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Formulation Evaluation and Optimization of Osmotically Controlled Floating Tablets of Bisoprolol Fumarate for the treatment of Hypertension

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Abstract
Osmotically controlled floating drug delivery system of anti-hypertensive drug Bisoprolol Fumarate has been designed in order to prolong the gastric retention time. The developed system consisted of osmotic core (containing drugs Bisoprolol Fumarate, osmotic agents Mannitol and hydrophilic polymers HPMC-E15) coated with ethyl cellulose (14.5%w/w) to form semipermeable membrane which is then further subjected to compression coating by gelling agent (HPMC-K4M) and gas generating agent (sodium bicarbonate). All the developed formulations were evaluated for floating lag time, duration of floating, drug content and in-vitro drug release. Drug release from developed formulation was directly influenced by concentration of polymers in core and thickness of semipermeable membrane but remain unaffected by pH, hydrodynamic condition of release medium and amount of gas generating agent in compression coat. All the developed formulation showed floating lag time of less than 2 min and floating log time up to 24 hours. Batch F8 containing 10% HPMC-K4M, 20% sodium bicarbonate and 14.5% weight gain after coating released 94.08% at the end of evaluation, and was selected as optimized formulation. It was concluded that the formulated tablets released the medicament for longer period of time.

Keywords: Floating Tablets, osmotic system, Bisoprolol Fumarate, hydrophilic polymer

1. Introduction

Oral drug delivery has been known for decades as the most widely utilized route of administration among all routes that have been explored for the systemic delivery of drugs in case of different dosage forms (1). The oral controlled-release system is usually made of polymers, and the mechanisms of release are generally regulated by diffusion, bioerosion or degradation, and swelling or generation of osmotic

pressure. Diffusion occurs when the drug–polymer mixture is exposed to the gastrointestinal fluid, resulting in release of the drug from the tablet or capsule. Oral controlled – release drug delivery is thus a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit (2).

Osmotic delivery systems or osmotic pumps are mainly composed of a core containing a drug and an osmogen. These are coated with a semi-permeable membrane containing one or more ports for drug delivery, such that the drug is released over time in the form of a solution or suspension(3). Oral osmotic systems are composed of a compressed tablet core coated with a semi-permeable membrane through which delivery orifices are created using a laser beam or mechanical drill (4). These controlled systems are based on osmosis and osmotic pressure and are independent of various gastrointestinal factors. However, it is noteworthy that there are critical factors that influence the design of osmotically controlled drug delivery systems, including the drug solubility, delivery orifices, osmotic pressure, semi-permeable membrane, type and nature of the polymer, membrane thickness, and type and amount of plasticizer. (5)(6)(7).

Hypertension is one of the most prevalent cardiovascular diseases worldwide. However, in the population of resistant hypertension, blood pressure is difficult to control effectively. Antihypertensive drugs may have adverse effect currently, therefore new therapeutic targets and treatments are needed to uncovered and exploited to control hypertension and cardiovascular diseases.(8)

Bisoprolol fumarate is an antihypertensive medication used to treat hypertension/high blood pressure and angina pectoris. Bisoprolol fumarate alters how the body responds to certain nerve impulses, particularly in the heart. As a result, Bisoprolol fumarate reduces the heart rate and makes it easier for the heart to circulate blood throughout the body. Thereby, bisoprolol fumarate aids in reducing the high blood pressure and the risk of having a stroke, heart attack, other heart problems, or kidney problems in the future.

Floating osmotic drug delivery system is a controlled oral drug delivery system which comes under the category of gastro-retentive drug delivery. It is based upon the osmotically controlled release mechanism which offers a sustained therapeutic action while reducing the side effect.

Floating osmotic drug delivery system also finds a unique place among the other gastro retentive drug delivery by surpassing their performance. Floating osmotic drug delivery system incorporates a variety of ingredients such as osmotic agents, semi permeable substance, gas generating agent and a gel forming agent (9).

The preparation of the system involves techniques like direct compression and coating process. Characterization studies like in-vitro dissolution study, in-vivo radiological study and pharmacokinetic study were adapted for evaluation of floating osmotic drug delivery system.

Many studies have been carried out to illustrate the efficiency of the floating osmotic drug delivery system in overcoming the drawbacks such as poor bioavailability, drug wastage etc. Active agents derived from the field of pharmacognosy have also been benefited by floating osmotic drug delivery system since they prevent the enzymatic degradation of the active agents and improve their bioavailability (10).

2. MATERIAL AND METHOD

2.1 Materials

Bisoprolol Fumarate a gift sample from Ajanta Pharmaceuticals, Mumbai India. HPMC E15 ,HPMC K4M and Ethyl cellulose were obtained as a gift sample from Colorcon Asia Pvt. Limited, Goa.

