolution and *in-vivo* absorption is further proven with another model drug, bosentan monohydrate, an antihypertensive agent. Bosentan monohydrate is poorly aqueous soluble and its oral bioavailability is very limited. In the present study it is aimed to improve the aqueous dissolution and *in vivo* oral absorption of bosentan monohydrate by using the lipid excipients. Upon spray drying a free flowing drug incorporated lipid solid dispersion particles are obtained with good yield. The prepared bosentan monohydrate loaded particles by the optimized composition and method are duly characterized for saturation solubility, particle size distribution, morphological conversion by DSC, chemical compatibility by IR and *in vitro* dissolution. Finally the formulation is evaluated for *in-vivo* oral bioavailability by administering the formulations to the rats by oral gavage. The saturation solubility data indicated the efficiency of the method and excipients in improving the solubility of bosentan monohydrate. The saturation solubility from the formulation is much higher compared to the plain drug and spray dried drug. The improvement in the solubility from the formulations can be attributed to the reduced particle size, drug morphological conversion to amorphous form and the impact of lipid excipients by improving the wettability and localized solubilization of the drug. These assumptions are confirmed by the particle size analysis and DSC evaluation. The particle size analysis data demonstrated the reduced particle size and narrow distribution of the particles of the formulation compared to the plain drug. The DSC thermograms have indicated the morphological conversion of the bosentan monohydrate from the crystalline to the amorphous form. The IR spectra indicated the chemical compatibility of the drug and the lipid excipients used in the formulation development.

The *in- vitro* dissolution tests, *in- vivo* bioavailability studies proved the efficacy of the formulation in the aqueous solubility and oral bioavailability enhancement compared to plain drug. The enhancement of aqueous solubility and oral bioavailability can be attributed to the factors such as reduced particle size, amorphous form of drug, increased solubility of drug by lipids and minimization of hepatic metabolism by lymphatic transport. Hence it is concluded that the oral bioavailability of poorly soluble drugs can be increased by preparation of solid dispersions by spray drying using lipid excipients.

Solid dispersions:

The concept of solid dispersions for the improvement of aqueous dissolution and *in-vivo* absorption is further proven with another model drug, bosentan monohydrate, an antihypertensive agent. Bosentan monohydrate is poorly aqueous soluble and its oral bioavailability is very limited. In the present study it is aimed to improve the aqueous dissolution and *in vivo* oral absorption of bosentan monohydrate by using the lipid excipients. The bosentan monohydrate incorporated solid dispersions are prepared by melt fusion method. Upon melt fusion a free flowing drug incorporated solid dispersion particles are obtained with good yield. The prepared bosentan monohydrate loaded particles by the optimized composition and method are duly characterized for saturation solubility, particle size distribution, and morphological conversion by DSC, chemical compatibility by IR and *in vitro* dissolution. Finally the formulation is evaluated for *in-vivo* oral bioavailability by administering the formulations to the rats by oral gavage. The saturation solubility data indicated the efficiency of the method and excipients in improving the solubility of bosentan monohydrate. The saturation solubility from the formulation is much higher compared to the plain drug and spray dried drug. The improvement in the solubility from the formulations can be attributed to the reduced particle size, drug morphological conversion to amorphous form and the impact of lipid excipients by improving the wettability and localized solubilization of the drug. These assumptions are confirmed by the particle size analysis and DSC evaluation. The particle size analysis data demonstrated the reduced particle size and narrow distribution of the particles of the formulation compared to the plain drug. The DSC thermograms have indicated the morphological conversion of the bosentan monohydrate from the crystalline to the amorphous form. The IR spectra indicated the chemical compatibility of the drug and the lipid excipients used in the formulation development.

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Liquisolid compacts:

The aim of this study was to improve the dissolution profile thereby increase solubility. Solubility is the major criteria to achieve the desired concentration of the drug in systemic circulation. About 80% of the drugs are poorly soluble in nature. So in order to overcome that problem, several techniques have been developed to enhance the solubility of those drugs. Among them liquisolid compacts is one of the most promising and new technique which promotes the dissolution rate of water insoluble drugs. Hence, in this study, liquisolid technique was chosen to enhance the dissolution properties of bosentan. The bosentan liquisolid compacts were prepared by using Tween 80 as the non volatile liquid vehicles. Avicel PH 102 and Aerosil were used as the carrier and coating material, respectively. From the results obtained from executed experiments it can be concluded that:

- The preformulation studies like melting point, flow properties of bosentan were compiled with IP standards.
- The FTIR spectra revealed that, there was no interaction between polymer and drug. Polymers used were compatible with bosentan.
- F6 was compared with prepared conventional formulation and result shows increased dissolution profile.
- The in vitro dissolution study confirmed enhanced drug release from liquisolid compacts compared with conventional and marketed tablet.

This research work has produced encouraging results in terms of increasing the in vitro dissolution of poorly soluble drugs such as bosentan using liquisolid technology and we expect a good correlation between the in vitro and in vivo performance of the formulations. The technique being simple and effective can also be extended to other poorly soluble drugs. The in vivo performance of the liquisolid compacts has to be studied using animal models to claim a complete success in the development of these formulations.

CONCLUSION:

The aim of this present study was to improve the dissolution profile thereby increase solubility. Solubility is the major criteria to achieve the desired concentration of the drug in systemic circulation. About 80% of the drugs are poorly soluble in nature. So in order to overcome that problem, several techniques have been developed to enhance the solubility of those drugs. Among them lipid solid dispersions, solid dispersions and liquisolid compacts

are few of the most promising and new technique which promotes the dissolution rate of water insoluble drugs of the three different techniques the lipid dispersion technique has shown highest increase in the solubility which is evident from its dissolution data. BMLS3 formulation has shown the highest drug release of 95.4% after 60mins. The second best method was solid dispersions with a release of 93.4% then followed by liquisolid compacts with a release of 90%.Bioavailability studies were performed for the best two formulations i.e of solid dispersion (SD4) and lipid dispersion (BMLS3).Of the both bioavalibility studies performed the formulation of BMLS3 has shown highest AUC along with showing multifold increase in the solubility.BMLS3 and SD4 has shown the AUC(0-inf) of 7821(ng.hr/ml) and 6624 (ng.hr/ml) respectively. BMLS3 has shown a 3.6 fold increase in AUC where as the SD4 has an increase of 3 fold.

The increase in the AUC is attributed by the decrease in the particle size and change of the drug from crystalline form to amorphous form.

The *in- vitro* dissolution tests, *in- vivo* bioavailability studies proved the efficacy of the formulation in the aqueous solubility and oral bioavailability enhancement compared to plain drug. The enhancement of aqueous solubility and oral bioavailability can be attributed to the factors such as reduced particle size, amorphous form of drug, increased solubility of drug by lipids and minimization of hepatic metabolism by lymphatic transport. Hence it is concluded that the oral bioavailability of poorly soluble drugs can be increased by preparation of solid dispersions by spray drying using lipid excipients.

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