WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.647
Volume 7, Issue 1, 284-293 Research Article ISSN 2278 – 4357

PREPARATION AND CHARACTERISATION OF BOSENTAN MICROCAPSULES

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Article Received on
5 November 2017,
Revised on 26 Nov. 2017,
Accepted on 17 Dec. 2017
DOI: 10.20959/wjpps20181-10712

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INTRODUCTION

HYPERTENSION

Hypertension (HTN or HT), also known as high blood pressure (HBP), is a long term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure usually does not cause symptoms. Long term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease. High blood pressure is classified as either primary (essential) high blood pressure or secondary high blood pressure. About 90–95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factors. Lifestyle factors that increase the risk include excess salt, excess body weight, smoking, and alcohol. The remaining 5–10% of cases are categorized as secondary high blood pressure, defined as high blood pressure due to an identifiable cause, such as chronic kidney disease, narrowing of the kidney arteries, an endocrine disorder, or the use of birth control pills.

Blood pressure is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively. Normal blood pressure at rest is within the range of 100–140 millimeters mercury (mmHg) systolic and 60–90 mmHg diastolic. High blood pressure is present if the resting blood pressure is persistently at or above 140/90 mmHg for most adults. Different numbers apply to children.[8] Ambulatory blood pressure monitoring over a 24-hour period appears more accurate than office best blood pressure measurement.

MICROENCAPSULATION

Microencapsulation is a process of applying relatively thin coatings to small particles of solids or droplets of liquids and dispersions. It provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and of controlling the release characteristics or availability of coated materials.[1]

Size for microcapsules range from 5-500-µm and may be isolated as free flowing powders called as aggregates, or suspended directly in a vehicle for administration.

Microcapsules assume various shapes such as globular, spherical, bean like, rice grain like, flocculated masses. The thickness exceeds 10 µm with the walls having single layered or multilayered structures. Further microcapsules may contain 1 to thousands of core substances.

The capsule wall should be inert to the substance it contains, possess enough strength to allow for normal handling without rupture. The contents of capsule are contained within the wall until related by some means that serve to break, crush, melt, dissolve, rupture or remove the capsule shell or until the internal phase is caused to diffuse out through the capsule wall.

2.1. Fundamental considerations[2]

For the microencapsulation to be successful, due attention must be given to the physical and chemical characteristics of the core material, nature and properties of the wall material (prior to and after encapsulation) and methods available for the encapsulation. The intended physical characters of the encapsulated product and the intended use of the final product must also be considered.

a) Characteristics of the core material/drug

The specific material to be coated is defined as the core material, can be either liquid or solid in nature. The composition of the core material can be varied as the liquid core can include dispersed and /or dissolved material. The solid core can be a mixture of active constituents, stabilizers, diluents, excipients and release rate retardants or accelerators.

b) Characteristics of the wall material

The coating material should be capable of forming a film that is cohesive with the core material, be chemically compatible and non reactive with the core material and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and

stability. The total thickness of the coatings achieved with microencapsulation techniques is microscopic in size.

c) Physical character of the final product

Microcapsule should have desirable physical properties like ability to flow, to be compacted or to be suspended and the capsule wall must be capable of resisting the pressure during compression etc.

d) Intended route of administration of the drug

Microcapsules intended for oral use may dissolve in the environment of the stomach or may be enteric coated. They may be designed to burst while being chewed or to release their ingredients on contact with saliva.

It can be seen that when the decision is made to microencapsulate particular material, it is imperative to have the necessary knowledge of the core material, the available coat material, the nature of the final wall, and the available methods for microencapsulation.

MATERIALS USED

Bosenton, Cellulose Acetate Phthalate, Cellulose acetate butyrate, Eudragit RL-100, Eudragit RS-100, Sodium alginate, Ethyl cellulose.

METHODOLOGY

BOSENTAN MICROCAPSULES WITH CELLULOSE POLYMERS

Preparation of microcapsules (Ionotropic gelation technique)

Bosentan microcapsules were prepared by Ionotropic gelation technique, the composition of the various Bosentan microcapsules formulations was summarized in Table 3.3 Bosentan and sodium alginate polymers were individually passed through sieve ≠ 60. The required quantities of sodium alginate were dissolved in purified water to form a homogenous polymer solution. The drug Bosentan was added to the polymer solution and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was sonicate for 30 min to remove any air bubbles. The bubble free dispersion was then added manually drop wise into crosslinking ion solution using polyethylene syringe (needle size 22 G) and stirred at 200-600 rpm.

