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Formulation and Evaluation of Sustained Release Pellets of Antihypertensive Drug

Jatin Dubey[1], Lokesh Kumar Gautam[2], Vaibhav Khatri[3], Vikas Agarwal[4], Manoj Kumar Gupta[5]

[1]Research Scholar, Jaipur College of Pharmacy, Jaipur
[2]Professor, Jaipur College of Pharmacy, Jaipur
[3]Manager, Department of Formulation and Development, Gracure Pharmaceutical Ltd
[4]Professor, Jaipur College of Pharmacy, Jaipur
[5]Assistant Professor, Jaipur College of Pharmacy, Jaipur

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Corresponding author: Jatin Dubey
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Abstract:

Objective: The aim of the present study was to formulate sustained-release pellets of bosentan by eudragit RL 100 and RS 100, which are the polymers used in the pan coating technique.

Methods: The sustained release pellets of bosentan were formulated by pan coating method. The drug was coated on nonpareil seeds along with EudragitRL100 by solution layering technique. Drug-loaded pellets were coated with EudragitRS100. The prepared pellets were evaluated for moisture content, drug content, particle size, and in vitro drug release. Stability studies were carried out on the optimised formulations for a period of 6 mo.

Results: The drug content was in the range of 98.89±0.32. The mean particle size of the drug-loaded pellets was in the range of 835 μm. The drug release rate decreased as the concentration of eudragit increased in the pellet formulations. Among the prepared formulations, PC 4 showed
89.35±0.52 drug release in 12 h from a good linear relationship was established between model-independent approaches (T25%, T50%, and T100%) and weight gain in coating. This indicated the possibility of extending the drug release by increasing the weight gain in the coating, and hence, it was proposed to extend the drug release for 24 h. From the prepared pellets, the optimised formulation PC 12 showed a 100.02±0.03 drug release in 24 h. Furthermore, these pellets were filled into capsules and compared the dissolution studies. The compatibility between drugs and polymers in the drug-loaded pellets was confirmed by DSC and FTIR studies. Stability studies indicated that the pellets were stable**.**

Conclusion: The prepared pellets were capable of releasing the drug for 24 h to treat the Pulmonary Arterial Hypertension.

Keywords: Pellets, Pan coating, Eudragit, Bosentan, Independent model.

Introduction

Pulmonary arterial hypertension is a severe condition marked by an increase in pulmonary vascular resistance, which can lead to right ventricular failure [1]. Scleroderma patients can develop pulmonary arterial hypertension in up to

50% of cases [2]. Long-term anticoagulant therapy and calcium-channel blocker therapy are two of the few oral treatment choices, the latter improves survival in a small number of individuals [3, 4]. Continuous intravenous infusion of epoprostenol (prostacyclin) has been shown to have beneficial effects, but it also has limitations [5].

The effectiveness of epoprostenol analogues that can be inhaled (e. g., iloprost) or given orally (e. g., beraprost) is still determined [5-7]. Endothelin-1 appears to play a harmful role in pulmonary arterial hypertension, with evidence that blocking endothelin receptors may be helpful [8, 9]. Endothelin-1 is a powerful endogenous vasoconstrictor and smooth-muscle mitogen that is overexpressed in patients with primary pulmonary hypertension and scleroderma's plasma and lung tissue. Two receptors, ETA and ETB, are involved in its activities [5]. Bosentan is the first Endothelin Receptor Antagonist (ERA) to be used successfully in the treatment of Pulmonary Artery Hypertension (PAH). It is a non-peptide, orally active, dual endothelin receptor antagonist [10].The drug of choice in this study was bosentan its oral bioavailability is 50% [11], biological half-life is 5 h [12]. Due to low bioavailability and less biological half-life need to be given frequent administration to maintain plasma levels effectively. Hence, the drug works best when plasma fluctuations are kept to a minimum; the sustained- release dosage form of bosentan is appealing, which makes it ideal for the development of sustained-release formulations.

Materials and Methods

Aurobindo Pharma, Hyderabad, provided a complimentary sample of bosentan. This study employed isopropyl alcohol, acetone and dibutylphthalate, which were purchased from Qualigens chemicals, India. Eudragit RL100 and eudragit RS100 were purchased from Loba Chemicals, India. All other chemicals were of analytical grade. Prior approval by the Institutional Animal's Ethics Committee was obtained for conducting the experiments (IAEC/BS/22/CLPT/dated: 08-05-2023).

Calculation of initial dose and maintenance dose for the design of sustained release DDS of bosentan for 12 h.

There are no sustained release formulations for bosentan in the market; hence the total dose (DT) consisting of initial (DI) and maintenance doses (DM) for formulating the bosentan sustained release was calculated as per Robinson and Eriksen equation with zero order release principle [13-15].

Preparation of drug-loaded pellets

200 g of Nonpareil®-101 seeds (purified sucrose, starch, grade 20- 24) were sieved through ASTM #20, #25 (841 µm, 710 µm respectively) and placed into a coating pan (VJ instruments). Bosentan was accurately weighed (74 g) and dissolved in 200 ml of isopropyl alcohol-acetone (50:50) by slow addition and continuous stirring. Eudragit RL100 (3.5 g) was weighed and dissolved in the above solution with constant stirring (100 rpm) by using paddle stirrer (Remi RQ-121/D, Mumbai, India). This drug solution was sprayed completely on to Nonpareil seeds by solution layering technique in a coating pan. The composition of the coating solution is shown in table 2.