Following chemicals and excipients were purchased from commercial sources and used such as micro-crystalline cellulose (Chem Filled pvt. Limited , Kalmeshwar), mannitol (Qualigens Fine Chemicals, Mumbai), magnesium stearate and talc (LOBA Chemie Pvt. Ltd.), sodium bicarbonate (Merck Specialities Private Limited) , hydrochloric acid (AR grade),acetone (both from LOBA Chemie Pvt. Ltd).(11)

2.2 Methods

2.2.1 Drug excipient compatibility studies :

1. **Fourier-transform Infrared spectroscopy (FT-IR)**

FT-IR spectrum was recorded for the physical mixture to check the presence of any incompatibility through the change in the peaks position and intensity and loss of peaks. Approximately 1–3mg of sample was mixed with dry potassium bromide, and the samples were examined in transmission mode over a wave number range of 4000-400 cm^{-1}. Shimadzu 8400S FT-IR system was used for recording the spectrum.(12)(13)

2. Differential scanning calorimetry

Differential scanning calorimetry studies for the pure drug, formulated tablets and physical mixture were performed. The experiment was carried out using a DSC instrument (DSC-1821e, Mettler- ToledoAG, Analytical, Schwerzenbach, Switzerland). 5mg samples were placed in aluminium pans (Al-Crucibles, 40 Al) and sealed. The probes were heated from 50 to 400˚C at a rate of 10 ˚C per min in nitrogen atmosphere.(14)

3. X-Ray Diffraction (XRD)

X-Ray diffraction perform to evaluate the physical state of drug , whether Amorphous or Crystalline X-ray diffraction patterns of plain drug ,physical mixture, and formulated tablets were recorded on an X-ray diffractometer (Brucker Axs, 08 Advance). Scanning rate employed was 50 min, over to 50 to 400 diffraction angle range.(15)

2.2.2 Preparation of core tablets

Core tablets of BPF were prepared by direct compression and batch size was kept as 100 tablets. Formula of different core formulations of Bisoprolol Fumarate .Formula of different core formulation of Bisoprolol fumarate listed in t**able 1**. Bisoprolol Fumarate was mixed with HPMC(E15), osmotic agent (mannitol), Microcrystalline cellulose for 10 min. After passing this mixture through #40 mesh sieve. To this mixture, #60 mesh sieve passed talc and magnesium stearate were added and mixing continued for another 10 min. The blend was then compressed into tablets having average weight of 190mg using a single station tablet punching machine (Rimek press II) fitted with 8 mm round standard concave punches. The punched tablets were of 5±0.96 kg/cm2 hardness on Monsanto hardness tester. The drug content of the tablets was found to be within the limit.(16)

Table No.1: Formula for different batches of core tablets

Sr.no	Formulation ingredient quantity (mg)	Formulation code											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13

1.	Drug	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2.	Manni-tol	10	20	10	20	10	20	10	20	15	15	15	15	15
3.	HPMC E15	5	5	15	15	10	10	10	10	5	15	5	15	10
4.	MCC 102	80.5	70.5	70.5	60.5	75.5	65.5	75.5	65.5	75.5	65.5	75.5	65.5	75.5
5.	Magne-sium Stearate	1	1	1	1	1	1	1	1	1	1	1	1	1
6.	Talc	1	1	1	1	1	1	1	1	1	1	1	1	1
	Total weight	100	100	100	100	100	100	100	100	100	100	100	100	100

2.2.3 Coating core tablet using polymers to get semipermeable layer

ODDS were prepared by coating of core tablets with a SPM in a conventional laboratory coating pan with outer diameter of 10 cm fitted with three baffles placed at an angle of 120°.The composition of coating solution used for coating of BPF tablets given in **table 2**. Ethylcellulose (5%, 10%, 15% w/w) dissolved in acetone was used as coating solution. Coating process was done on a batch of 30 tablets; pan speed was maintained at 20 rpm and hot air inlet temp was kept at 45-50 °C. The manual coating procedure based on intermittent spraying and coating technique was used with spray rate of 4–5 ml/min. Coat weight and thickness were controlled by the volume of coating solution consumed in coating process. Coating was continued until desired coat thickness was obtained on the core tablets.(17)

2.2.4 Formulation of floating osmotic tablet by re-compressing coated core tablets and drilling the tablets.

FODDS were prepared by compression coating of ODDS with a gelling agent (HPMC-K4M) containing gas generating agent (Sodium bicarbonate) table 3. About one third quantity of coating formulation is placed in die-cavity (8 mm diameter), the ODDS (6 mm diameter) was carefully positioned in the center of the die cavity and was then filled with the remainder of the coat formulation. It was then compressed around the core tablet using 8 mm round concave punches at an applied force so as to give 285µm thickness to compression coat · An appropriate size orifice was made on one face of all coated tablets using microdrill through SPM and compression coat (11)