Differential scanning calorimetric (DSC) study of Pure Bosentan

Thermal properties of pure drug was evaluated by Differential scanning caloriemetry (DSC) using a diamond (DSC) (Mettler star sw 8.10). Accurately weighed 5-6 mg samples were hermetically sealed in aluminium pans and heated at a rate 50 ^{O}C/min from 50^{0}C to 250 ^{0}C temperature range under nitrogen flow of 25 ml/min.

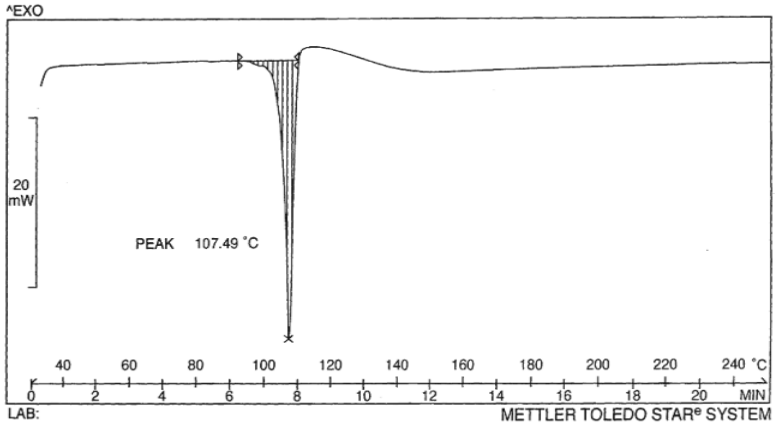

Fig.6.2 Results of DSC thermogram of pure Bosantan shows sharp endothermic peak at 107.49 ^{O}C confirms the crystalline nature of the Bosentan.

6.5. Peak areas of the Bosentan

Table. 6.4 Peak areas of the Bosentan.

Concentration in µg /ml	Peak Area
50	605989
100	1212160
150	1818255

BOSENTAN MICROCAPSULES WITH CELLULOSE POLYMERS

Table 6.5 Particle size distribution, percent drug content and entrapment efficiency of Bosentan microcapsules prepared with different polymers (n=3).

	BOS :CAP			BOS :CAB			BOS :EC		
Size	**1:0.5**	**1:1**	**1:1.5**	**1:0.5**	**1:1**	**1:1.5**	**1:0.5**	**1:1**	**1:1.5**
10/20(1242µ)	4±0.21	5±0.13	7±0.22	10±0.21	9±0.14	9±0.14	10±0.16	11±0.53	10±0.23
20/30 (666.5 µ)	77±0.11	79±0.33	81±0.12	77±0.21	73±0.31	74±0.11	80±0.21	77±0.27	75±0.22
30/40 (445 µ)	6±0.12	9±0.13	6±0.13	5±0.23	8±0.13	3±0.18	6±0.15	4±0.21	9±0.21
60/80 (225 µ)	13±0.11	7±0.22	6±0.13	8±0.13	10±0.21	12±0.12	7±0.11	10±0.21	3±0.11
Drugcontent (%)									
Theoretical (%)	66	50	40	66	50	40	66	50	40
Estimated (%)	49±1.22	31.7±2.5	21±1.31	54.1±2.2	30.7±1.6	22±1.57	46±1.63	30.1±1.6	19±1.31
Entrapment efficiency (%)	74.24	63.4	52.5	81.8	61.4	55	70	60.2	47.5

The particle size of the microcapsules prepared with CAP are between 4±0.21 to 13±0.1 and formulations prepared with CAB are between 5±0.23 to 77±0.21 and the formulations prepared with EC are between 6±0.15 to80±0.21 and the drug content of the formulations with CAP are found to be 21±1.31 to 49±1.22 and the formulations with has the drug content of 22±1.57 to 54.1±2.2 and the EC formulations drug content is between 19±1.31 to 46±1.63 and the entrapment efficiency of all the formulations are found to be between 19±1.31 to 46±1.63.

Fourier Transform Infrared spectroscopy (FT-IR)

The FT-IR spectra acquired were taken from dried samples. He FT-IR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 and 400cm^{-1}, and 4cm^{-1} resolution. The results were the means of 6 determinations. A quantity equivalent to 2mg of pure drug and drug loaded microcapsules were selected separately. The characteristic band peaks acquired were taken from the prepared microcapsules. The interaction study between drug and polymer was evaluated. The characteristics peak of aromatic N-H stretch (1556 cm–1), O-H stretch (3316 cm–1) and C-H bending at 2960 confirms the pure Bosentan. (Fig. 5.4to5.7). Similar peaks were observed in the microcapsules prepared with CAP, CAB and EC further confirms that there is no drug polymer interaction in the prepared microcapsules and good compatibility.