Table 1: Predicted theoretical drug release profile

Time (h)	Cumulative % drug release
1	16
2	23

3	30
4	37
5	44
6	51
7	58
8	65
9	72
10	80
11	88
12	96

Preparation of polymer solution

10% coating solution was prepared by using eudragit RS100 (10 g) in isopropyl alcohol and acetone (50:50) with continuous stirring (100 rpm) by using paddle stirrer (Remi RQ-121/D, Mumbai, India) for about 15 min and dibutyl phthalate (2 g) was added and continued stirring for another 10 min. The concentration of plasticizer is 20% of polymer concentration, which was decided based on the pre trials conducted. The composition of the coating solution is shown in table 3.

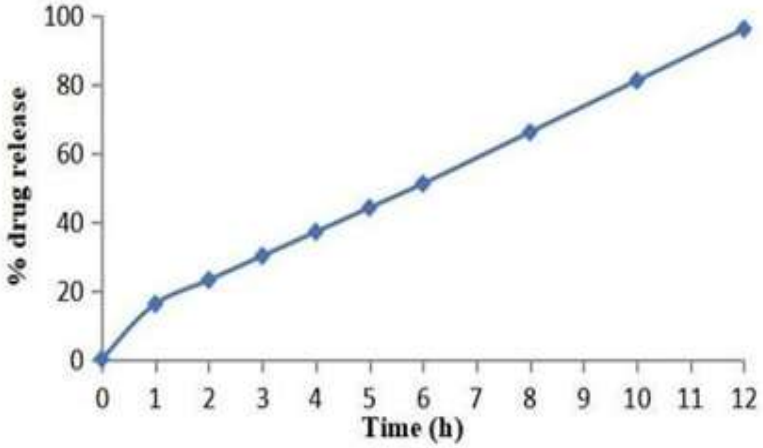

Fig. 1: Predicted theoretical release profile

Coating of drug loaded pellets with polymer solution

Drug coated pellets 277.5 g were charged in to conventional coating pan with diameter 375 mm. Different coating loads containing 10% coating solution was sprayed by solution layering technique with an intermittent spraying and drying time of 15-20 min in a coating pan until target weight was achieved. After coating, the pellets were further cured at 40 °C at 75% RH for 24 h.

The coating parameters used for coating the drug-loaded pellets were optimized with pre trials. The final composition of drug-loaded pellets coated with different % weight gain is shown in table 4.

Table 2: Composition of drug-loaded pellets

Ingredients	PC1	PC2	PC3	PC4	PC5	PC6

Bosentan (mg)	74	74	74	74	74	74
Eudragit RL100 (mg)	3.5	3.5	3.5	3.5	3.5	3.5
Nonpareil seeds (mg)	200	200	200	200	200	200
Isopropyl alcohol-acetone (1:1)(ml)	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Total weight (mg)	277.5	277.5	277.5	277.5	277.5	277.5

Table 3: Composition of coating solution

Ingredients	Quantities
Eudragit RS100 (gm)	10
Dibutyl phthalate (ml)	2
Isopropyl alcohol: Acetone (1:1)	Up to 100 ml

Table 4: Composition of polymer-coated pellets

Ingredients	PC1	PC2	PC3	PC4	PC5	PC6
Drug-loaded pellets (mg) containing 74 mg of bosentan	277.5	277.5	277.5	277.5	277.5	277.5
Weight of coat applied (%)	2.5	5	7.5	10	12.5	15
Total weight (mg)	284	291	298	305	312	319

Evaluation of coated pellets

The resulting pellets were assessed for percent yield, drug content estimation, moisture content, angle of repose, bulk density, tapped density, friability, and particle size before being tested in vitro.

Calculation of percent yield: The percentage yield is the difference between the actual quantity of coating applied to the pellets and the theoretical amount of coating applied. It might be the result of too much soaking or drying. A yield of greater than 90% was considered satisfactory. The % yield was calculated using the formula [16].

%yield= Practical yield of pellets ×100

Theoretical yield of pellets

Estimation of percent drug content: 100 mg of pellets were weighed and pulverised in total. The powder was completely dissolved in 100 ml of methanol: 0.1N HCl (60:40). The absorbance was measured using a UV spectrophotometer at 272 nm against a blank after the sample was filtered and diluted properly. The proportion of drug content was calculated. The experiment was carried out three times, with the average findings being recorded [17].

Moisture content

The residual water content in the coated pharmaceutical pellets was measured using a Karl Fisher titrator.

Crushed pellets totalled 3 g. Then, 0.5 g of the test sample was transferred to the titration tank of the Karl Fisher titrator and titrated to the endpoint with Karl Fisher reagent. Using the equation below, the moisture content was calculated [18].

% Moisture content = V×F×100

Weight of sample in mg

Where V= Volume in ml of Karl Fisher reagent consumed for sample titration.

F= Factor of Karl Fisher reagent.

Determination of micromeritic properties of coated drug pellets

Angle of repose, bulk density, and tapped density of the coated pellet s were all evaluated [19].

Angle of repose

Pellet flow parameters were studied using the fixed funnel and free- standing cone techniques [20].

Tan θ = (h)⁄r

Bulk density

Bulk density is defined as the quantity of powder/granules divided by the volume of the loose powder bed/granules. The unit volume refers to both the space between the particles and the envelope volume of the particle. The bulk density was estimated using a graduated cylinder technique [21].

Bulk density= M/Vb

Tapped density

The tapped density is the ratio of the mass of the powder/granules to the volume occupied by the powder after a particular number of taps. The tapping density of the pellets shows their dense random packing.

Tapped density= M/Vt

Friability

Pellets must be durable enough to survive the physical pressures of manufacture and transportation. 6.5 g of coated pellets samples were pre-weighed in the Roche friabilator's spinning chamber.