Table No. 2: Formula of compression coating

Sr.no	**Ingredients quantity(in mg)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
1.	HPMC K4M	30	35	40	50	30	35	40	50	50	30	35	50	30
2.	Sodium bicarbonate	40	35	30	20	40	35	30	20	20	40	35	20	40

2.2.5 EXPERIMENTAL DESIGN (18)

A 3-level 3-factor, 15-run experimental Box-Behnken design was adopted to optimize levels of variables in the tablet formulations. The selected independent variables were concentration of Mannitol, concentration of HPMC E15, i.e., Hydroxypropyl Methylcellulose, concentration of EC, i.e. Ethyl Cellulose as shown in Table (3). The dependent variables were % drug release, % friability, weight gain. The generation of experimental runs, ANOVA study and optimization were carried out by Design-expert software 13. The prepared formulation batches are indicated in (Table 4).

Table No.3: Variables in Box-Behnken design

Independent variables	**Variable levels**		
	low (-1)	**Medium (0)**	**High (+1)**
Concentration of mannitol (% w/w)	10	15	20
Concentration of HPMC E15 (%w/w)	5	10	15
Concentration of ethyl cellulose (%w/w)	5	10	15

Table No. 4: Formulation of tablets using box-behnken design

Runs	**Concentration of mannitol (% w/w)**	**Concentration of HPMC E15 (% w/w)**	**Concentration of ethyl cellulose (% w/w)**
1.	10	5	10
2.	20	5	10
3.	10	15	10
4.	20	15	10
5.	10	10	5
6.	20	10	5
7.	10	10	15
8.	20	10	15
9.	15	5	5
10.	15	15	5
11.	15	5	15
12.	15	15	15
13.	15	10	10
14.	15	10	10
15.	15	10	10

2.3 Evaluation of Formulated Tablets

2.3.1 Evaluation of Powder Blend

The bulk and tap density of the powdered blend was determined using USP method II on tap density tester

(ETD-1020, Electro lab India) and Compressibility index and Hausner Ratio were calculated.

1. Bulk density

Weighed quantity of the blend was transferred into a graduated cylinder to measure the volume occupied by the blend and then the bulk density of the blend was calculated using the following formula.

Bulk density = Weight of powder (g)
Bulk volume (ml)

2. Determination of tapped density

Tapped density of the blend was measured using USP type 1 apparatus. Weighed quantity of the blend was transferred into a graduated cylinder. The cylinder was fixed in tapped densitometer holder, tapped for 500 times and observed up to not more than 1 ml difference after tapping 500 times. The tapping was continued till the constant volume was reached and the density values were calculated using following formula,

Tapped density = Weight of powder (g)
Volume after tapping (ml)

3. Carr's index

Carr's index or compressibility index, measuring the tendency of a blend to be compressed, was calculated using the tapped density and bulk density values using the mentioned formula.

Carr's index = Tapped density-Bulk density
Tapped density

4. Angle of repose

Angle of repose is defined as the maximum angle viable between the surface of a pile of the powder and horizontal aircraft [1,6]. The frictional pressure in a unfastened powder or granules can be measured by using angle of repose [7,12].

$\tan \Theta = h/r$

$\Theta = \tan^{-1} (h/r)$

Where, Θ is the angle of repose his height of pile r is radius of the base of pile

2.3.2 Evaluation of core tablets

The core tablets were evaluated for weight variation ,hardness, friability, thickness, diameter.

2.3.3 Evaluation of ODDS

The ODDS were also evaluated for weight variation, hardness and diameter.

2.3.4 Evaluation of FODDS

Hardness

Monsanto hardness tester was used to measure the hardness. Tablets from each batch were used. Each tablet was held along its axis between two jaws of the tester and scale was adjusted to zero. A constant force was applied by rotating the knob until the tablet was fractured. Hardness was noted in kg/cm^2.

Weight variation test

Twenty tablets of each formulation type were weighed individually using in electronic balance. The average weight was calculated and individual tablet weight was compared with average value and the deviation was recorded.

