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FORMULATION AND *IN-VITRO* CHARACTERIZATION OF BOSENTAN MONOHYDRATE FAST DISSOLVING FILMS

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ABSTRACT

Bosentan monohydrate is one of the medicines used to treat pulmonary arterial hypertension, is a dual endothelia receptor antagonist. It prevents pulmonary veins from contracting. Because the traditional route of bosentan monohydrate has a modest onset of effect, it is necessary to improve the onset of action by converting it to FDF. In the present study an attempt was made to formulate solid dispersion of bosentan to enhance the solubility. Further the formulated solid dispersion of bosentan was fabricated as an oral film with the suitable polymer such as HPMC E15 and HPMC K15 by solvent casting method. The findings of thickness, weight uniformity, folding durability, tensile, percentage elongation, drug content uniformity, disintegration duration and *in vitro* dissolution experiments were found satisfactory. At the end of 5 minutes drug release study, Formulation F5, which included 500mg of HPMC E15, had the highest release rate of 89%.

KEYWORDS

Fast dissolving films, Bosentan monohydrate, HPMC K15, HPMC E15 and Solvent casting method.

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INTRODUCTION

Poorly water-soluble drugs are often a challenge in front pharmaceutical industry. The improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system. To solve the solubility problem we discuss the various traditional as well as newer method of solubility enhancement. The traditional method includes solid dispersion, complexation and pH adjustment while newer methods include liquid solid, hydrotropy, sonocrystallization, self-emulsifying system. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be

selected and nature of intended dosage form. The aim of this present study is to enhance solubility of Bosentan monohydrate by formulating as solid dispersions.

The main objectives of this study are as follows:

To prepare the solid dispersion of Bosentan monohydrate using different carriers by solvent evaporation technique

To evaluate the solubility and *in vitro* drug release of solid dispersions.

To prepare the fast-dissolving films.

To evaluate the drug release from the film prepared with solid dispersion by *in vitro* dissolution study.

MATERIAL METHODS

STANDARD CALIBRATION CURVE OF BOSENTAN MONOHYDRATE

10µg/ml solutions were taken to determine absorption maxima. Initially blank buffer solution was kept and scanned in the region of 200-400nm. Then sample was kept for analysis and scanned in the same region. Absorption maxima were found to be 242nm. Hence all further analysis was carried out at 242nm for pH 6.8 buffers and water.

Preparation of pH 6.8 phosphate buffer

28.8g Disodium hydrogen phosphate and 11.45g Potassium dehydrogenate ortho phosphate are added to 1000ml volumetric flask, completely dissolved in distilled water and the final volume is made up the volume to 1000ml.

Preparation of stock-I solution of Bosentan monohydrate

Standard stock solution was prepared by weighing 100mg of Bosentan monohydrate and was transferred to 100ml volumetric flask. It was dissolved in phosphate buffer 6.8 pH and the volume was made up to 100ml to get a concentration of 1mg/ml.

Preparation of stock-II solution of Bosentan monohydrate

Take 10ml of stock-I solution and dilute to 100ml with phosphate buffer 6.8 pH to get the concentration of 100µg/ml.

Preparation of aliquots and scanning

From stock-II solution Aliquots were pipette out and diluted to 10ml with phosphate buffer 6.8 pH to get the concentration of 10, 20, 30, 40, 50, 60, 70µg/ml. One of the aliquot was subjected to UV scanning between 200 to 400nm wavelengths to get the 242λmax. Each aliquot's absorbance was measured at obtained 242λmax. The obtained data was plotted by considering concentration on X-axis and absorbance on Y-axis. Calibration curve is plotted and regression factor and slope are calculated.

SOLID DISPERSION

0.5gm of Bosentan monohydrate was taken in a china dish and was dissolved in 5ml of methanol. To the methanol solution, 1.5gm of carrier was added and allowed to dissolve. The mixture was evaporated at room temperature for 1h and then dried at 65°C in a hot air oven. The mass obtained in each case was crushed, pulverized and sifted through 100mesh.

Schematic representation of the bioavailability enhancement of a poorly water- soluble drug by solid dispersion.