Pellets were subjected to 100 six-inch falls (25 rpm for four minutes). After the rotation was complete, the pellets were dedusted and reweighed. The percentage of friability was calculated using this formula [22].

% Friability = (Wo-W)/Wo×100 Where W0 = Initial weight (gm)

W = Final weight after rotation (gm).

Particle size determination

The average particle size of pellets was determined using sieve analysis. The sample collection and sieves were layered with the biggest mesh apertures on top and the smallest mesh apertures below. A sieve shaker was filled with 100 g of coated pellets and a series of sieves (#14, #16, #18, #20, #25). All of the sieves were removed after ten minutes, and the weight of the retained pellets on each sieve was determined. On each filter, the average particle size and % weight retained were determined [23].

In vitro dissolution study

The USPXXIV apparatus was used to investigate the in vitro dissolving of pellets. The first two hours of dissolving were done in 900 ml of 0.1N HCl, followed by the remaining hours in pH 6.8 phosphate buffer. The temperature in the centre was adjusted at 37

°C+0.5 °C. In the dissolving vessel, bosentan pellets containing 74 mg were inserted with the paddle moving at 50 rpm. 5 ml of material was collected at predetermined intervals and replaced with the same volume of fresh media. The samples were filtered using a 0.45 m membrane filter.

The samples were examined using a UV spectrophotometer. The drug release experiments were repeated three times, with the average cumulative percentage of drug released being recorded each time. Drug release from a commercial immediate-release formulation of bosentan tablet (Bosentas 62.5, a product of Cipla, India, Batch No: G28257, Mfg. Date: 12/2022, Exp. Date: 11/2024) was examined using 900 ml of 0.1 N HCl as the dissolving medium [24].

Establishment of drug release kinetics and mechanisms

The amount of medication released from pharmaceutical dosage forms and the methods by which it is released are crucial but difficult processes that are readily apparent in matrix systems.

Zero-order [25] or first-order kinetics [26, 27] were used to characterise the sequence of drug release from matrix systems. The Higuchi diffusion model [28] and the Hixon-Crowell erosion model [29] were used to investigate the mechanism of drug release from matrix systems. The Korsmeyer-Peppas equation was also utilised to distinguish between Fickian/non-Fickian/ anamolus drug release mechanisms [30, 31]. The release exponent 'n' value is used to define distinct release processes for a dosage form, according to the Korsmeyer-Peppas equation.

Stability studies of the optimized formulations

The study employed the ICH's Zone VI guiding principles. The capsules were kept in a polyethylene-lined aluminium container. The aluminium pack was then securely closed. The pack was stored in a humidity chamber for at least 6 mo, with the temperature set at 302 °C/705% RH for long-term conditions and 402 °C/755% RH for expedited settings. The product is considered stable when no significant changes are discovered during stability tests. 6 mo of stability data is sufficient for long-term research where there is no discernible change under accelerated conditions2. Moisture content, drug content, and an in vitro dissolution investigation were all performed on the samples [32].

In vivo evaluation of bosentan sustained release pellets and commercial product

Drug development currently includes bioavailability and pharmacokinetic investigations of newly discovered formulations. The researchers' goal is to investigate the bioavailability of the newly produced formulations [33].

Products tested for in vivo evaluation

The following products were studied in vivo pharmacokinetically.

Product 1: Commercial immediate-release bosentan tablet (reference formulation) (Bosentan 62.5, Cipla).

Product 2: (Test formulation): Bosentan pellets (FC6) similar to 3.2 mg/kg rabbit dose [34].

Experimental design for pharmacokinetic evaluation

Adult male albino rabbits weighing 2.5±0.56 kg were taken. The rabbits were kept in normal cages in an animal room with air, humidity, and temperature control, as well as a 12-hour light/12 h dark cycle. Rabbits were given free access to ordinary home chow and water. The animals were admitted to the animal house conditions at least one week before the inquiry began.

Three groups of rabbits were formed, each with two rabbits. The trial was repeated three times using a one-week washout interval between treatments and a single dosage crossover design. Before receiving the experimental formulations, the rabbits were fasted for at least 10 h (overnight). One hour after receiving the experimental formulations, they were permitted to drink water. Four hours after the medicine was administered, the animals were given access to the diet.

Pharmacokinetic evaluation of the selected products

A wooden rod was put between the rabbit's jaws to prevent the mouth from closing, and a gastric intubation tube (4 mm) was introduced into the stomach.

Group I administered a 2 ml suspension of commercial tablet powder followed by a 10 ml water wash. Group II took FC6 pellets that were comparable to the rabbit's dosage and were rinsed down with 10 ml of water. The treatments were repeated in all of the groups with a one-week washout period in between.

Collection of blood samples: Approximately 0.8-1.0 ml of blood was taken from rabbits' marginal ear veins and placed in pre-labeled 2 ml K2 EDTA-coated tubes. Blood samples were taken at regular intervals before and after the dosage. We took samples at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h. After collection, the blood samples were centrifuged at 3000 rpm for 10 min. The supernatant plasma was separated and kept at-20 °C until analysis in appropriately labelled containers. 250 litres of plasma were collected and estimated.

Assessment of pharmacokinetic parameters

Using plasma drug concentration data, non-compartmental analysis was used to calculate all relevant pharmacokinetic parameters such as peak plasma concentration (Cmax), time at which Cmax occurred (Tmax), elimination rate constant (Kel), biological half-life (t1/2), absorption rate constant (Ka), area under the curve (AUC), and mean residence time (MRT).