Determination of drug content

Accurately weigh 10 mg of Bisoprolol Fumarate was dissolved in 10 ml of 0.1M HCl in 10 ml volumetric flask, the solution was considered as standard. Similarly, accurately weigh the 10 mg equivalent dose of floating tablets containing Bisoprolol Fumarate crush then with mortar and pestle dissolved it in 10 ml of

0.1M HCl, and considered as a test. Absorbance of both standard and test were measured out, by using the UV-visible spectrophotometer (UV- 1800, Shimadzu, Japan) at 221nm wavelength. By using following formula and comparing test with standard, % drug content was calculated.

$$\% \text{ Drug content} = \frac{\text{absorbance of test}}{\text{absorbance of standard}} \times 100$$

2.4 In-vitro drug release

In-vitro drug release studies were performed using the USP type II dissolution apparatus (Electro lab Dissolution Tester (USP) TDT- 08L) at 50 rpm using 0.1 NHCI as dissolution medium at temperature 37 ± 0.5°C. Aliquots (5 ml) were withdrawn at different time intervals. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatman filter paper and solutions were analysed at 221 nm using UV spectrophotometer. Three replicates were performed (n=3)

2.5 Floating properties (Buoyancy studies)

The time FODDS took to emerge on the dissolution medium surface (floating lag time) and the time the tablet constantly floated on the water surface (duration of floating) were evaluated in a dissolution vessel (apparatus USP-XXIV type II) filled with 500 ml of simulated gastric fluid (pH 1.2) without pepsin at 37±0.5 °C, with paddle rotation of 100 rpm (13).Three replicates were performed (n=3).

2.6 Stability study

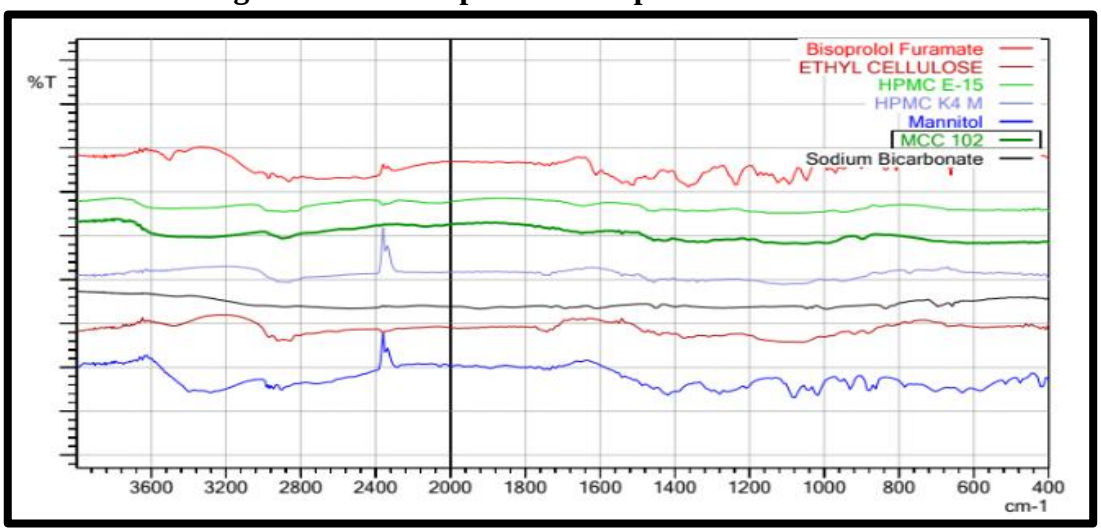
Stability studies were carried out at room temperature 40±2°C and 75±5% RH for a specific time period up to 1 month for selected formulations. For stability study, the tablets were sealed in Aluminium packaging coated inside with polyethylene. These sample containers were placed in Stability chamber and various parameters were studied [25].

3. RESULTS AND DISCUSSION

3.1 Fourier Transform Infra-Red (FT-IR) study

Figure 1 shows the characteristic peaks of excipients, pure drug ,physical mixture .The presence of vibration in the region of 1734, 1240, 3423,1417 of -C=O, C-O,-NH3, -CH3 group showed its presence in BPF. There was neither origin of any new characteristic peaks nor absence of any original characteristic peaks which revealed no incompatibility between drug and excipients.