PREPRATION OF FAST DISSOLVING FILMS OF BOSENTAN MONOHYDRATE

Selection of polymers and other Excipient

↓

Polymer is swelled in purified water by keeping it for overnight

↓

Water soluble hydrocolloids other ingredients including dissolved in water to form active agents dissolved in small

↓

Homogenous viscous solution portion of aqueous solvent high shear processor

↓

Both mixtures are mixed to form homogenous viscous solution

↓

Degassed under vacuum

↓

Bubble free solution is coated on non-treated casting film

↓

Coated film is sent to aeration drying oven dried in normal atmosphere for 24 hrs

↓

Film is cute in to desired shape and size

↓

Film is evaluated for physical parameters

EVALUATION OF FAST DISSOLVING FILMS OF BOSENTAN MONOHYDRATE

The prepared formulations were evaluated for the following parameters

Thickness uniformity

Three films are selected from each formulation and the thickness of the film was measured by micrometer screw gauze at 5 different positions (4 corners and center). The mean thickness and standard deviation were calculated.

Weight uniformity

Three films of each formulation were selected. The weights of films were noted by weighing in an electronic digital balance. Mean weight and standard deviation were calculated.

Tensile strength

Three films of each formulation were taken and breaking force of each film was determined.

Mean and standard deviation was calculated.

Tensile strength = Load at failure × 100/film thickness × film width

Percentage elongation

Formulated films of each formulation were selected. The percentage elongation was calculated by measuring the increase in the length of the film after tensile strength measurement and adding this in the formula. % Elongation = Increase in length× 100/ Initial length of film %elongation = (L- L0) ×100/L0

Where, L = final length

L= Initial length

Folding endurance

The folding endurance is expressed as number of folds (the number of times a film is folded at the same place) required to break the film or to develop a visible crack. This gives an indication of brittleness of the film. Three films of each formulation were selected and subjected to this test by folding the film at the same place repeatedly several times until a visible crack was observed.

Mean and the standard deviation were calculated.

Disintegration time

Is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast-dissolving film, the time of disintegration should be in the range of 5-30s. The film size required for dose delivery (2×2cm) was placed on glass Petri dish containing 10ml of distilled water. The time required for breaking of the film was noted as in vitro disintegration time

***In-vitro* dissolution**

An *in vitro* dissolution study was performed for the different formulated film in USP basket apparatus using phosphate buffer pH 6.8. Dissolution medium was kept at 37ºC ± 0.5ºC and rotated at 50rpm with 900ml of phosphate buffer pH 6.8. The samples (1ml) were withdrawn after every 1min and replaced with fresh phosphate buffer pH 6.8. 1ml to maintain the sink condition samples was then taken and diluted up to 10ml in volumetric flask. The samples were analyzed for the drug content using UV Spectrophotometer at 242nm (λmax of Bosentan monohydrate).

RESULTS AND DISCUSSION

Calibration curve of Bosentan monohydrate by UV spectroscopic method

The standard calibration curve (absorbance v/s concentration) of bosentan monohydrate andit represents the slope of 0.001 and correlation co efficient of 0.970. The curve was found to be linear in the concentration range of 10-70µg/ml at 242nm.

Calibration curve of Bosentan monohydrate in Phosphate buffer pH 6.8.

Pre formulation Studies of Bosentan monohydrate Solid Dispersions

All the solid dispersions prepared were evaluated for bulk density, tapped density, angle of repose, Compressibility index, Hausner's ratio. It was found that all the dispersions exhibited excellent flow properties and good compressibility index as well as Hausner's ratio. Thus all the solid dispersions are suitable for further formulations.

Phase Solubility and drug content of Bosentan monohydrate solid dispersions

The phase solubility study for the complex formation between Bosentan monohydrate was shown in Table. The aqueous solubility of the drug increased linearly as function of mannitol concentration. At all the concentration of mannitol used for the preparation of inclusion complex showed significant increase in the solubility of Bosentan monohydrate. As the concentration of mannitol increased, the solubility of the drug was found to be increased.

Evaluation parameters of films

Thickness

The mean thickness value of formulated film(s) found to be in range of 0.09µm-0.4µm, more over the values were within the appreciable limits and the mean value were tabulated in the Table No.4. This suggests that upon the application of the experimental film on the oral cavity the film will not be unnecessarily bulky due to saliva. This may cause comfort to patients for its use.

Weight uniformity

The formulated FDFs weight variations were in the range of 21.3-24.3mg and the mean weight variation weight value was given in the Table No.5. The weight uniformity result show that the formulated FDFs mass was almost uniform in the formulation

Folding endurance

Folding endurance data of the all best FDFs are given in the Table No.6. The folding endurance of film was in the range of 59.3-83.6folds. Result the folding endurance suggests that structural integrity of the formulation was maintained and also indicates that the formulated film can withstand while placing the film at the site of administration as well as Formulation show good folding endurance.

