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Formulation and Evaluation of Bosentan Monohydrate Sustained Release Tablets Using Thermal Sintering Technique

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ABSTRACT

The objective of the present study is to prepare thermally sintered sustained release tablets of Bosentan monohydrate and to study the effect of sintering conditions on in-vitro dissolution study, hardness and friability. The tablets were prepared by direct compression and wet granulation technique. The prepared tablets were sintered at three different temperatures like 50^0C, 60^0C and 70^0C for three different time periods 1hr, 2hr and 3 hr in a hot air oven. Pre compression and Post compression parameters were performed. Results shown that the release rate of the drug was inversely related to the sintering temperature and the time of sintering. The optimum drug retardation occurred in the tablets sintered at 60 and 70^0C. The hardness of the sintered tablets was increased with increase in sintering temperature and duration of sintering, whereas friability of tablets was found to be decreased with increasing sintering time. From the FTIR, it was observed that there was no interaction between drug and excipients. Hence, the stearic acid, carnauba wax and EVA 1802 can be used as sintering polymers for controlling the drug release by Thermal sintering technique. F7($60^0$1 hr sintering) showed the maximum sustained release of 99.8%. From the kinetic profile it shows that the drug release followed zero order and Non fickian diffusion with erosion mechanism. From the stability it was observed that the F7(60^0 1hr sintering) was stable for 3 months under standard conditions. Thus F7(60^0 1hr sintering) was considered to be the best formulation among all the 7 formulations sintered at various temperatures and various time periods. Hence it shows the suitability of EVA polymer for preparing the Bosentan monohydrate sustained release tablets by Thermal sintering technique. F7(60^0C 1 hr sintering) got good the results in Preformulation studies. The angle of repose was 24.45, Hausner's ratio is 1.08 Compressibility index is 8.81 which indicates the good flowing properties. From the FTIR studies it was observed that there is no interaction between the drug and excipients. As Bosentan is having the high intestinal absorption, by preparing sustained release tablets of Bosentan monohydrate, its bioavailability can be enhanced. Only the drugs which are having the high melting point are selected for using thermal sintering technique. As Bosentan is having melting point of 108^0C, it is used in the preparation of Sustained release tablets of Bosentan monohydrate using Thermal sintering technique.

Keywords: Thermal sintering technique, Bosentan monohydrate.

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INTRODUCTION

Bosentan is a sulfonamide and pyrimidine derivative that acts as a dual endothelin receptor antagonist used to manage Pulmonary arterial hypertension. Pulmonary hypertension is a type of high blood pressure that affects the arteries in your lungs and the right side of your heart. Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to ET_A and ET_B receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease. Bosentan is a specific and competitive antagonist at endothelin receptor types ET_A and ET_B. Bosentan has a slightly higher affinity for ET_A receptors than for ET_B receptors.

Thermal sintering involves heating of a compact at a temperature below the melting points of the solid constituents in a controlled environment. The sintering method involves the exposure of the dosage form to temperature which softens the polymer matrix and leads to the formation of welded bonds. The drug particle gets entrapped in the matrix formed and these results in the controlled release of the active ingredient. Sintering affects the physic technical properties of granules, tablets dissolution rate as well as the release kinetics. Carli F and Simioni L in 1981 investigated the effect of sintering on drug release from vinyl chloride vinyl acetate copolymer (CPVC) tablets as well as acrylic tablets by using aspirin as model drug. They observed that sintering initially enhanced release of aspirin from CPVC tablets but prolonged sintering decreased the release rate. However, in case of acrylic tablets, the release rate of aspirin decreased drastically upon sintering. They attributed the changes in the release rate of the as the result of sintering to the alteration of the capillary network within the matrix[1]. A Kondaiah and K Prakash in 2002 prepared and evaluated controlled release polymeric matrix tablets theophylline using sintering technique. They found that irrespective of the drug: polymer ratio in the formulation, with the increase in the time of sintering and or temperature of sintering, the percent of theophylline released was reduced [2]. B. Seshagiriet.al in 2011 designed Hydrodynamically Balanced Systems for Glipizide with sintering technique. It is an approach to increase the gastric residence time of drugs in stomach. This system is designed for site specific oral drugs with low bulk density than gastric fluids so as to buoyant the dosage form in stomach to increase the residence time of the drug. In the present investigation, HPMC K4M and HPMC K15M polymers were used by solvent casting sintering technique The study reveals that the formulations of HBS of Glipizide formulated has exhibited a floating lag time of less than 5 minutes and floating time of more than 22 hrs [3]. Sameer Shafi et.al in 2011 prepared the sustained release (SR) sintered matrix tablets of Diltiazem hydrochloride by

trituration method using 4% and 8% HPMC K4M and HPMC K15. Formulations with HPMC K exhibited sustained drug release profiles with maximum sustaining effect when compared with unsintered formulation in about 8 hours by using sintering [4].Vaibhav Bhamre et al in 2013 have prepared and evaluated sintered matrix tablets of Stavudine by using Eudragit RS100 & Compritol 888ATO with direct compression method. Also studied effect of different three temperatures on stability of sintered tablets. Storage condition & period of storage affect stability of Stavudine sintered tablet[5]. M U Uhumwangho and K V Ramanamurthy in 2011 studied the effect of sintering condition on drug release profile of Diltiazem hydrochloride wax-matrix granules for sustained release application using thermal sintering technique. They found that as the temperature and duration of sintering of the matrix granules increased, the drug release rate decreased and the time to attain maximum release increased correspondingly. They concluded that the thermal sintering technique enhanced the extent of retardation of drug release and drug was not affected by the temperature and time period used for sintering[6]. Chandan Mohanty et.al in 2016 prepared thermally sintered floating matrix tablets of Nicardipine HCL and studied the effect of sintering conditions on in-vitro dissolution study, in-vitro buoyancy properties, hardness and friability. The tablets were prepared by direct compression method using HPMC K100M as matrix forming polymer and sodium bicarbonate as gas generating agent. By using sintering technique floating lag time and total floating time of tablets was found to be decreased and increased respectively, with increase in the sintering temperature and sintering time. In addition the hardness of the sintered tablets was increased with increase in sintering temperature and duration of sintering, whereas friability of tablets was found to be decreased with increasing sintering time[7]. Samra Rumman et.al in 2017 formulated Tapentadol Hydrochloride sintered tablets were using sustaining polymer-eudragit RL-100, sintering waxes-stearic acid and carnauba wax, disintegrating agent-microcrystalline cellulose, Glidant-talc and lubricant-magnesium stearate by direct compression method. The drug release from optimized formulation (F17-Tapentadol Hydrochloride with stearic acid and carnauba wax sintered at 60^0C for 2 hours) was found to be 100.38% in 12 hours. Stability studies revealed that optimized formulation was stable at 40±2°C and 75±5% RH for 3 months. Thus, the developed F17 formulation by sintering technique has great future potential to be prepared as sustained release tablets [8]. Collins O Airemwen et.al in 2017 formulated sustained release matrix tablets of metronidazole using sintering technique. Controlled release metronidazole matrix tablets were prepared by wet granulation technique using Irvingia gabonesis (IG) gum as binder. Prepared tablets were kept for thermal sintering .There is increase in tablet hardness with increase in sintering temperature and time while the percentage friability decreased. The in-vitro dissolution

profile of the prepared controlled release matrix tablet of metronidazole showed that the optimum drug release retardation occurred in tablets sintered at 60 ºC for 5 h**.** The study has revealed that IG gum at a concentration of 10%w/w possesses good binding properties and can be utilized in the formulation of controlled release matrix tablets of metronidazole by thermal sintering [9].

This method can be applied to the drugs that are temperature resistant on exposure, which are having high melting points. As Bosentan is having high melting point at 108^{0}C, it is suitable to prepare tablets by Thermal sintering technique. Historically, sintering is a method used to fabricate parts from metals, ceramics and glass. Microwave sintering, plasma-activated sintering and laser sintering are the more recent advancements in Thermal sintering technologies [11,12]. The sintering process has been used for the formulation of sustained – release matrix tablets and for the stabilization of the drug permeability of film coatings derived from various pharmaceutical lattices [13,14].There are two types of sintering methods, namely thermal sintering method (heat treatment) and solvent casting method (acetone saturation method) [15]. Among 2 methods, heat treatment is followed.