Figure 1 : FT-IR Spectrum of optimal formulation

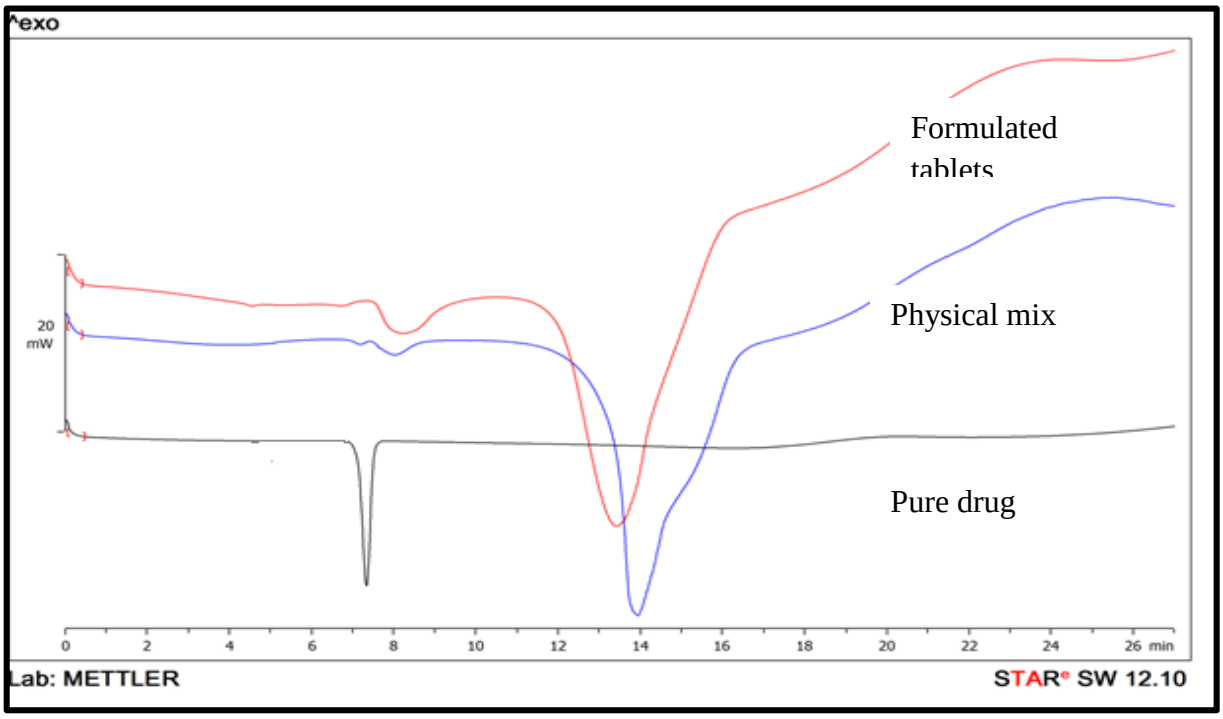


3.2 Differential Scanning Calorimeter (DSC)

The thermal behaviour of the pure drug and the combination of drug and excipients was compared. The DSC thermograph of Bisoprolol Fumarate showed a sharp endothermic peak at 102.67°C. In the DSC data of mixture of Bisoprolol Fumarate and excipients, the sharp endothermic peak was observed near to 163.20 °C. Melting endothermic peak of the drug was well observed with a slight change in term of broadening of peak or shifting toward the lower temperature. Thus, these minor changes in the melting endothermic peak of drug could be due to the mixing of drug and excipients, which lowers the purity of each component in the mixture.

There was no change in the melting endotherm of the drug and drug polymers mixture. Hence, it was concluded that drug and polymers were compatible with each other.

Figure 2: Thermograph of Formulated Tablets (overlay of pure drug + physical mixture + Formulated tablets)