Tensile strength

Tensile strength determination gives an indication of the strength and elasticity of film. Result revealed that the strength of the film of formulation was in the range of 1.12-1.5kg/mm^2. Tensile strength of all prepared formulation was show in Table No.7.

Percentage elongation

The viscosity of polymer(s) greatly plays a vital role in tensile strength and % elongation. The result revealed that % elongation value increases when increase in concentration of polymer(s) % elongation of all formulation were tabulated in Table No.8. The value of %elongation was in the range of 8.0-12.0.

***In vitro* disintegration time**

The disintegration time is the time when a film start to disintegrate. The disintegration time data represents that, if the formulation thickness is lowers, indicate less fast disintegration rate and the disintegration lower when the thickness of the film increases. Disintegration time was in range of 31.6±1.25 to 51±2.36 sec. The results shown in Table No.9.

Drug Release Profiles of Bosentan monohydrate Fast Dissolving Films

The release study data suggests that drug release rate was predominantly improved after the individual addition of polymer (HPMC K15, HPMC E15) along with the drug in the formulation. The %cumulative drug release of the formulation films (F1, F2, F4, F5) in a period of 5minutes duration was found in the range of 61%-89%. Among all formulation, F5 formulation consists of HPMC E15 show maximum % cumulative drug release of 89% within 5 minute of study period. The % CDR of all the formulation is tabulated.

Solid Dispersion

S.No	Composition	Ratio
1	BSM+Mannitol	1:1
2	BSM+Mannitol	1:2
3	BSM+Mannitol	1:3

Formulation

S.No	Ingredients	F1	F2	F3	F4	F5	F6
1	SD of Mannitol	62.5	62.5	62.5	62.5	62.5	62.5
2	HPMC E-15	-	-	-	250	500	750
3	HPMC K-15	250	500	750	-	-	-
4	PEG 6000	400	400	400	400	400	400
5	Tween80	0.5	0.5	0.5	0.5	0.5	0.5
6	Citric acid	100	100	100	100	100	100
7	Pineapple flavor	QS	QS	QS	QS	QS	QS
8	Water	20ml	20ml	20ml	20ml	20ml	20ml
9	Alcohol	10 ml	10ml	10ml	10ml	10ml	10ml

Table No.1: Linearity absorbance

S.No	Conc. (µg/ml)	Absorbance			Mean ± *SD
		Trial 1	Trial 2	Trial 3	
1	10	0.0470	0.0471	0.0464	0.0458±0.008
2	20	0.0971	0.0963	0.0964	0.0966±0.025
3	30	0.1416	0.1400	0.1402	0.1406±0.033
4	40	0.1954	0.1927	0.1926	0.1936±0.002
5	50	0.2522	0.2507	0.2501	0.2510±0.017
6	60	0.3021	0.3024	0.3031	0.3025±0.023
7	70	0.3495	0.3492	0.3487	0.3491±0.013

Table No.2: Pre formulation

S.No	Formulation code	Solid Dispersions	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
1	F1	BSM +Mannitol (1:1)	0.41	0.46	21.57	10.86	1.12
2	F2	BSM +Mannitol (1:2)	0.42	0.48	20.14	12.5	1.14
3	F3	BSM +Mannitol (1:3)	0.39	0.42	19.31	7.14	1.07

Table No.3: Drug content of Bosentan monohydrate

S.No	Formulation code	Solubility in pH 6.8 Phosphate buffer (mg/ml)	Drug Content (%)
1	F1	0.567	98.89±1.01
2	F2	0.688	98.88±1.23
3	F3	0.849	99.12±1.32

Table No.4: Thickness uniformity of the prepared formulations *SD; n=3

S.No	Formulation	Thickness (*µ*m)			Mean ± *SD
		Film 1	Film 2	Film 3	
1	F1	0.6	0.2	0.1	0.3±0.72
2	F2	0.5	0.4	0.3	0.4±0.91
3	F4	0.1	0.2	0.1	0.13±3.95
4	F5	0.1	0.08	0.1	0.09±2.0

Table No.5: Weight uniformity of the prepared formulations *SD; n=3

S.No	Formulation	Weight (mg)			Mean ±*SD
		1	2	3	
1	F1	22	22	20	21.3±0.20
2	F2	24	23.8	24	23.6±0.29
3	F4	23	22	23	22.6±0.16
4	F5	24	25	24	24.3±0.16