Differential scanning calorimetry (DSC) study

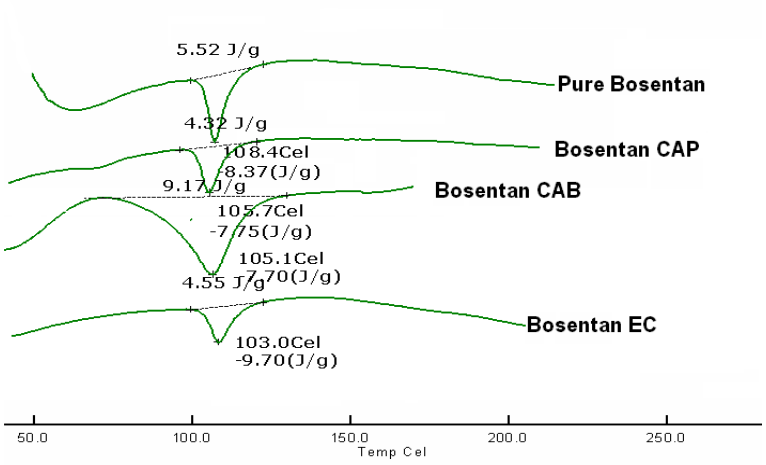

Fig. 6.12 DSC thermo grams of Bosentan and Bosentan CAP, CAB and EC microcapsules.

Differential scanning calorimetry (DSC) study of drug loaded microcapsules was performed using a Diamond DSC (Mettler Star SW 8.10) to determine the drug-excipient compatibility

study. The analysis was performed at a rate 5 ^{0}C min^{-1} from 50 ^{0}C to 200 ^{0}C temperature range under nitrogen flow of 25 ml min^{-1}. Thermograms of pure Bosentan showed sharp endothermic peak at 108.4°C. Similar peaks were obtained in the prepared microcapsules with different polymers. This clearly indicated that there was no drug polymer interaction.

In-Vitro Drug Release Studies

Table 6.7 In vitro dissolution data of Bosentan microcapsules prepared with different polymers (n=3).

TIME (Hrs)	BOS :CAP			BOS :CAP			BOS :CAP		
	1:0.5	1:1	1:1.5	1:0.5	1:1	1:1.5	1:0.5	1:1	1:1.5
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
1	21	17	11	17	11	7	33	22	12
2	47	36	26.8	42	23	14.4	56	39	31
3	52	42	35	44	39	18.7	64	53	40
4	69	56	46.4	63	51	33	78	62	49
5	72	64	51	68	59	44.4	83	71	63
6	84	81	63	78	72	51.4	94	83	71
7	87	84	77	84	77	60	99	94	82
8	93	89	84	89	85	73.9		99	90
9	97	92	87	92	86	78			96
10		96	88.3	97	89	82.7			99
11		99	93	99	94	89.4			
12			94		99	92.6			
14			97			95			

In vitro dissolution studies were carried out with the prepared microcapsules. As shown in (Table 5.3), the release was found 9-14 hours in the microcapsules prepared with cellulose acetate phthalate. The release rate was retarded with increased polymer proportion in the prepared microcapsule.

The drug release from microcapsules prepared with cellulose acetate butyrate was found to be 11-14 hours and more. Highest release retardation was found with the cellulose acetate butyrate.

The release from the microcapsule prepared with ethyl cellulose was found to be 7-10 hours. The release was retarded more in the microcapsules prepared with combination of CAB and CAP than EC.

The order of drug release with respect to retardation was found as follows CAB>CAP>EC.

The release kinetics was best fitted to the Higuchi model in the formulation (Table 5.3, Fig. 5.12 to 5.20). This confirms that the drug release was diffusion controlled.

Table 6.8 Release kinetics data of Bosentan microcapsules prepared with different polymers.

	BOS :CAP			BOS :CAB			BOS :EC		
Zero order	0.9267	0.9151	0.9133	0.9212	0.9331	0.9583	0.9552	0.9857	0.9773
First order	0.9499	0.9338	0.9821	0.9238	0.9692	0.9648	0.8611	0.8282	0.8683
Higuchi	0.9771	0.9804	0.9702	0.9773	0.9836	0.9791	0.9887	0.9954	0.9948
Peppas	0.9548	0.9755	0.9679	0.9507	0.9682	0.9828	0.9836	0.9961	0.9805
Peppas(n)	0.6586	0.7251	0.8191	0.6919	0.87	1.0608	0.5509	0.7183	0.8894

The release kinetics was best fitted to the first order model with correlation coefficient of above 0.9338 to 0.9821 in the microcapsules prepared with CAP, 0.9238 to 0.9648 in the microcapsules prepared with CAB. The release kinetics were best fitted to the zero order in the formulations prepared with EC with a correlation coefficient of 0.552 to 0.9773. This indicates the concentration independent drug release.