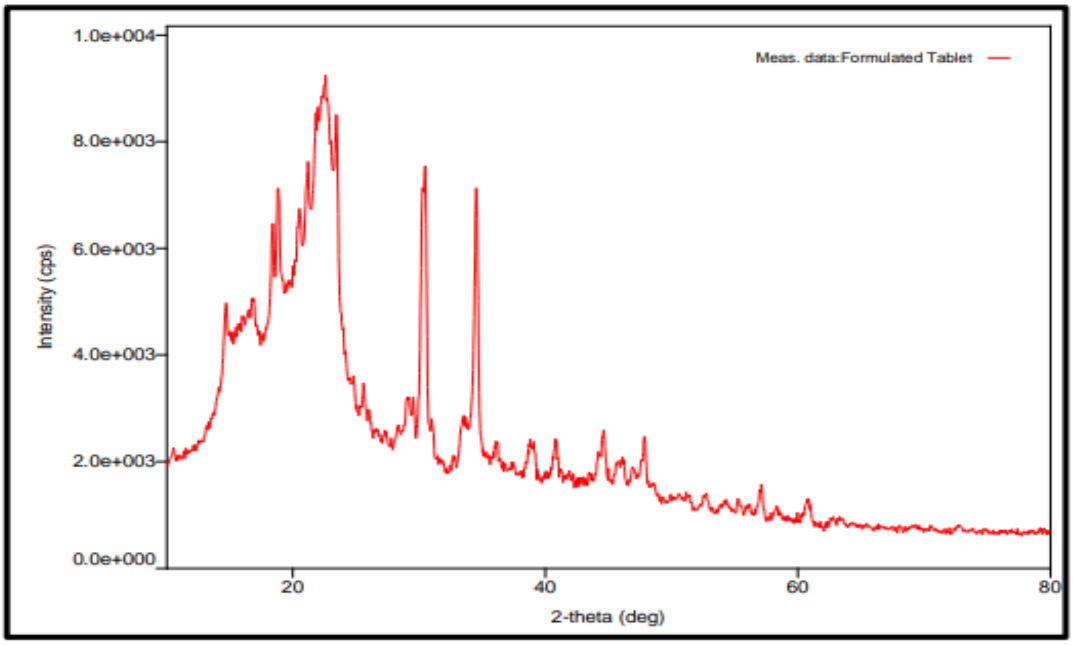


3.3 XRD (X-ray Diffraction Study):

The X-ray diffraction pattern of physical mixture recorded on an x-ray diffractometer shown in Figure 41.The sharp peaks of drug and excipients were observed at diffraction angles, indicating the typical crystalline nature.

The osmotically controlled floating tablet showed a broad peak that indicating the amorphous state. The absence of some crystalline peaks of Bisoprolol Fumarate in tablets confirmed that the drug was molecularly dispersed in the polymer and conversion of drug into the amorphous form has occurred. Some sharp peak present in X-ray diffraction pattern were due to molecularly undispersed in osmotically controlled floating tablets.

Figure 3: X-ray diffractogram of formulated tablets



3.4 Optimization of osmotic controlled floating tablets.

Figure 4: 3D surface response plot showing effect of concentration of independent variables on in-vitro drug release

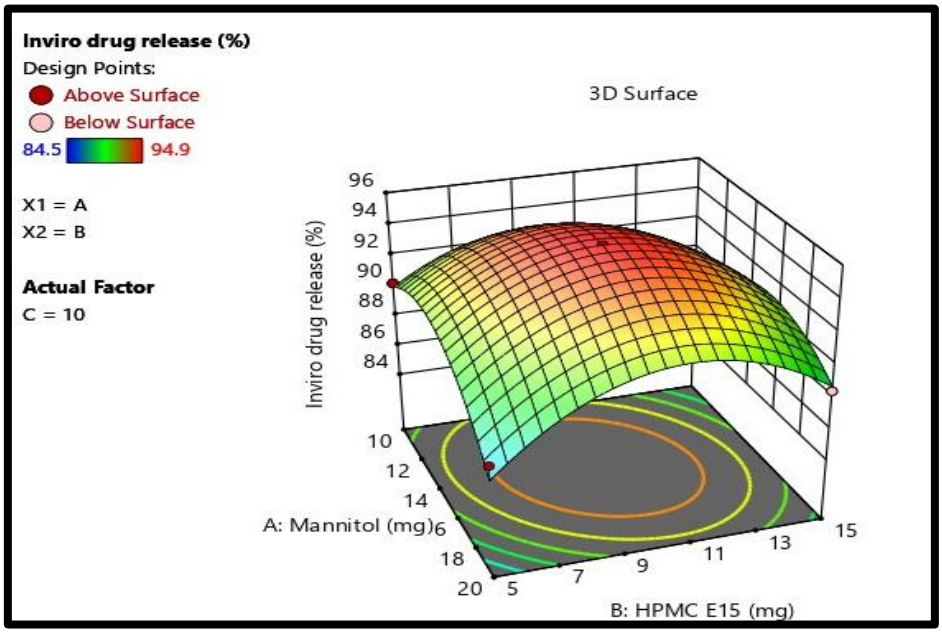
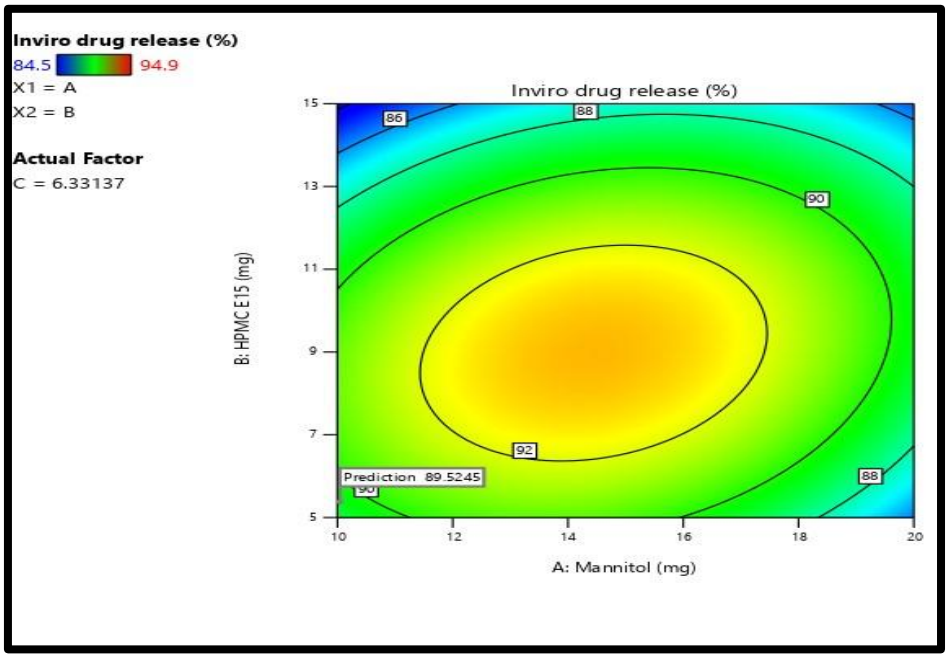