Table No.6: Folding endurance of the prepared formulations *SD; n=3

S.No	Formulation	No. of folds			Mean ±*SD
		Film 1	Film 2	Film 3	
1	F1	60	58	60	59.3±2.94
2	F2	75	73	75	75.3±3.39
3	F4	80	78	77	78.3±2.44
4	F5	93	90	92	83.6±3.68

Table No.7: Tensile strength of the prepared formulations*SD; n= 3

S.No	Formulation	No. of folds			Mean ±*SD
		1	2	3	
1	F1	0.70	0.75	0.73	1.16±0.06
2	F2	0..67	0.60	0.07	1.12±0.07
3	F4	0.75	0.75	0.73	1.16±0.07
4	F5	1.62	1.479	1.519	1.5±0.14

Table No.8: **Percentage elongation of the prepared formulations*SD; n= 3**

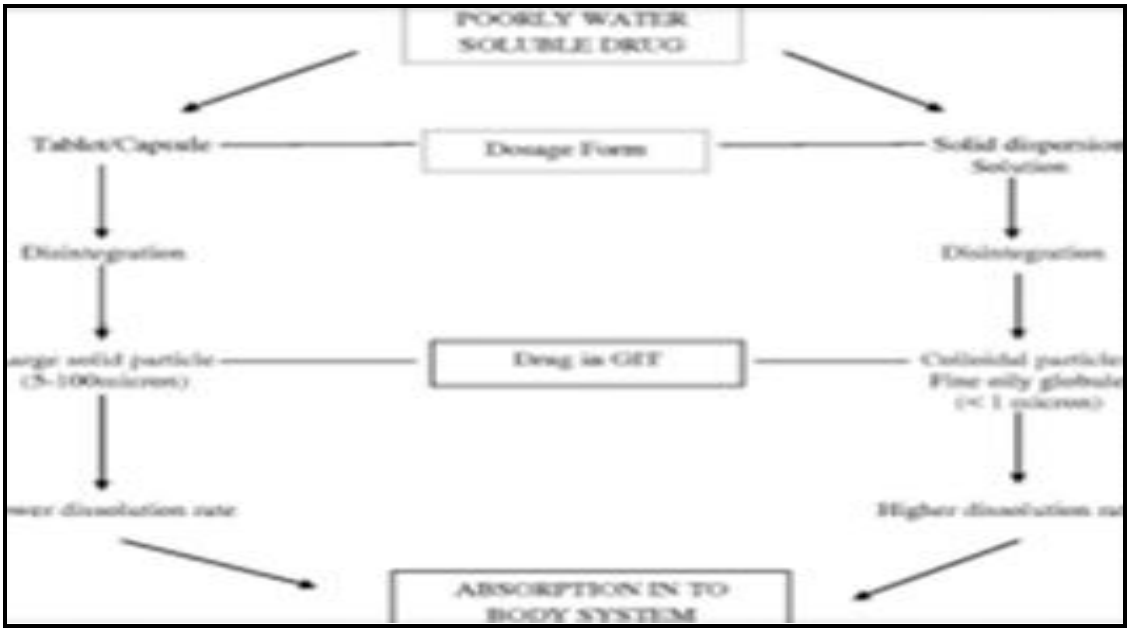
S.No	Formulation	No. of folds			Mean ±*SD
		Film 1	Film 2	Film 3	
1	F1	12.24	11.02	12.26	11.8±0.71
2	F2	8.22	7.74	8.06	8.0±0.24
3	F4	11.56	11.34	11.84	11.5±0.25
4	F5	12.06	11.94	12.24	12.0±0.08