The plasma concentration-time profile was used to determine the maximum plasma concentration (Cmax) and time to attain maximum plasma concentration (Tmax).

Results and Discussion

Table 5: Evaluation parameters of bosentan pellets

Batch	% Yield	%Drug content	Moisture content (%)	Angle of repose (˚)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Friability (%)	Cumulative (%) drug release
PC1	92.78±0.32	87.51±0.25	2.21±0.12	10.18±0.06	0.78±0.015	0.80±0.025	0.04	99.72±0.62
PC2	93.71±0.21	90.97±0.14	2.11±0.21	10.38±0.12	0.71±0.009	0.86±0.091	0.05	99.82±0.05
PC3	93.79±0.22	89.94±0.11	2.42±0.14	11.22±0.14	0.79±0.004	0.86±0.004	0.03	99.72±0.51
PC4	94.81±0.15	98.97±0.24	2.19±0.11	09.44±0.21	0.81±0.023	0.81±0.011	0.03	97.84±0.23
PC5	91.71±0.64	92.05±0.14	2.37±0.15	09.54±0.13	0.79±0.004	0.88±0.012	0.04	99.96±0.14
PC6	93.73±0.35	91.86±0.14	2.19±0.13	10.18±0.11	0.73±0.022	0.84±0.022	0.05	98.32±1.25

Values are expressed in (mean±SD, n=3)

Model-independent approaches: A good linear relationship was established between model- independent approaches (T25%, T50% and T100%) and % weight gain in coating. This indicated the possibility of extending the drug release by increasing the %weight gain in coating and hence, it was proposed to extend the drug release for 24 h. accordingly, the initial and maintenance doses of bosentan were calculated employing the similar approach adopted for 12 h release.

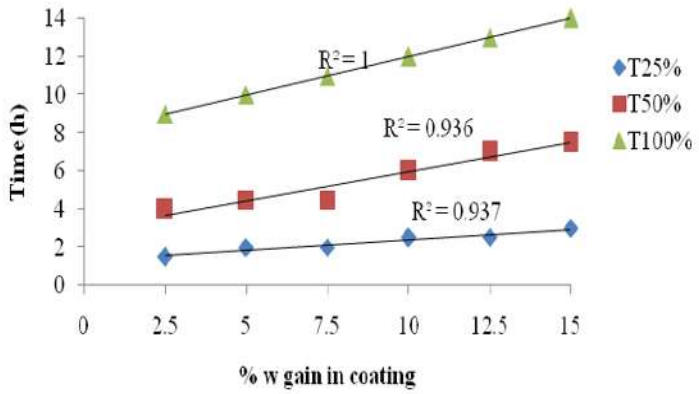

Fig. 2: Relationship between T25%, T50%, T100% and % weight gain in coating

Calculation of initial dose and maintenance dose for the design of sustained release drug delivery systems of bosentan for 24 h

The initial (DI) and maintenance doses (DM), was calculated using th e Robinson and Eriksen equation with the zero- order release principle according to above procedure [13-15]. The obtained initial dose = 37.44 mg

Maintenance dose (DM) =123.84 mg
Corrected initial dose (DI*) =11.64 mg

Total dose = DI+DM = 11.64+123.84 = 135.48 mg.

Method of preparation

Based on theoretical predictions, Nonpareil seeds (200 mg) will be coated with 135 mg of the drug and 3.5 mg eudragit RL100 i.e., 338.5 mg (equivalent to 135 mg of bosentan dose). The drug-loaded pellets will be coated with 10% eudragit RS100 polymer solution with plasticizer dibutyl phthalate to achieve a percentage weight gain in coating in the range of 17.5-30%. The formulation will be optimized based on drug release for 24 h. Coated pellets equivalent to 135 mg (based on drug content) from optimized formulation will be filled in to a suitable size of capsule.

Table 6: Predicted theoretical release profile

Time (h)	Cumulative % drug release
1	8
2	12
4	20
6	28
8	36
10	44
12	52
14	60
16	68
18	76
20	84
22	92
24	100

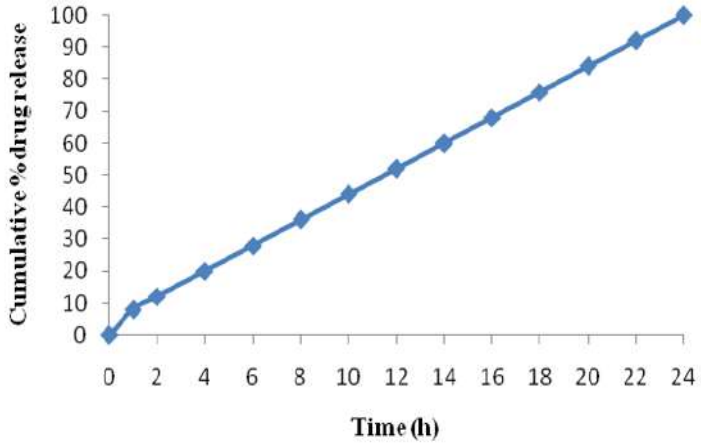

Fig. 3: Predicted theoretical profile

Table 7: Composition of drug-loaded pellets

Ingredients	PC7	PC8	PC9	PC10	PC11	PC12
Bosentan (mg)	135	135	135	135	135	135
Eudragit RL 100 (mg)	3.5	3.5	3.5	3.5	3.5	3.5
Nonpareil seeds (mg)	200	200	200	200	200	200
Isopropyl alcohol-acetone (1:1)(ml)	q. s.	q. s.	q. s.	q. s.	q. s.	q. s.
Total weight (mg)	338.5	338.5	338.5	338.5	338.5	338.5

Table 8: Composition of polymer coated pellets

Ingredients	PC7	PC8	PC9	PC10	PC11	PC12
Drug loaded pellets (mg) containing 135 mg of bosentan	338.5	338.5	338.5	338.5	338.5	338.5
Weight of coat applied (%)	17.5	20	22.5	25	27.5	30
Total weight (mg)	397	406	414	423	431	440

Evaluation of coated pellets

The resulting pellets were assessed for percent yield, drug content estimation, moisture content, and angle of repose, bulk density, tapped density, friability, and particle size before being tested in vitro.