Figure 5 : A counterplot showing relationship between various levels of concentration of independent variables on *in-vitro* drug release



In-vitro drug release = 90.50+0.4500A+0.9125B+0.3775C+0.2500AB-1.57BC+1.97AC -5.4A^2–5.09B^2+1.41C^2

In-vitro drug release is an important parameter to understand rate of release of drug. HPMC E15 and Mannitol was two factor which used to determine the rate release of drug. From Figure 4, it was observed that with increase in concentration of HPMC E15 there is significantly decreased in rate of drug release, and increase in concentration of mannitol leads faster rate of drug release.

Figure 6: 3D surface response plot showing effect of concentration of independent variables on hardness

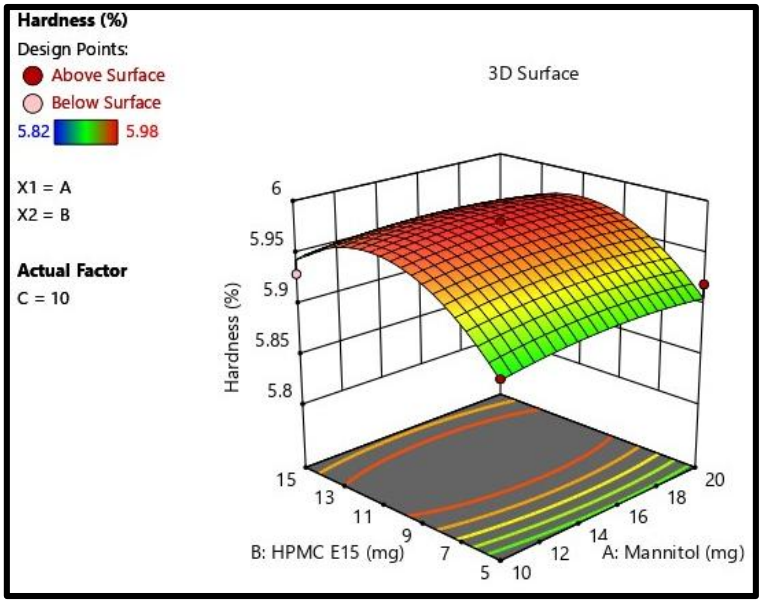
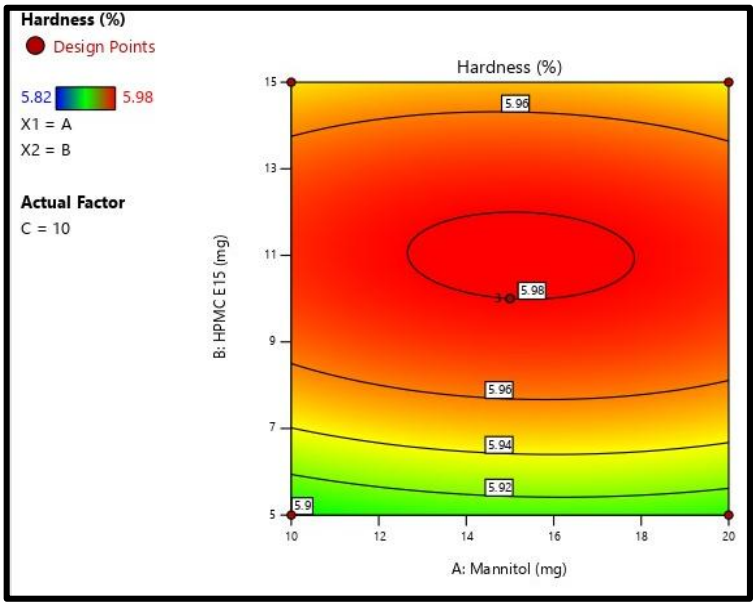


Figure 7: A counterplot showing relationship between various levels of concentration of independent variables on hardness



Hardness = 5.98 + 0.001A+0.0200B+0.02800C – 0.0025AB+0.0100AC -0.0075BC -0.0075A^2- 0.0500B^2 – 0.0425C^2

From the Figureure.7, it was observed that mannitol has significant effect on hardness. However, HPMC E15 also have significant effect on friability as concentration of HPMC E15 increases hardness also increases, and increased mannitol concentration decreased in friability due to enhanced mechanical properties.