BOSENTAN MICROSPHERES USING IONTROPIC GELATION METHOD

In vitro dissolution and release kinetics of Bosentan sodium alginate microspheres

Time (Hrs)	BF-13	BF-14	BF-15	BF-16
0	0	0	0	0
1	25.4	17.3	13	7.31
2	40.9	29.2	24	13.7
3	55.3	43.7	35.2	23.6
4	63.2	55.6	46.8	34.9
5	72.5	64.8	55.3	44.7
6	81.4	73.6	63.6	54.6
7	86.3	80.3	72.5	62.3
8	90	85.2	77.8	68
9	95	89.1	82	73.9
10	99	92.6	87	79.6
11		96	90.1	83.8
12		99	92.3	86.3
13			94.7	88.7
14			96.8	89.8
Zeor order	0.9452	0.9322	0.9827	0.9908
First order	0.8842	0.9120	0.9281	0.9815
Higuchi	0.9899	0.9852	0.9895	0.9903
Peppas	0.9889	0.9802	0.9834	0.9834
Peppas(n)	0.5882	0,7101	0.7828	1.0140

DSC study of Bosentan microspheres prepared with sodium alginate

Differential scanning calorimetry (DSC) study of drug loaded microcapsules was performed using a Diamond DSC (Mettler Star SW 8.10) to determine the drug-excipient compatibility study. The analysis was performed at a rate 5 ^{0}C min^{-1} from 50 ^{0}C to 200 ^{0}C temperature range under nitrogen flow of 25 ml min^{-1}. Thermograms of pure Bosentan showed sharp endothermic peak at 107.4°C. Similar peaks were obtained in the microcapsules prepared with sodium alginate. This clearly indicated that there was no drug polymer interaction.

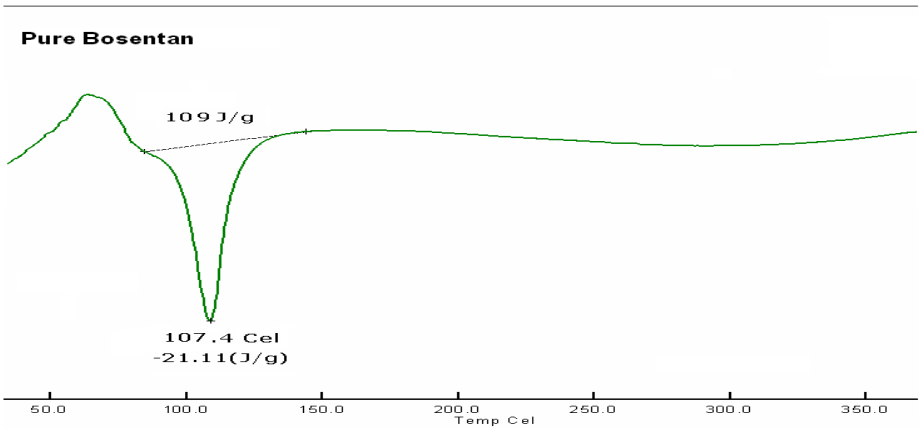

Fig.6.35 DSC thermogram of pure Bosentan.

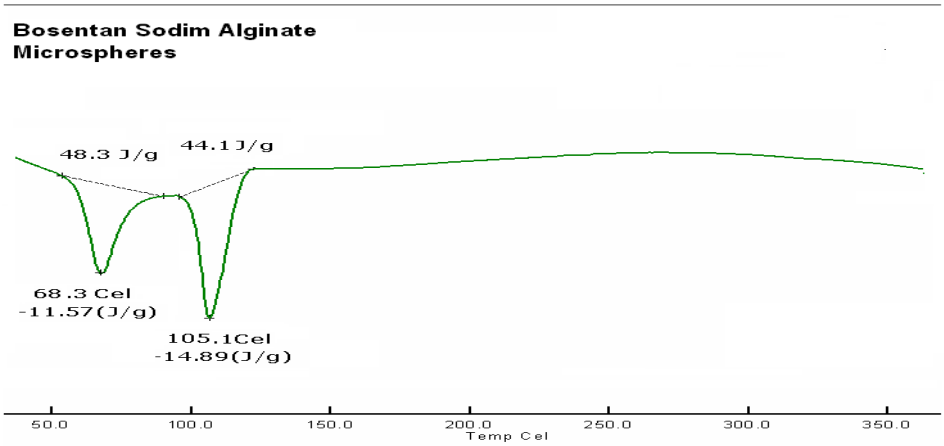

Fig.6.36 DSC thermogram of Bosentan microspheres with sodium alginate.