Results and Discussion

Percentage Yield

Among all formulations, PC12 has achieved highest percent yield (96%) and PC11 has achieved lowest percentage yield (90%) which indicated that every formulation has received satisfactory level of coating.

Drug content

Drug content of pellet formulations (PC7-PC12) was found to be 85 to 98%, which revealed that the drug content was within the limits prescribed by I. P.

Moisture content

Percentage moisture content values for all the prepared coated pellets were found to be in the range of 1.25% to 2.47%. From the results no significant percent moisture content was observed.

Micromeritic properties: The bulk density tapped density for all the formulations were found to be less than 2 g/cm3. The angle of repose values were in the range of 11.48° to 19.32°. The results of the micromeritic

properties indicated excellent flow properties for pellets, which may be due to the spherical shape of the pellets.

Friability: The percentage weight loss in the friability test was found to be less than 1% for the all the formulated batches. It indicated the ability of the pellets to withstand abrasion in packing, handling and shipping. The evaluated test observations are shown in table 9.

Table 9: Evaluation parameters of bosentan pellets

Batch	% Yield	Drug content (%)	Moisture content (%)	Angle of repose (°)	Bulk density (g/cm3)	Tapped density (g/cm3)	Friability (%)
PC7	91.82±0.23	87.05±0.63	1.25±0.11	14.32±0.24	1.82±0.008	1.36±0.008	0.5
PC8	93.76±0.35	85.67±0.52	2.47±0.14	11.48±0.15	1.76±0.025	1.87±0.025	0.4
PC9	94.76±0.24	89.70±0.21	2.25±0.13	15.88±0.28	1.80±0.003	1.62±0.011	0.8
PC10	96.80±0.65	90.21±0.13	2.47±0.15	19.52±0.16	1.72±0.007	0.80±0.009	0.7
PC11	90.72±0.81	91.51±0.21	2.25±0.11	16.65±0.13	1.75±0.004	1.81±0.008	0.8
PC12	96.92±0.47	98.89±0.32	2.46±0.14	19.29±0.22	1.74±0.012	0.98±0.077	0.9

Values are expressed in (mean±SD, n=3)

Particle size determination

According to experimental findings the average particle size was found to be 835 µm. Overall, 90% of the pellets were obtained in the desired particle size range proving that the process is very reproducible.

In vitro dissolution studies: In vitro dissolution studies showed that 5-10% of drug was released in one hour. The results indicated that increased coating weight decreased the drug release [24]. This was observed in all the formulations. The formulations PC7, PC8 coated with 17.5%, 20% of weight gain pellets released 25% of the drug within 2 h. Formulations PC9, PC10 coated with 22.5%, 25% of weight gain pellets released 25% of the drug in 4-5 h. Formulations PC11, PC12 coated with 27.5%, 30% of weight gain pellets released 25% of the drug in 5-6 h.

Drug release kinetics

The zero and first order correlation coefficient (r) values of PC7 to PC12 are presented in table 10. In all the cases the appropriate correlation coefficient (r) values were in favor of zero order release rather than the first order release [25].

Optimization of formulation

Based on physical properties like friability, drug content and % yield formulation PC12 showed high desirable values, which indicated more suitability of formulation for extending the drug release over a period of 24 h. The dissolution profile of optimized formulation was compared with the theoretical profile. Comparative release profile is shown in table 12 and fig. 5. To confirm the matching of dissolution with the theoretical profile f1 and f2 values were calculated.

Optimized formulation f1 was<15 and f2 value was more than '50' (table 9) indicating the similarity between the optimized formulation and theoretical profile. The results clearly indicated that the optimized formulation followed zero order release kinetics with diffusion mechanism as per the predicted theoretical release rate confirming the suitability of the predicted theoretical release profile.

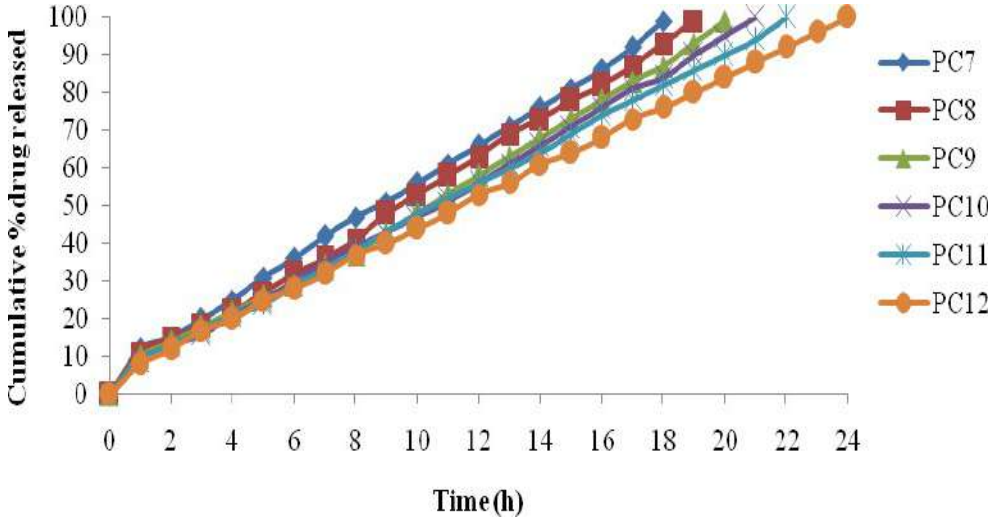

Fig. 4: Bosentan release profile of PC7 to PC12 pellets (mean, n=3)