Table No.9: *In vitro* disintegration time of the prepared formulations*SD; n=3

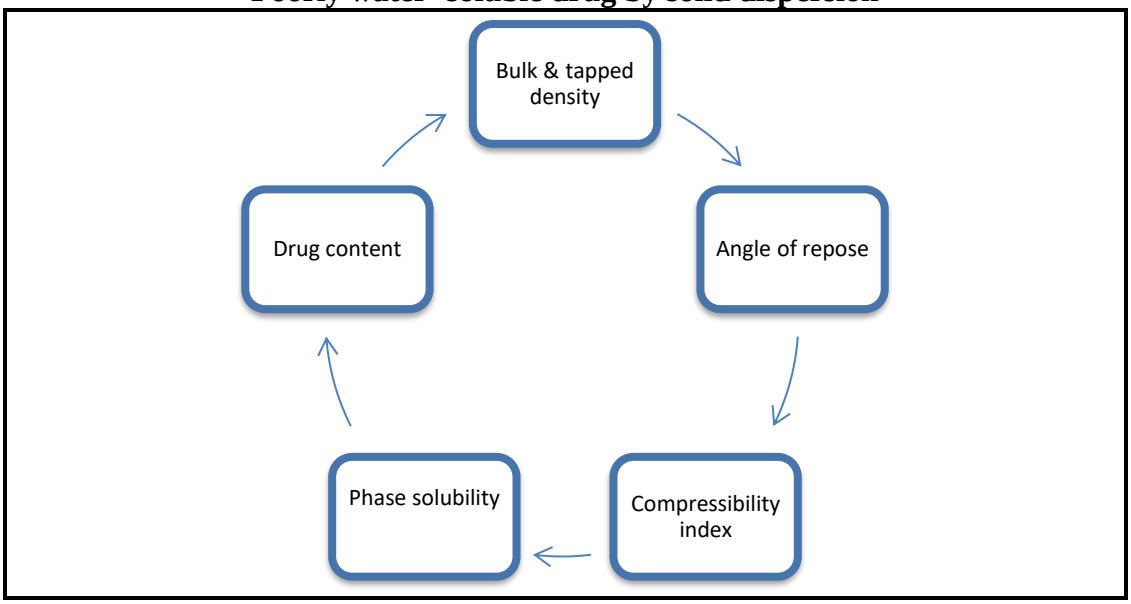
S.No	Formulation	No. of folds			Mean ±*SD
		Film 1	Film 2	Film 3	
1	F1	32	32	31	31.6±1.25
2	F2	50	51	53	51.3±2.36
3	F4	22	23	23	22.6±3.09
4	F5	43	42	41	42±2.62

Table No.10: *In vitro* drug release profile

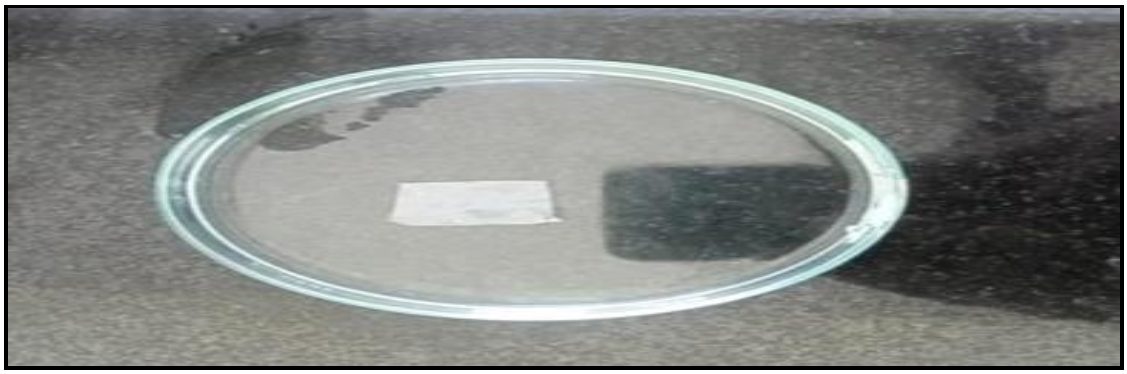
S.No	Time (min)	% CDR			
		F1	F2	F4	F5
1	0	0	0	0	0
2	1	35.4±3.5	54.6±1.4	56.6±1.6	61.63±1.6
3	2	54±2.5	60.4±1.0	68.3±1.9	70.54±1.4
4	3	58.2±2.8	65.8±1.5	72±1.5	75.99±1.6
5	4	58.7±2.8	67.8±1.8	73.3±1.3	79.64±1.9
6	5	60.2±1.6	68.6±1.9	77.6±1.6	89.28±0.9