FTIR study of Bosentan microspheres prepared with sodium alginate

The FT-IR spectra acquired were taken from dried samples. The FT-IR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 and 400 cm^{-1}, and 4 cm^{-1} resolution. The results were the means of 6 determinations. A quantity equivalent to 2 mg of pure drug and drug loaded microcapsules were selected separately. The characteristic band peaks acquired were taken from the prepared microcapsules. The interaction study between drug and polymer was evaluated. The characteristics peak of

aromatic N-H stretch (1556 cm–1), O-H stretch (3316 cm–1) and C-H bending at 2960 confirms the pure Bosentan. (Fig. 6.8 and 6.9). Similar peaks were observed in the microcapsules prepared with Bosentan sodium alginate further confirms that there is no drug polymer interaction in the prepared microcapsules and good compatibility.

CONCLUSION

This research study will divided into different major parts to support the primary goal of this research. Preformulation Studies, Drug Recovery from Microcapsules, Investigation of Formulation Parameters on Drug Release, Formulation, Drug excipient interaction study The prepared microcapsules will characterized for Drug entrapment efficiency, Particle size distribution, Assay, Invitro dissolution, Differential scanning calorimetry, FTIR, Scanning Electron microscopy, In vivo studies, To analyze the pharmacokinetic parameters of the prepared microcapsule formulations. Bosentan Microcapsules Were prepared with Cellulose Polymers and sodium alginate. Preformulation and evaluation studies were performed for all the microcapsules. HPLC method for the estimation of Bosentan was used for routine analysis of Bosentan in its formulations like drug content and in vitro dissolution and drug content uniformity. The mobile phase was prepared using phosphate buffer of pH 7.4 and Acetonitrile at a ratio of 40:60 (Buffer: Acetonitrile).The retention time was found to be 2.971.Among all the formulations of bosenton the combinations prepared with CAP, CAB and EC by using solvent evaporation method of all the ratios the formulation with ratio 1:15 shown maximum drug release, in the formulations prepared with sodium alginate beads the formulation BF-16 shown maximum drug release.

REFERENCES

1. Bakan, J.A., Microencapsulation. In;Lachman, L., Herbert,A.L., Joseph ,L.K., The Theory and Practice of Industrial Pharmacy. 3rd Ed. Varghese Publishing House, Bombay, 1991; 412-429.
2. Leon Lachman, Liberman, HA, Joeph L Kanig. The Theory and Practice of Industrial Pharmacy, 3 rdedn. 1987; 414-419.
3. Vyas SP and Khar RK. Targeted and controlled drug delivery. 1st edn, CBS Publisher and distributors (New Delhi); 2002.
4. Kondo A, Eds., In; Microcapsule processing and Technology, Marcel Dekker, Inc., New York, 1979; 32.

5. Manekar CN, Joshi SB. Microencapsulation technique. Eastern Pharmacist 1998; 12(6): 47-49.
6. Chowdhry KPR. Microencapsulation for controlled drug release. Pharm mag 1992; 5(1): 1-5.
7. Microencapsulation of Pharmaceuticals and related materials. The national cash register co., Dayton, Ohio, 1996.
8. Apul costa, Jose manuel Sousa lobo. Modeling comparison of dissolution profiles. Eur J Pharm Sci., 2001: 13: 123-133
9. Korsmeyer RW, Peppas NA, Gurny R, Dockar B, Buri PP. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm, 1983; 15: 35-38.
10. Martin A. Physical Pharmacy, 4 thedn, BI Waverly(P) Ltd. New delhi, 1994.
11. Hemant KSY, Singh MN, Shivakumar HG. Chitosan/ Sodium tripolyphosphate cross linked microspheres for the treatment of gastric ulcer. Der Pharmacia Lettre. 2010; 2: 106–113.
12. Hughes PM, Olejnik C, inventors. Delivery of a drug via subconjuctival or periocular delivery of a prodrug in a polymeric microparticle. AU2004260645 (A1) 2005.
13. Lee JY, Seo MH, Choi IJ, Kim JH, Pai CM, inventors. Locally administrable, biodegradable and sustained-release pharmaceutical composition for periodontitis and process for preparation thereof. US6193994. 2001.
14. Yang YY, Chia HH, Chung TS. Effect of preparation temperature on the characteristics and release profiles of PLGA microspheres containing protein fabricated by double-emulsion solvent extraction/evaporation method. J Control Rel., 2000; 69: 81–96.