Table 10: Correlation coefficient (r) values of PC7 to PC12

Formulation	Zero order		First order	
	K0(%/h)	r	K1(h^{-1})	r
PC7	4.41	0.9965	-0.61	0.9658
PC8	12.61	0.9631	-0.75	0.9555
PC9	4.16	0.9928	-0.18	0.8866
PC10	7.87	0.9916	-0.26	0.9045
PC11	9.23	0.9862	-0.08	0.5926
PC12	8.21	0.9965	-0.31	0.8745

Table 11: Release kinetics of bosentan pellets

Formulation	Higuchi R	Hixon-crowell r	Korsmeyer-peppas n
PC7	0.9989	0.9325	0.67
PC8	0.9923	0.9854	0.57
PC9	0.9995	0.9452	0.60
PC10	0.9839	0.8769	0.77
PC11	0.9941	0.9912	0.65
PC12	0.9971	0.9256	0.80

Table 12: Dissolution data of optimized PC12 and theoretical release profile

Time (h)	PC12	Theoretical release (%)
1	8.08±0.12	8
2	12.56±0.25	12

4	20.56±0.36	20
6	28.35±0.25	28
8	37.14±0.54	36
10	44.25±0.85	44
12	53.12±0.17	52
14	61.14±0.85	60
16	68.45±0.65	68
18	76.15±0.87	76
20	84.24±0.36	84
22	92.36±0.15	92
24	100.02±0.03	100
f1	0.96	
f2	96.56	

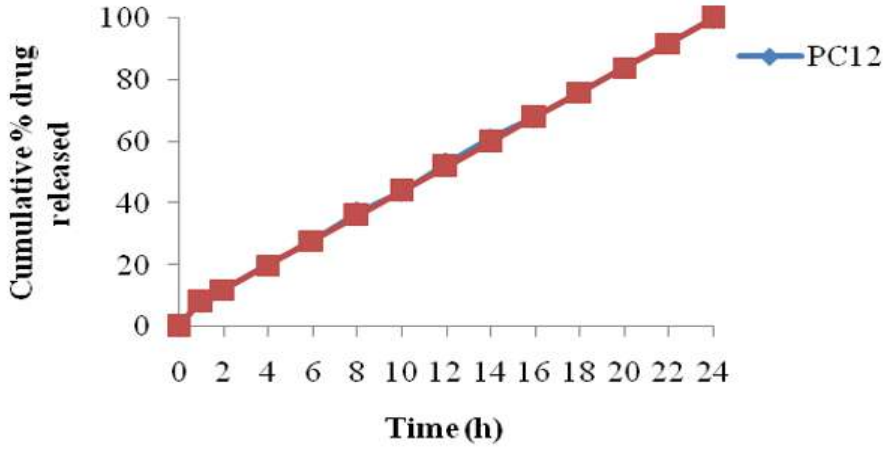

Fig. 5: Comparative dissolution profiles of PC12 and theoretical release profiles

Drug-excipients compatibility studies FTIR

Table 13: Interpretation of FT-IR spectra

Bond	Characteristic bands (cm^{-1})	Observed bands of pure drug (cm^{-1})	Observed bands of PC4 (cm^{-1})
O-H stretch	3300-2500	3064.25	3061.14
N-H stretch	3000-2850	2962.86	2960.32
C-N stretch	1335-1250	1292.32	1170
C-H bend	1470-1450	1453.42	1383.8
N-O asymmetric	1550-1475	1490.56	1504.14
N-O symmetric	1360-1290	1334.45	1341.24