Poorly water- soluble drug by solid dispersion



Pre-formulation study of solid dispersion



***In vitro* evaluation of film**

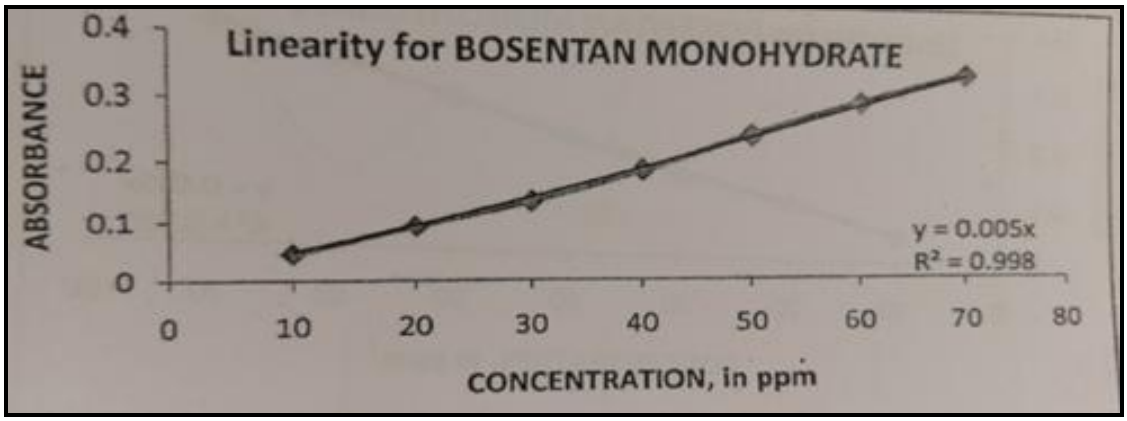


Figure No.1: Standard calibration curve of Bosentan monohydrate

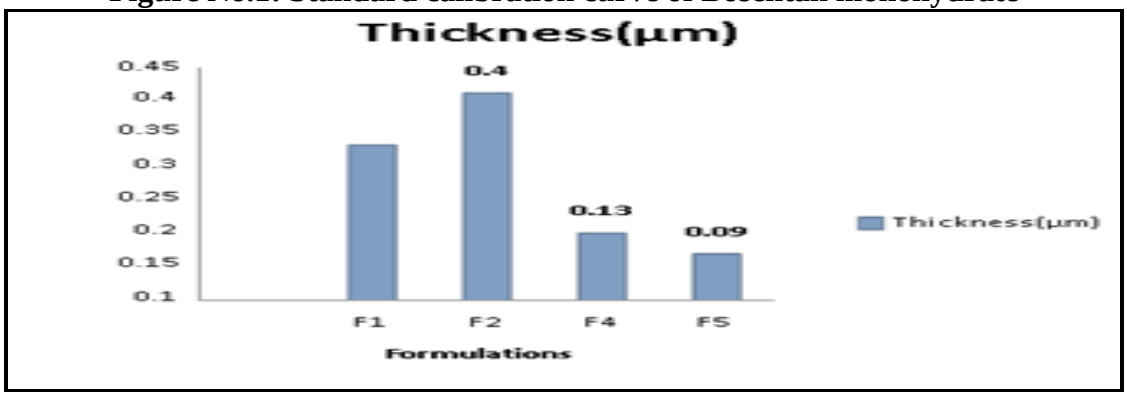


Figure No.2: Thickness

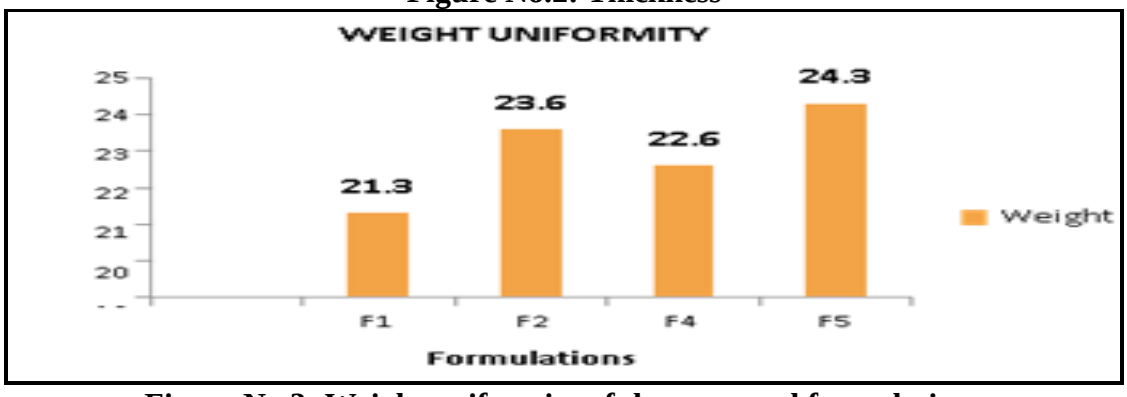


Figure No.3: Weight uniformity of the prepared formulations

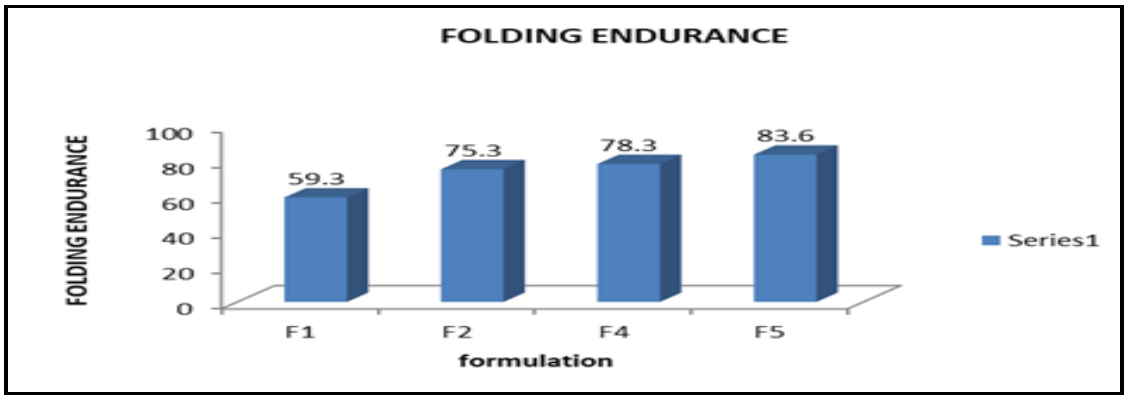


Figure No.4: Folding endurance of the prepared formulations

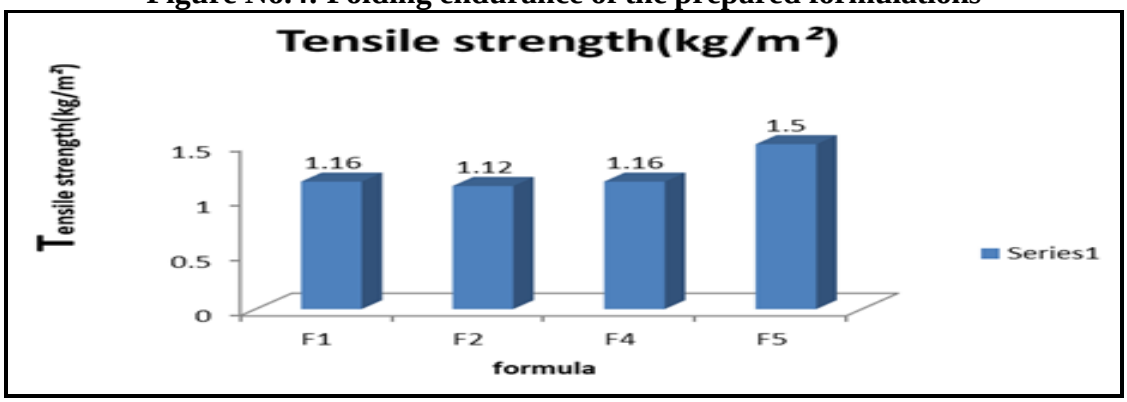


Figure No.5: Tensile strength of the prepared formulations