MATERIALS AND METHOD

Materials:

Bosentan monohydrate was obtained from Natco Research Centre, Hyderabad as a gift sample. Eudragit, stearic acid, carnauba wax were obtained from SD Fine chem. Ltd Mumbai. EVA1802 was obtained from Sigma-Aldrich were used in the preparation of thermally sintered tablets. All other excipients used were of a standard pharmaceutical grade.

Methods:

Preparation of Standard Stock Solution (1mg/ml or 1000µg/ml):

Bosentan monohydrate equivalent to 10mg was weighed and transferred into 10ml volumetric flask, dissolved in dichloromethane and the volume was made up with dichloromethane.

Preparation of Working Standard (100µg/ml):

From the standard stock solution 1ml was pipetted out into a 10ml volumetric flask and the volume was made up with 6.8 phosphate buffer

Preparation of series of Standards:

From the above solution 0.2,0.4,0.6,0.8,1ml was transferred into separate 10ml volumetric flasks and the volume was made up with 6.8 phosphate buffer. This gives 2,4,6,8,10µg/ml solutions respectively. The absorbance of these solutions was measured against the blank at λmax 242nm using double beam UV spectrophotometer. The method was validated for linearity, accuracy,

precision. From the obtained absorbance, the calibration curve was plotted by taking concentration on X-axis and absorbance on Y-axis.

Drug-Excipient Compatibility by FTIR Studies

In the preparation of controlled release tablet, drug and polymer may interact as they are in close contact with each other, which could lead to instability of drug. Preformulation studies regarding drug-polymer interactions are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Bosentan and selected polymers. The individual drug and drug with excipients were scanned separately.

Procedure

Completely dried potassium was transferred into a mortar. About 2% of pure drug or with excipients was weighed in a digital balance, mixed and ground to a fine powder. Two stainless steel discs were taken out of the desiccator. A piece of the pre-cut cardboard on top of one disc was placed and cut out hole was filled with the finely ground mixture. The second stainless steel disc was kept on top and transfers the sandwich onto the pistil in the hydraulic press. With a pumping movement, hydraulic pump handle moved downward. The pistil will start to move upward until it reaches the top of the pump chamber. Then, the pump handle moved upwards and continued pumping until the pressure reaches 20,000 prf. Rest for a few seconds and with the small lever on the left side, the pressure was released. Removing of the discs and pulling apart. The obtained film was homogenous and transparent in appearance. Then inserted into the IR sample holder and attach with scotch tape and run the spectrum.

EVALUATION OF PRE-COMPRESSION PARAMETERS

Angle of repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend were measured. The angle of repose was calculated using following formula.

$\text{Tan } \theta = h/r$

Where "h" is a height of the heap and "r" is the radius of the heap of blends.

Bulk Density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume.

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was slightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume.

Carr's compressibility index

The Carr's compressibility Index was calculated from Bulk density and tapped density of the blend. A quantity of 2g of a blend from each formulation was filled into a 10mL of measuring cylinder. Initial bulk volume was measured and the cylinder was allowed to tap from the height of 2.5cm.The tapped frequency was 25±2 per min to measure the tapped volume of the blend. The bulk density and tapped density were calculated by using the bulk volume and tapped volume [16]. Compressibility index was calculated using the following formula:

$$\% \text{ Compressibility index (I)} = \frac{\text{Tapped density } (D_t) - \text{Bulk density } (D_b)}{\text{Tapped density } (D_t)} \times 100$$

METHOD OF PREPARATION:

Sustained release tablets were prepared by direct compression method and wet granulation technique. Direct compression is the process by which tablets are compressed from powder mixture of API and suitable excipients. Compression of tablets was done by automatic punching machine using 6 mm punch. Prepared tablets were kept in hot air oven at 3 different temperatures of 50°,60° and 70°C for 3 different time periods at 1hr, 2hr and 3hrs.

Wet granulation involves the mixing of dry primary powder particles using a granulating fluid. API and other excipients were weighed accordingly and transferred in a mortar. Then add the prepared binder solution drop wise to the mortar. Granulation was achieved by slowly adding the binder solution to the dry mixture, after reaching the desired consistency, it is passed through 12 mm mesh screen. The granules were dried in the oven at 45°C and then removed and sieved with an 18mm mesh. To this add magnesium stearate and talc, mix it properly weigh 120 mg of granules then punch it under 6mm punch. Prepared tablets were kept in hot air oven at 3 different temperatures of 50°,60° and 70°C for 3 different time periods at 1hr, 2hr and 3hrs.

Table 1: Formulation table

Ingredients (mg/tablet)	F1(10% stearic acid)	F2(10% carnauba Wax)	F3(15% Stearic acid)	F4(15% Carnauba wax)	F5(20% Stearic acid)	F6(20% Carnauba wax)	F7 (5% EVA)
Bosentan Monohydrate	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Stearic acid	6.3	-	9.4	-	12.5	-	-
Carnauba wax	-	6.3	-	9.4	-	12.5	-
EVA 1802	-	-	-	-	-	-	5%

Eudragit	15.6	15.6	15.6	15.6	15.6	15.6	-7.5
MCC	7.5	7.5	7.5	7.5	7.5	7.5	3
Magnesium Stearate	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3
Lactose	22.1	22.1	19	19	15.9	15.9	15.4
Total weight	120	120	120	120	120	120	120

EVALUATION OF TABLETS

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical strength while handling. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2.Three tablets were randomly picked from each formulation and the mean and standard Deviation values were calculated.

Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (Wt.initial) and transferred into friabilator. The friabilator was operated at 25 rpm for4 minutes or run up to 100 revolutions. The tablets were weighed again

Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. To study weight variation, 20tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method.

Drug content:

Each formulation was taken in dose equivalent amounts of Bosentan monohydrate and dissolved in 6.8 pH Phosphate buffer. The solutions were filtered and filtrates were analyzed for drug content using UV Spectrophotometer at 242nm.

In-vitro drug release studies

Drug release from the prepared tablets was determined up to 12hrs using USP type II (paddle type) dissolution test apparatus 6.8 pH Phosphate buffer (900 ml) was used as dissolution medium. The paddle was adjusted at 50 rpm and the temperature of 37±0.5°C was maintained throughout the experiment. Samples were withdrawn at known time intervals and were replaced with the same volume of fresh dissolution media after each withdrawal. The samples were analyzed for drug contents by measuring absorbance by using UV spectrophotometer.

Dependent-model method (Data analysis)

In order to describe the Bosentan release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models: zero order, first order, Higuchi, Korsmeyer-Peppas. When these models are used and analyzed in the preparation, the rate constant obtained from these models is an apparent rate constant. The release of drugs from the matrix tablets can be analyzed by release kinetic theories. To study the kinetics of drug release from matrix system, the release data were fitted into Zero order as the cumulative percentage of drug release vs. time (Eqn.1), first order as log cumulative percentage of drug remaining vs. time (Eqn.2), Higuchi model as cumulative percent drug release vs. square root of time (Eqn.3). To describe the release behavior of the polymeric systems, data were fitted according to well known exponential Korsmeyer – Peppas equation as log cumulative percent drug release vs log of time equation (Eqn.4).

(i) Zero-order kinetics

$Qt=K0t$……(1)

Where,

Q= Amount of drug release in time t

K0 = Zero order rate constant expressed in unit of concentration /time

t = Release time

(ii) First order kinetics

Log Q=Log Q0-kt/2.303.....(2)

Where,

Q0= is the initial concentration of drug

k= is the first order rate constant

t =release time

(iii) Higuchi kinetics

$Q=kt_{1/2}$.....(3)

Where,

k= Release rate constant

t=release time,

Hence the release rate is proportional to the reciprocal of the square root of time.

(iv) Korsmeyer-Peppas

First, 60% *in-vitro* release data were fitted in an equation of Korsmeyer-peppas to determine the release behavior from controlled release polymer matrix system. The equation is also

called a power law,

$Mt/M\infty = Kt^n$.....(4)

Where,

Mt = amount of drug released at time t

$M\infty$ = amount of drug released after infinite time

$Mt/M\infty$ = fraction solute release

t = release time

K = kinetic constant incorporating structural and geometric characteristics of the polymer system

n = diffusional exponent that characterizes the mechanism of the release of traces.