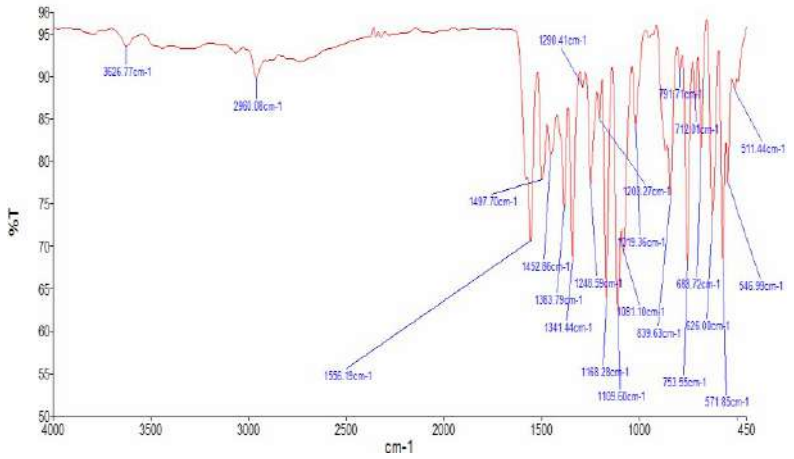

Fig. 6: FTIR spectrum of bosentan

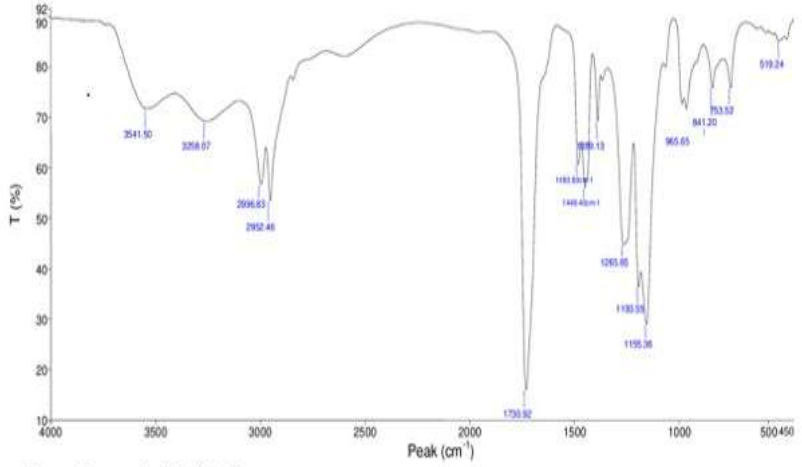

Fig. 7: FTIR spectrum of eudragit RS100

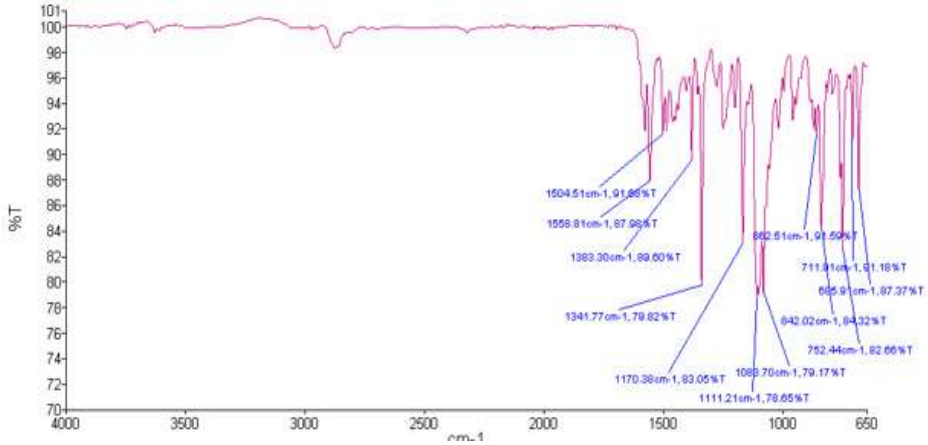

Fig. 8: FTIR spectrum of optimized (PC12) formulation

DSC

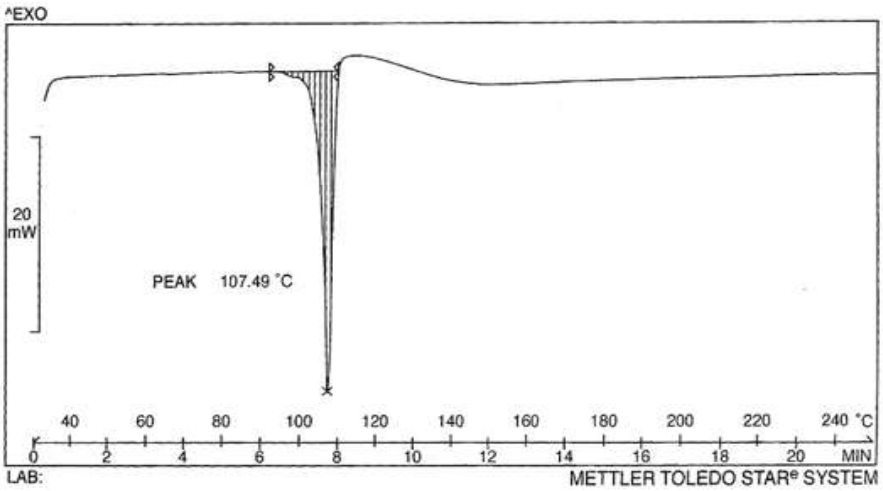

Fig. 9: DSC thermogram of bosentan

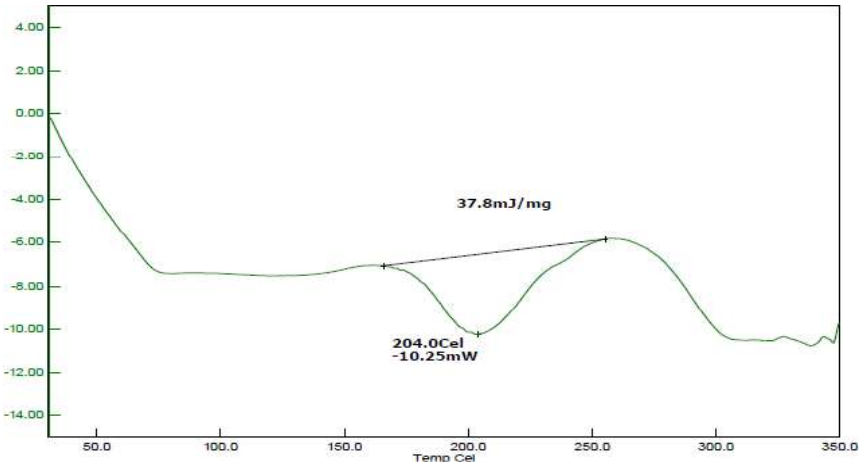

Fig. 10: DSC thermogram of eudragit RS100

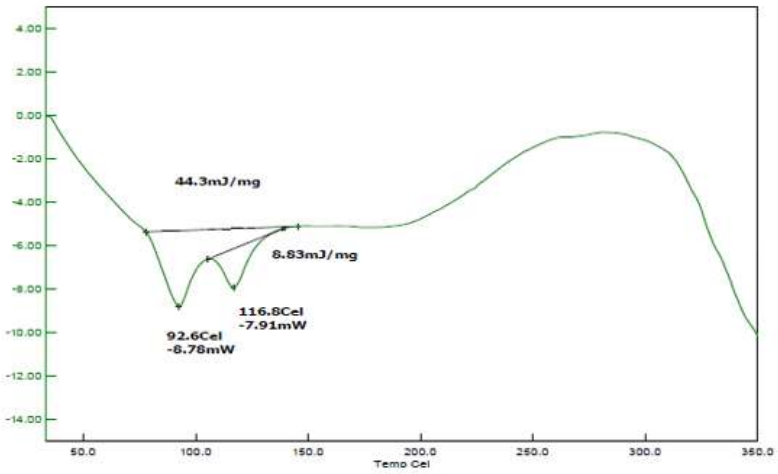

Fig. 11: DSC thermogram of optimized (PC12) formulation

Formulation of capsule dosage form for 24 h:

PC12 pellets equivalent to 135 mg of bosentan were taken for preparation of each capsule i.e. 440 mg. Avicel PH101 (microcrystalline cellulose) and magnesium stearate as glidants. All the ingredients were mixed sufficient for 30 capsules and mixed in a polybag and filled into capsule size '0' using hand filling capsule machine. The formula of the prepared capsules is shown in table 14.

Table 14: Formula of bosentan ER capsule

PC12 pellets equivalent to 135 mg of bosentan (mg)	440
Avicel PH101 (mg)	3.5
Magnesium stearate (mg)	1.5
Total weight (mg)	445

Table 15: Comparative dissolution data of bosentan ER capsules and PC12 pellets

Time (h)	Bosentan ER capsules	PC12 pellets
1	07.12±1.22	8.08±0.12
2	11.22±0.34	12.56±0.25
4	20.66±0.87	20.56±0.36
6	27.42±0.77	28.35±0.25
8	36.18±0.78	37.14±0.54
10	44.99±0.74	44.25±0.85
12	52.36±0.77	53.12±0.17
14	61.45±0.85	61.14±0.85
16	69.05±0.25	68.45±0.65
18	76.84±0.21	76.15±0.87
20	85.48±0.21	84.24±0.36
22	94.18±0.22	92.36±0.15
24	99.89±0.17	100.02±0.03

Values are expressed in mean±SD (n=3)