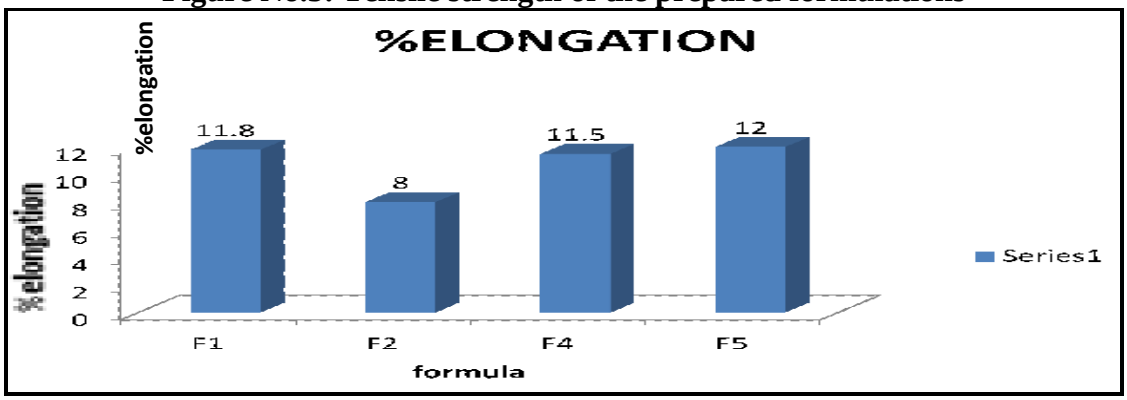


Figure No.6: Percentage elongation of the prepared formulations

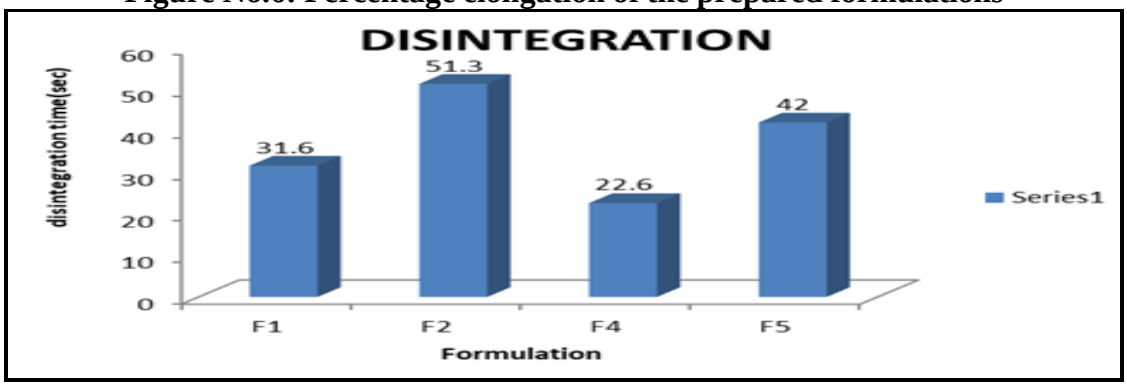


Figure No.7: *In vitro* disintegration time of the prepared formulations

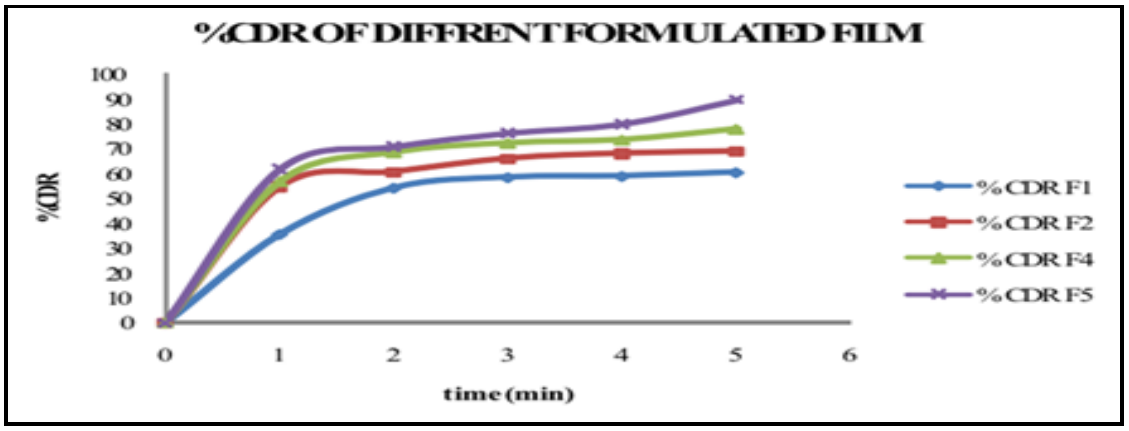


Figure No.8: % CDR of formulation

CONCLUSION

BSM has poor water-soluble drug. It's posing problem in absorption leads to poor bio-availability.

SD's of BSM were prepared with Mannitol in different ratio (1:1, 1:2, and 1:3) by solvent evaporation method to enhance solubility.

Pre-formulation studies were performed and ratio 1:3 shows enhanced solubility

All the physicochemical characterization studies shows that formulated film of small in size, uniform mass and good withstanding property. PEG 6000 as a plasticizer shows better film formation in the formulation.

Formulation F5 prepared with the HPMC E15 (500mg) showed good results & maximum release in the range of 89±0.9% at 6min in vitro drug release.

Further direction of studies required to conform the prepared solid dispersion ability to treated pulmonary arterial hypertension.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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