The magnitude of the release exponent "n" indicates the release mechanism (i.e Fickian diffusion, Non fickian super case II release). For the tablets, values of 'n' of near 0.5 indicates Fickian diffusion controlled drug release, and an 'n' value of nearly 1.0 indicates erosion or relaxation control (case II relaxational release transport , non Fickian, zero order release). Values of n between 0.5 and 1 regarded as an indicator of both diffusion and erosion as overall release mechanism commonly called as anomalous release mechanism.

Stability study:

The stability study of the optimized formulations was conducted at 40 ± 2^0C/75% RH in humidity chamber for a period of 3 months. After every month, the tablets were tested for *in-vitro* drug release studies, weight variation, Hardness and Friability. There is no much difference has been observed after 3 months of stability study.

RESULTS AND DISCUSSION:

Analytical Method for Construction of calibration curve

In order to conduct the *in vitro* drug dissolution studies, the calibration curve was plotted to determine R^2 and the equation of a straight line is used to calculate drug release. Calibration curve of Bosentan monohydrate in 6.8 pH Phosphate buffer was constructed against the respective buffer as blank at λmax of 242 nm.

Drug excipient compatibility study:

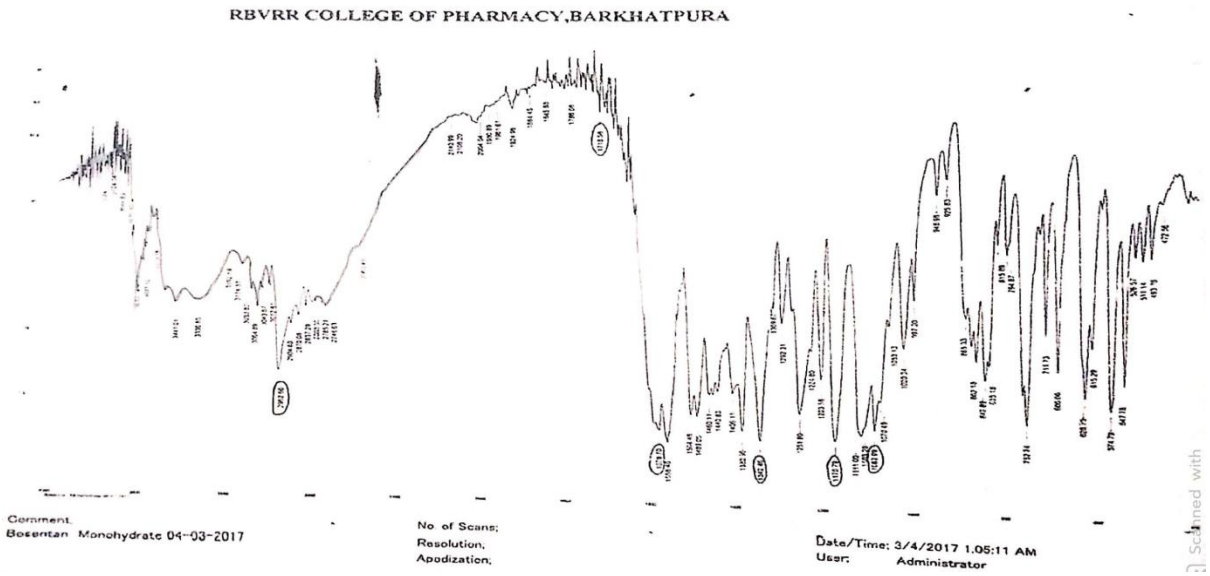

Figure 1: Fourier-transform infrared spectroscopy spectrum of Bosentan monohydrate

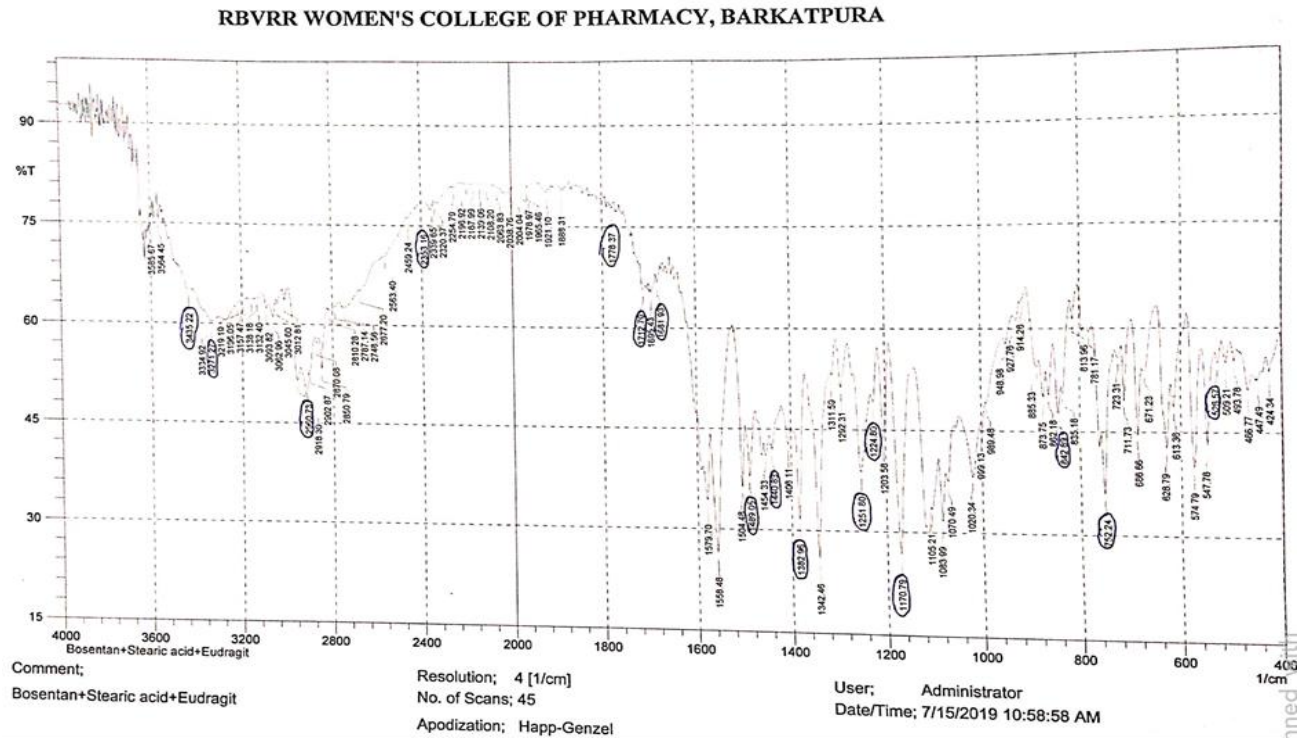

Figure 2: Fourier-transform infrared spectroscopy spectrum of Bosentan monohydrate, stearic acid and Eudragit