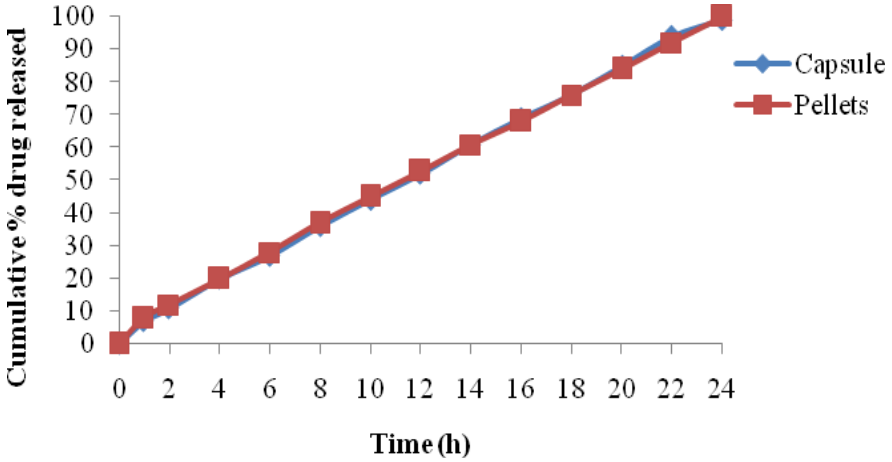

Fig. 12: Comparative dissolution profile of optimized pellets (PC12) and bosentan ER capsules

Table 16: In vivo pharmacokinetic parameters

Parameter	Bosentas 62.5	PC12
Cmax (ng/ml)	89.94±1.32	79.14±2.92
Tmax (h)	2.21±0.25	4.14±1.21
Kel (/h^{-1})	0.138±0.32	0.131±1.21
t1/2 (h)	5.02±0.25	5.29±1.25
Ka (h^{-1})	2.18±0.45	1.45±0.12
AUC(0-24) (ng/h/ml)	342.54±1.25	525.25±0.25
AUC(0-∞) (ng/h/ml)	367.25±1.56	765.89±2.35
MRT (h)	4.5±0.36	14.14±0.21
Percent relative bioavailability	-	208

Values are expressed in mean±SD (n=3)

The pharmacokinetic parameters of Bosentas 62.5 and PC12 pellets were analyzed by t-test. Statistical analysis results revealed that the Bosentan 62.5 and pellets had significant differences in Cmax, Tmax, Ka, AUC0-24, and MRT0-24 values (PC12). The t1/2 values of Bosentan 62.5 and pellets did not differ significantly (PC12). In vivo pharmacokinetic investigations on bosentan sustained release pellets revealed that these pellets were capable of extending drug release and increasing bioavailability to maintain the therapeutic effect.

Conclusion

The pan coating procedure produced multiunit dosage form pellets with sustained release of bosentan over a long period of time. Based on the results, the pan-coating process pellets were determined to be optimal, and the results were within the limitations. In vivo pharmacokinetic tests on bosentan sustained release pellets revealed that the drug was released over a longer period of time, with enhanced bioavailability and maximal therapeutic impact.

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