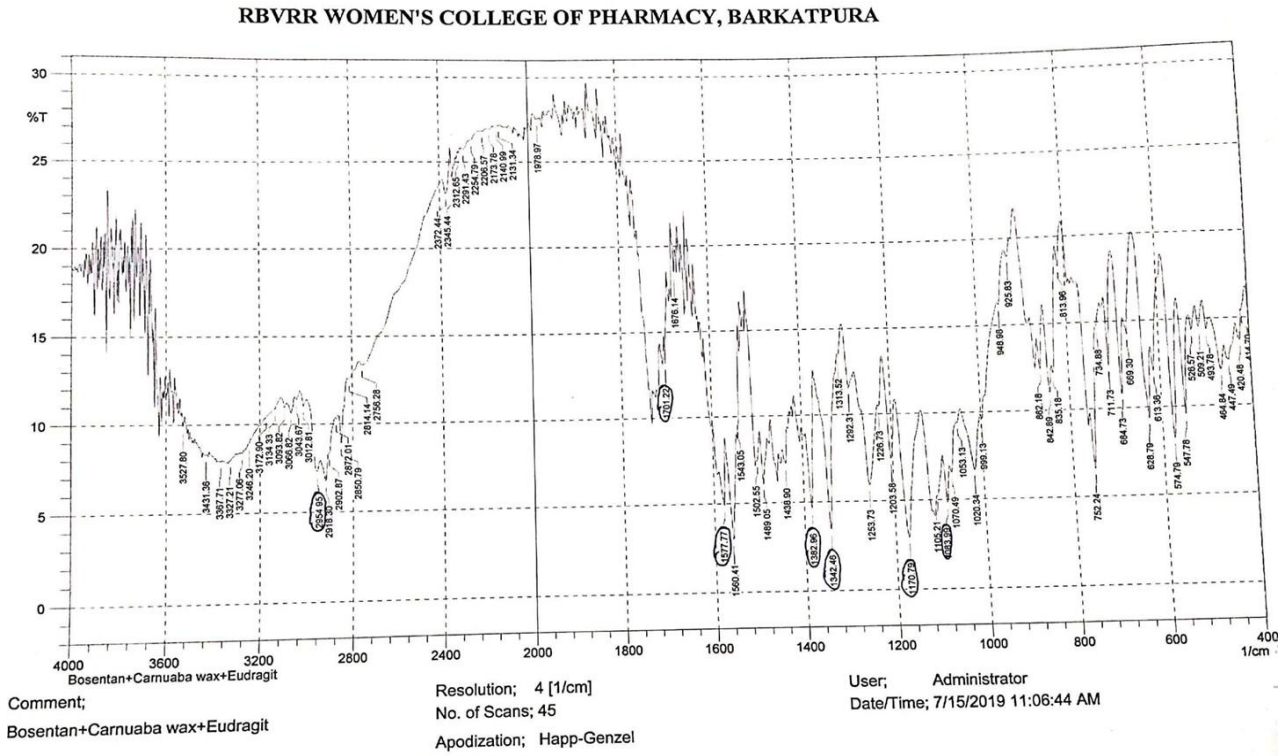

Figure 3: Fourier-transform infrared spectroscopy spectrum of Bosentan monohydrate, Carnauba wax and Eudragit

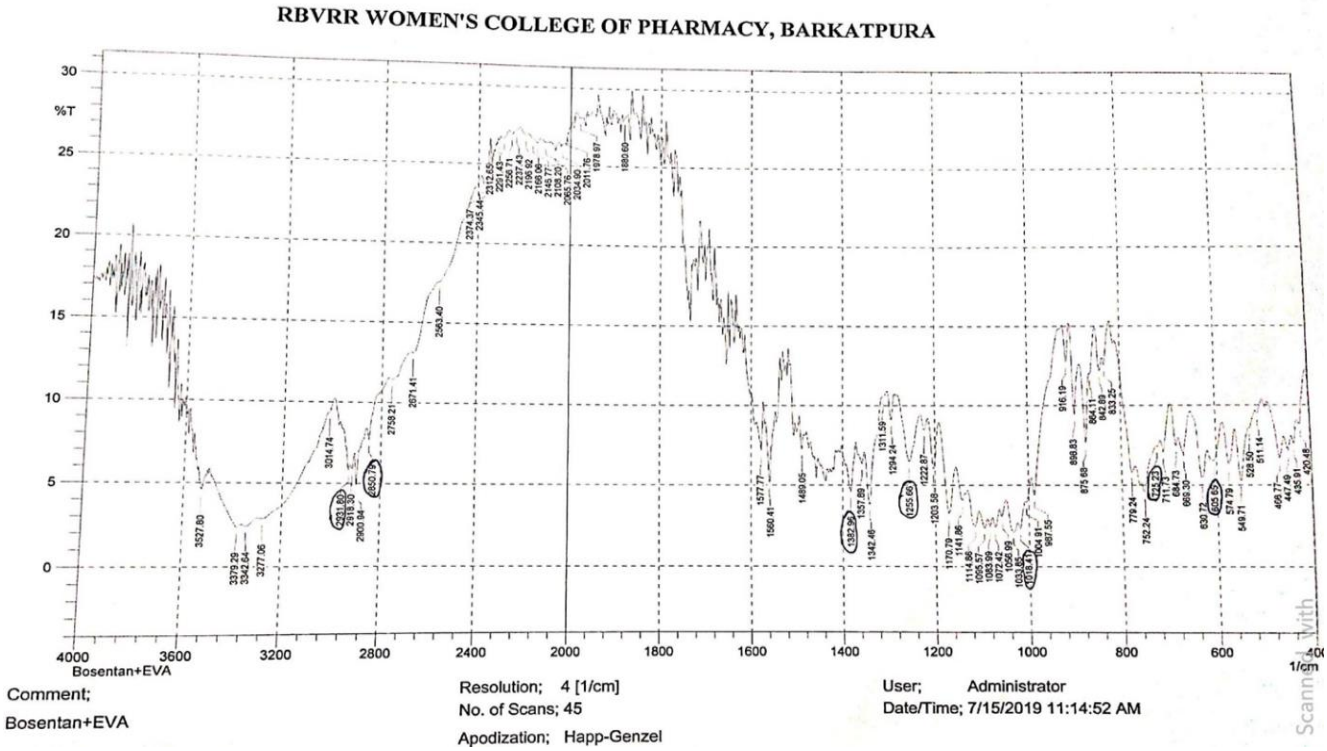

Figure 4. Fourier-transform infrared spectroscopy spectrum of Bosentan monohydrate and EVA 1802

Preformulation study

The angle of repose for a pure drug was very high and hence the poor flow of drug was exhibited whereas the angle of repose of formulations was very less showing good flow. The Carr's index of the pure drug was found to be high confirming that the drug has poor flow property and compressibility.

Table 2: Pre-formulation studies of all the formulations.

Formulations	Angle of repose (o)	Bulk density (g/cc)	Tapped density (g/cc)	Hausner's ratio	Carr's compressibility index
F1	28.33±0.11	0.47±0.21	0.56±0.19	1.18±0.13	16.06±1.37
F2	27.48±1.24	0.48±0.22	0.57±0.24	1.22±0.01	15.77±2.34
F3	27.14±0.02	0.50±0.33	0.59±0.36	1.19±0.04	15.24±4.31
F4	28.41±0.16	0.63±0.41	0.74±0.46	1.16±0.06	14.85±8.47
F5	27.58±0.26	0.54±0.25	0.62±0.25	1.13±0.02	12.9±0.76
F6	26.12±0.06	0.51±0.15	0.58±0.12	1.12±0.11	12.05±2.39
F7	24.45±0.35	0.62±0.42	0.68±0.43	1.08±0.02	8.81±1.61

All the values are expressed as mean ± S.D. n=3

Angle of repose from F1 to F7 was found to be within the range of 24.45 to 28.33 indicating good flow property, Hausner's ratio from F1 to F7 was in the range of 1.08 to 1.22 and Carr's compressibility index was found to be within the range of 8.81 to 16.06, showed the good flow properties, whereas F7 showed the Free flowing properties.

Post-compression parameters of unsintered tablets

The hardness of the unsintered tablets is less when compared to the sintered tablets, whereas % friability is more than the sintered tablets

Table 3: Post-compression parameters of unsintered tablets

Formulations	Weight variation(mg)	Hardness (kg/cm^2)	Friability (%)
F1	120.34±0.32	3.33±1.25	0.33±0.2
F2	119.45±0.45	3.45±0.74	0.31±0.1
F3	120.07±0.12	3.81±0.61	0.29±0.2
F4	120.29±0.25	3.79±0.85	0.26±0.1
F5	121.32±0.17	4.48±0.55	0.19±0.2
F6	120.28±0.16	4.53±0.74	0.16±0.3
F7	119.47±0.26	5.25±0.25	0.23±0.1

All the values are expressed as mean ± S.D. n=3.The above values are the post compression parameters of unsintered tablets. The hardness is less when compared to the sintered tablets, whereas % friability is more than the sintered tablets.

Table 4: Hardness test of sintered tablets

Temperature	Time	Formulation code						
		F1	F2	F3	F4	F5	F6	F7
	1hr	3.3±0.2	3.4±0.2	4.2±0.2	3.5±0.2	3.6±0.2	4.4±0.3	5.0±0.5
50^{0}C	2hr	3.6±0.5	3.8±0.5	4.4±0.1	3.7±0.4	4.2±0.3	4.8±0.2	5.2±0.4
	3hr	3.9±0.4	4.0±0.3	4.6±0.6	3.8±0.3	4.5±0.4	4.9±0.1	5.4±0.3
	1hr	4.2±0.3	4.5±0.3	5.1±0.2	4.0±0.3	4.3±0.4	5.1±0.4	5.5±0.4
60^{0}C	2hr	4.5±0.2	5.2±0.2	5.4±0.4	4.3±0.5	4.7±0.3	5.3±0.3	5.7±0.3
	3hr	4.8±0.1	5.4±0.5	5.7±0.6	4.6±0.7	4.9±0.3	5.5±0.2	6.0±0.2
	1hr	5.1±0.4	5.2±0.1	5.3±0.2	4.4±0.5	4.6±0.2	4.8±0.4	5.6±0.7
70^{0}C	2hr	5.4±0.2	5.6±0.5	5.5±0.4	4.6±0.6	5.0±0.4	5.1±0.2	6.0±0.3
	3hr	5.6±0.3	5.7±0.2	6.0±0.3	5.0±0.3	5.2±0.3	5.3±0.3	6.3±0.4

All the values are expressed as mean ± S.D, n=3

From the above table it indicates that the hardness increases with increase in sintering temperature and time of exposure and it was found to be within the limits of official compendia.

Table 5: Friability test of sintered tablets

Temperature	Time	Formulation code						
		F1	F2	F3	F4	F5	F6	F7
	1hr	0.42±0.3	0.39±0.2	0.35±0.2	0.35±0.2	0.36±0.1	0.35±0.1	0.27±0.1
50^{0}C	2hr	0.39±0.2	0.34±0.2	0.31±0.2	0.31±0.2	0.34±0.3	0.33±0.2	0.25±0.2
	3hr	0.32±0.1	0.30±0.1	0.28±0.1	0.28±0.1	0.32±0.2	0.28±0.1	0.22±0.3
	1hr	0.39±0.4	0.28±0.2	0.27±0.3	0.27±0.3	0.28±0.1	0.27±0.1	0.21±0.4
60^{0}C	2hr	0.35±0.2	0.26±0.1	0.24±0.4	0.24±0.4	0.26±0.2	0.24±0.2	0.19±0.2
	3hr	0.23±0.2	0.22±0.1	0.20±0.1	0.20±0.1	0.20±0.2	0.20±0.2	0.15±0.2
	1hr	0.20±0.3	0.19±0.2	0.17±0.2	0.17±0.2	0.19±0.3	0.17±0.1	0.16±0.1
70^{0}C	2hr	0.19±0.1	0.16±0.3	0.15±0.1	0.15±0.1	0.15±0.2	0.15±0.2	0.13±0.2
	3hr	0.18±0.1	0.15±0.1	0.13±0.2	0.13±0.2	0.14±0.1	0.13±0.3	0.10±0.2

All the values are expressed as mean ± S.D, n=3

From the above table it indicates that the Friability decreases with increase in sintering temperature and time of exposure and it was found to be within the limits of official compendia.

***In-vitro* drug release profile of Bosentan monohydrate tablets**

According to the formulation mentioned in table1 total 7 formulations of Bosentan monohydrate were prepared and sintering was carried at 50,60,70^{0}C for 1hr,2hr and 3hrs.then the tablets were subjected to in vitro drug release studies for 12 hrs using 6.8 phosphate buffer.

Table 6: *In-vitro* drug release profile of Bosentan monohydrate from unsintered tablets

Time(hrs)	F1(stearic acid 10%)	F2(carnauba wax 10%)	F3(stearic acid 15%)	F4(carnauba wax 15%)	F5(stearic acid 20%)	F6(carnauba wax 20%)	F7(EVA 5%)
0.5	18.1±0.2	17.2±0.3	11.4±0.2	11.8±0.3	9.06±0.3	9.5±0.5	7.6±0.3
1	36.2±0.3	35.2±0.5	34.2±0.5	33.5±0.1	16.8±0.4	16.5±0.2	14.1±0.2
2	44.5±0.5	44.1±0.4	42.1±0.5	42.2±0.7	31.5±0.2	30.2±0.6	26.5±0.5
3	62.3±0.4	62.3±0.2	52.1±0.3	53.2±0.4	34.5±0.1	35.6±0.4	32.6±0.5
4	71±0.5	70.5±0.3	67.1±0.1	67.2±0.5	46.2±0.5	46.2±0.2	46.2±0.5
5	84.8±0.7	84.1±0.6	73.6±0.6	74.5±0.5	53.3±0.6	53.2±0.5	51.9±0.8
6	99.9±0.2	99.8±0.1	80.6±0.9	80.2±0.2	64.7±0.5	64.6±0.8	62.3±0.3
7			85.5±0.4	84.5±0.2	70.7±0.6	70.1±0.5	71.5±0.7
8			89.6±0.5	88.1±0.5	74.5±0.4	74.3±0.3	77.9±0.9
9			99.9±0.3	99.7±0.2	86.1±0.6	85.5±0.3	82.4±0.1
10					99.8±0.8	99.9±0.5	98.8±0.3

All the values are expressed as mean ± S.D, n=3

From the above drug release values it was observed that the F1 and F2 released the drug within 6 hrs, So, the concentration of the is not sufficient for maximum sustained release of drug. Whereas, F3, F4 released the drug within 9 hrs and F5, F6 and F7 released the maximum amount of drug within 10 hrs. As the concentration of polymer increased sustained release of drug increased.

Table 7: *In-vitro* drug release profile of Bosentan Monohydrate from sintered tablets

Temperature	Sintering duration	F1(10% stearic acid)	F2(10% carnauba wax)	F3(15% stearic acid)	F4(15% carnauba wax)	F5(20% stearic acid)	F6(20% carnauba wax)	F7(5% EVA)
50^{0}C	1hr	99.9±0.3	98.8±0.3	97.5±0.5	97.5±0.3	99.4±0.8	99.16±0.5	99.8±0.5
	2hr	98.3±0.3	98.08±0.3	97.2±0.4	97.2±0.1	98.8±0.8	98.6±0.5	98.6±0.9
	3hr	97.8±0.4	97.5±0.3	96.9±0.4	96.9±0.2	97.8±0.7	97.5±0.6	98.02±1.7
60^{0}C	1hr	98.08±0.1	98.3±0.6	89.3±0.5	89.9±0.5	88.3±0.7	88.03±0.3	99.98±0.6
	2hr	97.5±0.3	97.5±0.2	87.7±0.2	87.4±0.2	86.4±0.6	86.4±1.8	93.7±1.5
	3hr	96.9±0.1	97.2±0.3	85.8±0.3	85.3±0.3	84.7±0.4	84.2±1.9	90.4±1.4
70^{0}C	1hr	97.8±0.1	97.5±0.2	86.6±0.2	86.6±0.1	85.3±0.6	85.04±0.3	80.1±0.6
	2hr	97.5±0.2	96.7±0.5	84.4±0.1	84.7±0.3	84.2±0.5	84.2±0.4	79.06±1.4
	3hr	96.7±0.3	96.4±0.5	83.1±0.4	83.4±0.5	82.8±0.7	80.1±0.3	78.5±1.5

All the values are expressed as mean ± S.D, n=3

From the above drug release values it was observed that the F1 of stearic acid(10%) and F2 of carnauba wax (10%) sintered at 50, 60 and 70^{0}C released the drug within 6 hrs. so the concentrations of sintering polymers is not sufficient for maximum sustained release of the drug.F3 of stearic acid (15%) sintered at 50^{0}C released the drug within 9 hrs. the tablets sintered at 60^{0}C showed the drug release of 89.3, 87.7 and 85.8% and 70^{0}C showed the drug release of 86.6, 84.4 and 83.1%. It indicates that the maximum sustained release occurred at 70^{0}C 3hr sintering with the drug release of 83.1. F4 of carnauba wax (15%) sintered at 50^{0}C released the drug within 9 hrs. the tablets sintered at 60^{0}C showed the drug release of 89.9, 87.4 and 85.3% and the tablets sintered at 70^{0}C showed the drug release of 86.6, 84.7 and 83.4%. It indicates that the maximum sustained release occurred at 70^{0}C 3hr sintering with the release of 83.4% of drug.F5 of stearic acid (20%) sintered at 50^{0}C released the drug within 9 hrs. the tablets sintered at 60^{0}C showed the drug release of 88.3%, 86.4% and 84.7% and the tablets sintered at 70^{0}C showed the drug release of 85.3%, 84.2% and 82.8%. It indicates that the maximum sustained release occurred at 70^{0}C 3hrs sintering with the drug release of 82.8%. F6 of carnauba wax (20%) sintered at 50^{0}C released the drug within 9 hrs. the tablets sintered at 60^{0}C showed the drug release of 88.03%, 86.4% and 84.2% and the tablets sintered at 70^{0}C showed the drug release of 85.04%, 84.2% and 80.1%. It indicates that the maximum sustained release occurred at 70^{0}C 3hrs sintering with the drug release of 80.1%. F7 of EVA (5%) sintered at 50^{0}C released the drug within 9 hrs. the tablets sintered at 60^{0}C showed the drug release of 99.98%, 93.7% and 90.4%. the tablets sintered at 70^{0}C showed the drug release of 80.1%, 79.06 and 78.5% From the above results, it indicates that the tablets sintered at 60^{0}C for 1hr has shown 99.98% within the period of 12hrs. As further increase in sintering temperature and time the drug release was prolonged.

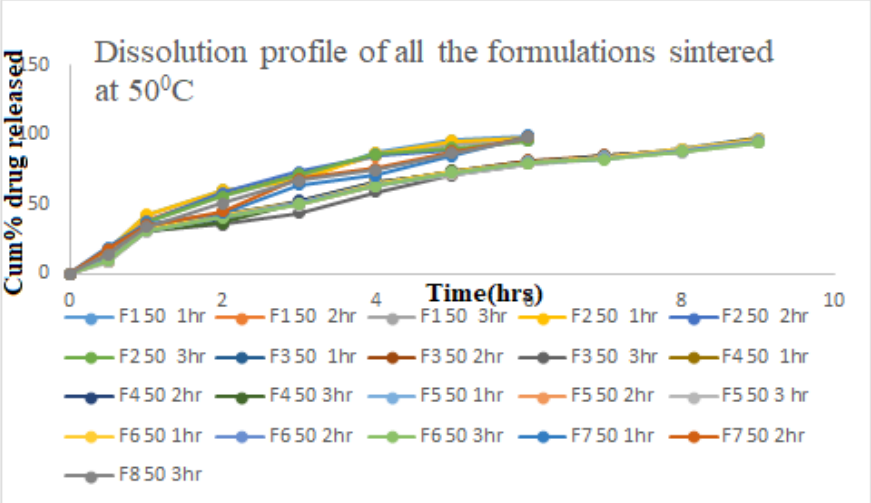

Figure 5: Cumulative % drug release of all the formulations sintered at 50^{0}C

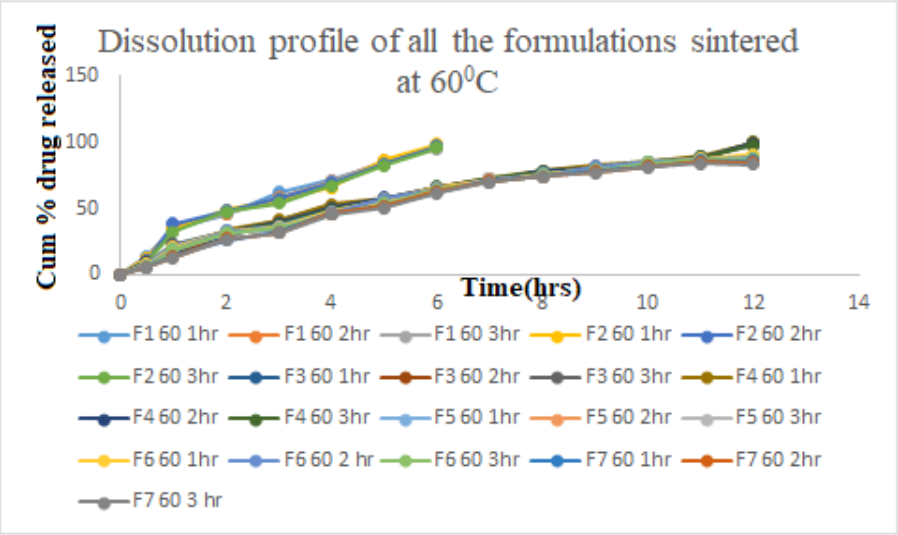

Figure 6: Cumulative % drug release of all the formulations sintered at 60⁰C

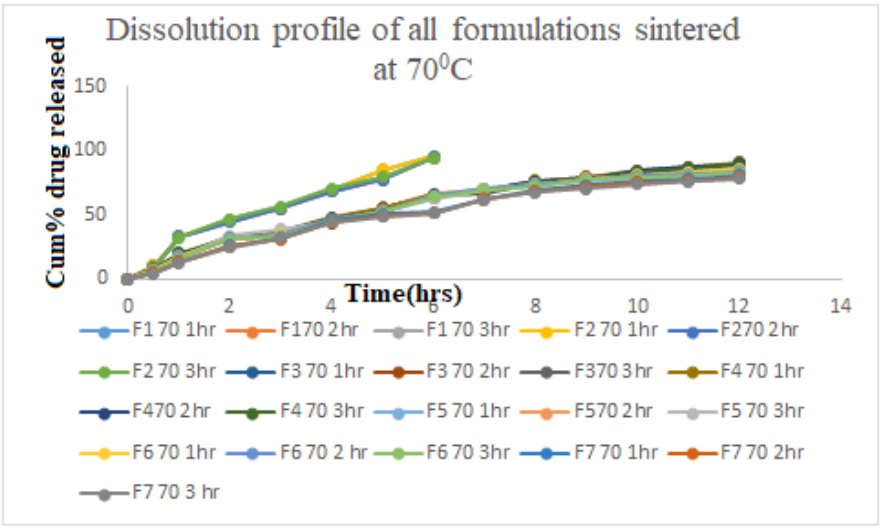

Figure 7: Cumulative % drug release of all the formulations sintered at 70⁰C

The formulations F3, F4, F5, F6, and F7 which were sintered at 60 and 70⁰C showed the good sustained release. Among these formulations F7 (5% EVA) sintered at 60⁰C for 1hr is the optimized formulation as it has showed the maximum sustained release of drug within 12hrs

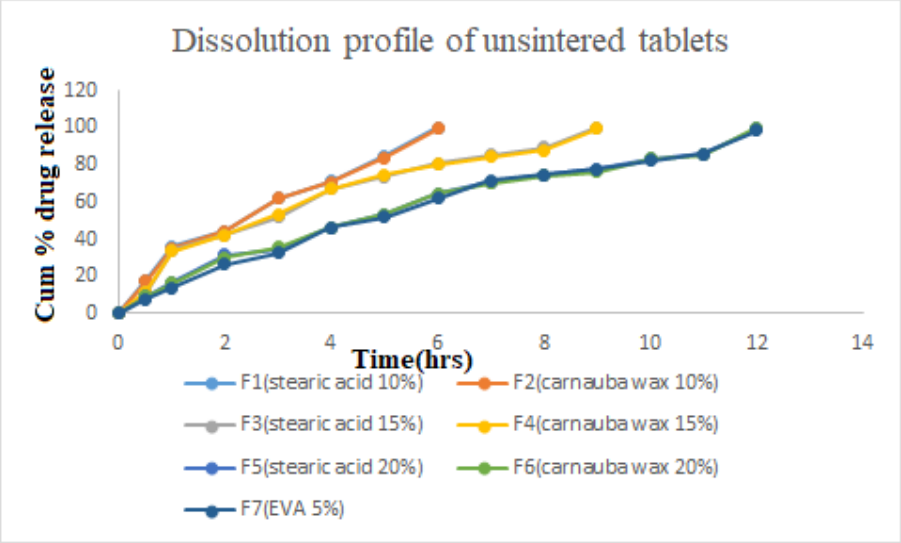

Figure 8: Cumulative % drug release of all the unsintered formulations

Comparison of optimized formulation with marketed formulation

The formulations F3(15% stearic acid), F4(15% carnauba wax),F5(20% stearic acid), F6(20% carnauba wax), F7(5% EVA) sintered at 70^0C were compared with marketed formulation (Bosentas – 62.5mg manufactured by Cipla).

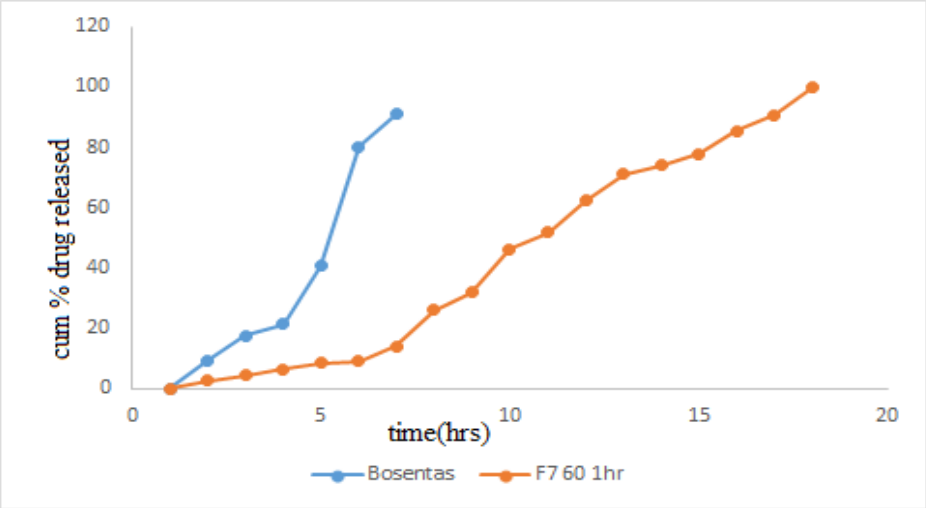

Figure 9: Comparison of optimized formulation with marketed formulation

From the above graph, it can be concluded that the marketed tablet(Bosentas) is showing 91% drug release in 1hr, whereas F7(60^0 1hr sintering) 99.8% drug release in 12 hrs.

Drug-Excipient Compatibility studies

Fourier transform infrared spectroscopy (FTIR)

FTIR analysis revealed that there was no interaction between the drug and the polymers. The FTIR spectra of the pure drug and formulation indicated that the characteristic peaks due to pure

Bosentan monohydrate have appeared in tablets and the positions of characteristic peaks of Bosentan were not altered after their successful transformation into tablets, suggesting the absence of interactions between the drug and other components of the formulation indicated the stability of drug during formulation process.

Phenomenon of Drug Release Kinetics

The profile of drug release can be known by plotting Zero order and First order kinetic plots. The mechanism of drug release of Bosentan monohydrate was determined by the application of Korsmeyer – Peppas model and Higuchi model.

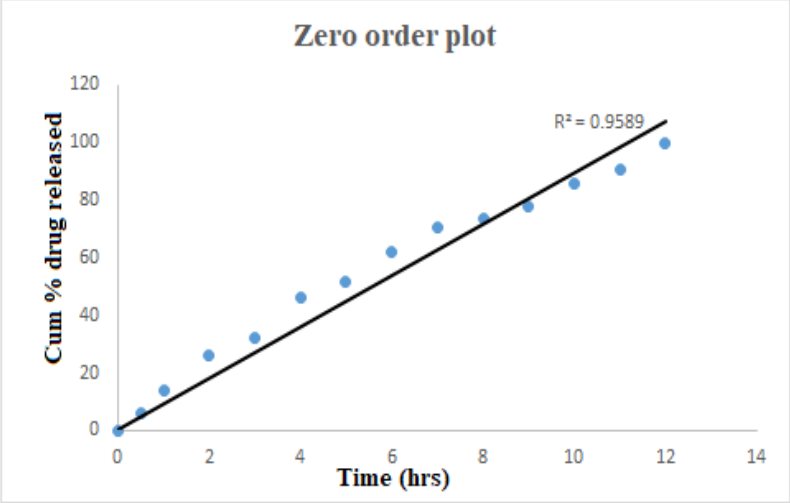

Figure 10: Zero order plot of F7 sintered at 60^{0}C for 1hr

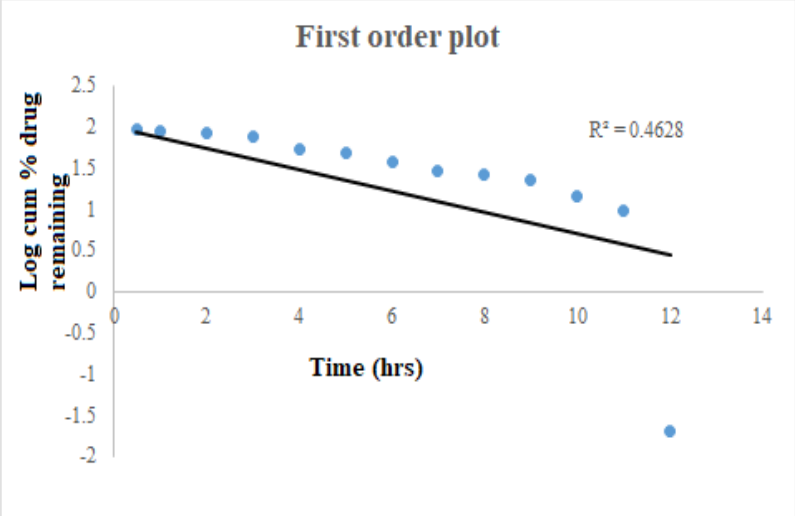

Figure 11: First order plot of F7 sintered at 60^{0}C for 1hr

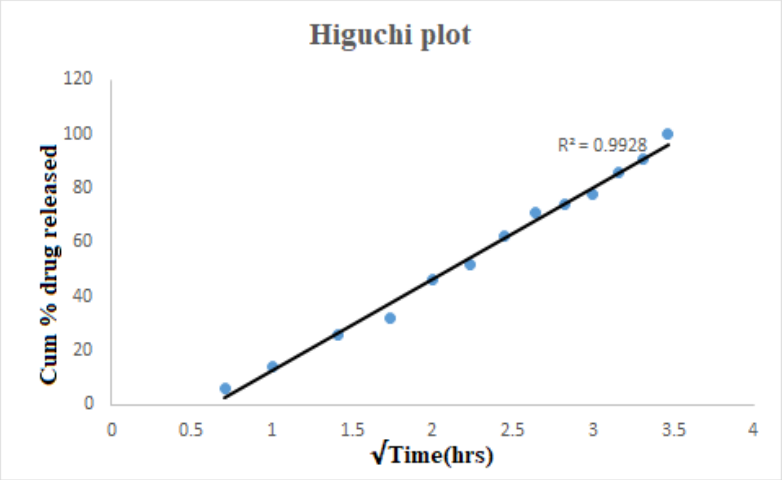

Figure 12: Higuchi plot of F7 sintered at 60^{0}C for 1hr

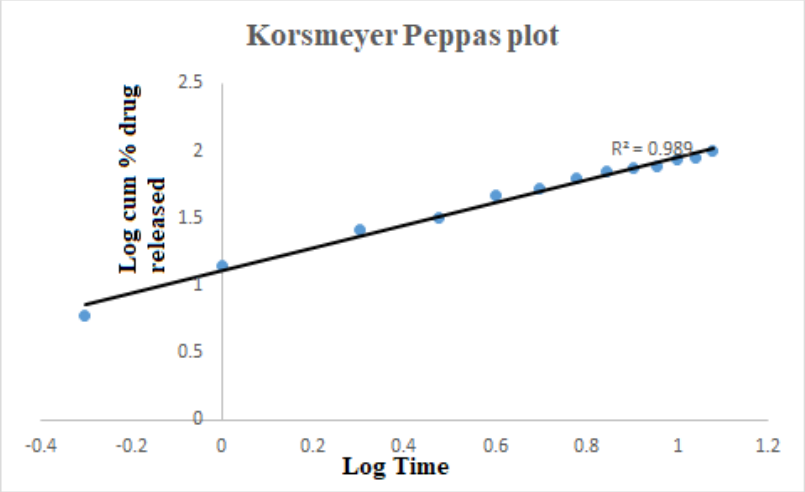

Figure 13: Korsmeyer Peppas plot of F7 sintered at 60^{0}C for 1hr

Table 8: Correlation values of the optimized formulation

Formulation	Zero order	First order	Higuchi	Peppas
F7 (EVA5%)	0.9589	0.4628	0.9928	0.989

Table 9: Post compression parameters after stability studies

Time	Physical appearance	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Cumulative % drug released	Drug content
Before stability	White in colour	119.43±0.26	5.5±0.4	0.21±0.4	99.98±0.3	99.8±0.4
After 1 month	No change was observed	119.45±0.31	5.22±0.5	0.32±0.6	98.35±0.2	98.2±0.3
After 2 months	No change was observed	119.51±0.61	5.33±0.2	0.38±0.8	96.45±0.4	96.3±0.5
After 3 months	No change was observed	119.53±0.5	5.35±0.6	0.41±0.9	95.63±0.5	95.3±0.2

DISCUSSION

Bosentan monohydrate is having poor solubility in acidic pH and as the pH increases, the solubility of the drug increases. It is having the high intestinal absorption due to alkaline pH. By preparing sustained release tablets of Bosentan monohydrate, its bioavailability ca be enhanced. Bosentan monohydrate is having high melting point of 108^0C which is best suitable for thermal sintering technique. When the tablets were exposed to higher temperatures like 50, 60 and 70^0C for 1,2 and 3hrs, the polymer will melt enclose the drug by forming pores. By this mechanism the controlled release property has been enhanced.

From the obtained results it was proved that thermal sintering was the best method to obtain Sustained release dosage form. The polymer melts at high temperature and forms matrix entrapping the drug molecule. The formation of matrix in sintering depends both on temperature and time of exposure of tablets. As both increase the stronger matrices will be formed prolonging the drug release.

As the Gastric emptying time plays an important role in the release of drug from dosage the formulation containing EVA 1802 sintered at 60^0C for 1hr was opted as best formulation. As it has released 99.98% of drug within a period of 12hrs. Hence good therapeutic window can be achieved.

Among all the formulations F7(60^0C 1hr sintering) had shown the best sustained release of 99.98%. Hardness increased with increase in sintering temperature and duration of exposure, whereas friability decreases with increase in sintering temperature and time of exposure. From the literature review it can be observed that few works have been done on Bosentan monohydrate viz, mucoadhesive microspheres, matrix tablets, mini tablets, transdermal patches and solid dispersions to increase the solubility and bioavailability. Previously the anti-hypertensive like Propranlol, Carvidilol and Tapentadol sustained release tablets were prepared by thermal sintering technique.

Samra Rumman*et. al.*, developed different formulations of Tapentadol Hydrochloride sintered tablets using sustaining polymer-eudragit RL-100, sintering waxes-stearic acid and carnauba wax, disintegrating agent-microcrystalline cellulose, glidant-talc and lubricant-magnesium stearate by direct compression method. The prepared tablets were exposed to temperatures 40^0 C and 60^0 C to sinter at three different time durations of 1, 2 and 3 hours. The pre compression and post compression studies results were found to be within the limits. The drug release from optimized formulation (F17-Tapentadol Hydrochloride with stearic acid and carnauba wax sintered at 60^0C for 2 hours) was found to be 100.38% in 12 hours. when compared to the tablets prepared by

stearic acid and carnauba wax as sintering polymers, EVA 1802 showed the better sustained release of drug.

Satish Polshettiwar*et, al.,* developed different formulations of gastroretentive drug delivery system of carvdilol by sintering technology. The polymers like HPMC K4M, Eudragit L 100, Guar gum, Sodium bicarbonate, Citric acid were utilized in the formulation of matrix tablets containing Carvedilol phosphate by direct compression[17]. Granules were prepared and evaluated for bulk density, tapped density, compressibility index and angle of repose shows characteristic results. The tablets were placed on the aluminum foil and subjected to thermal treatment at 60, 70 and 80^{0}C for 1.5, 3, 4.5 hrs in hot air oven. On thermal sintering, it was found that F6, L2, I2 and H4 gave better results compared to other formulations. Therefore thermal sintering was optimized based on loading dose release and sustain action. All the tablet formulations showed control properties like hardness, thickness, friability, weight variation, drug content uniformity etc. and complied with in the specifications for tested parameters. Based on the FT-IR studies, there appears to be no possibility of interaction between Carvedilol phosphate and polymers/other excipients used in the tablets. The XRD study results revels that the powder characteristics were same as that of standard one after stability. Thus stability results prove that the formulation was stable at accelerated condition.

So, owing to the above literature and past works Thermal sintering technique can be applied for selected API i.e Bosentan monohydrate, as there is no sintering was applied previously to this drug. Stearic acid, carnauba wax and EVA 1802 were selected as sintering polymers. The formulation F7 containing EVA 1802 sintered at 60^{0}C for 1hr showed better results and improved bioavailability as drug is more absorbed from the intestine. As mentioned earlier the drug is more soluble at that pH. Hence, the objective of current work can be achieved.

CONCLUSION

Bosentan monohydrate is a dual endothelin receptor antagonist. It is used in the treatment of Pulmonary Arterial Hypertension (PAH). Bosentan monohydrate sustained release tablets were prepared by direct compression and wet granulation technique and then subjected to thermal sintering. Thermal sintering technique is a method of heating polymer matrix in a heating furnace at a temperature below the melting point of main constituent for the purpose of increasing its bond strength. In this process the polymeric particles undergo fusion of welded bonds between the particles and completely encloses the drug. As Bosentan is having the high intestinal absorption, by preparing sustained release tablets of Bosentan monohydrate, its bioavailability ca be enhanced. Only the drugs which are having the high melting point are selected for using thermal sintering

technique. As Bosentan is having melting point of 108^{0}C, it is used in the preparation of Sustained release tablets of Bosentan monohydrate using Thermal sintering technique. Previously the Anti hypertensives like Propranlol and Tapentadol sustained release tablets were prepared by thermal sintering technique.

Among all the formulations F7(60^{0}C 1 hr sintering) got good the results in Preformulation studies. The angle of repose was 24.45, Hausner's ratio is 1.08 Compressibility index is 8.81 which indicates the good flowing properties. From the FTIR studies it was observed that there is no interaction between the drug and excipients.

The tablets were prepared by using Eudragit, stearic acid and carnauba wax of 10%, 15% and 20% by direct compression and EVA 1802 (5%) by Wet granulation method. Prepared tablets were sintered at 50^{0}C, 60^{0}C and 70^{0}C for 1hr, 2hr and 3hrs. The tablets were evaluated for Hardness, Friability, weight variation and *In-vitro* drug release studies before and after sintering. The release rate of the drug was inversely related to the sintering temperature and the time of sintering. Hardness increases with increase in sintering temperature time of exposure. Friability decreases with increase in sintering temperature and time of exposure. All the results were within the limits of official compendia. Hence, all these above parameters aid in prolonged drug release. Hence F7(EVA 5%) sintered at 60^{0}C for 1hr is selected as best formulation as it showed the maximum sustained release of 99.98% keeping in view of gastric emptying time. 'r' value is more for Zero order 0.9589 than the First order 0.4628. the 'n' value for the Peppas plot was calculated, which was found to be 0.74 which indicates the Non Fickian diffusion. From the kinetic profile it shows that the drug release followed Zero order and Non fickian diffusion with erosion mechanism. From the stability it was observed that the F7(60^0 1hr sintering) was stable for 3 months under standard conditions. Thus F7(60^0 1hr sintering) was considered to be the best formulation among all the 7 formulations sintered at various temperatures and various time periods. Further increase in sintering temperature and time prolonged the drug release Hence it shows the suitability of EVA polymer for applying Thermal sintering technique. By this technique dose and dosing frequency can be reduced and Bosentan can be taken as once a daily tablet. Hence Sintering can be applied for preparing various dosage forms like Gastroretentive drug delivery systems, Controlled release and Sustained release dosage forms.

Finally it can be concluded that the aim of current research work i.e Formulation and Evaluation of Bosentan monohydrate Sustained release tablets using Thermal Sintering

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AUTHORS' CONTRIBUTIONS

We here by submit a manuscript entitled: "Formulation and Evaluation of Bosentan monohydrate sustained release tablets using Thermal sintering technique" author by P.Madhuri*, Dr. K.V Ratnamala for consideration for publication as a research paper in the American Journal of Pharmtech Research. P.Madhuri carried out the whole experiment and Dr. K.V Ratnamala designed the whole research work and carried out the supervision of experiments.

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