Figure 8: 3D surface response plot showing effect of concentration of independent variables on weight gain

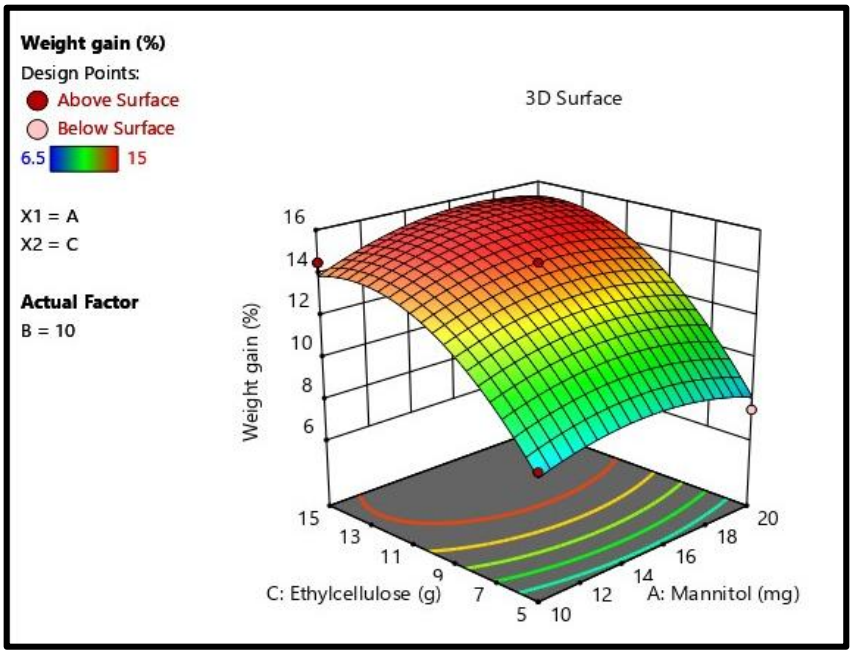
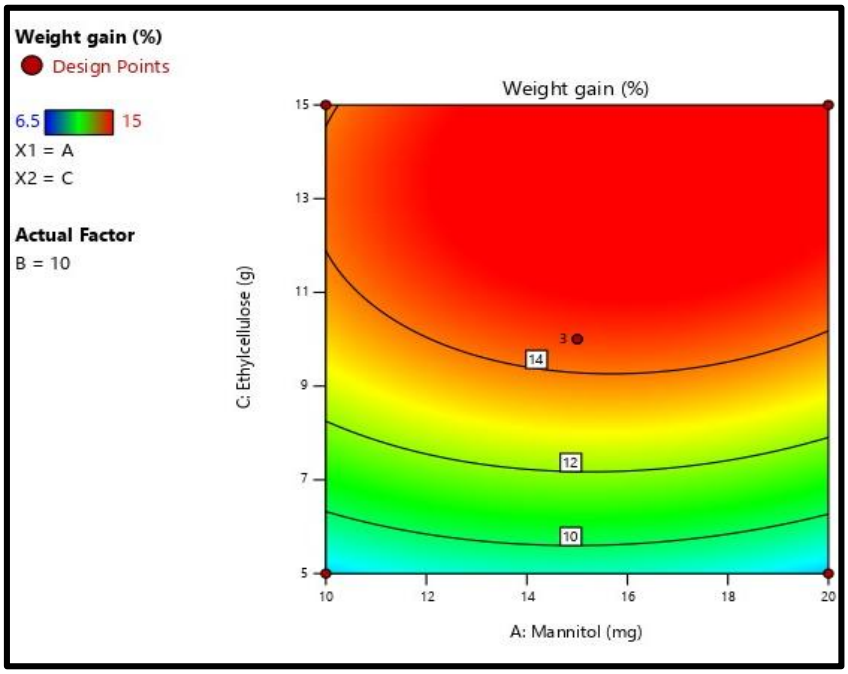


Figure 9 : A counterplot showing relationship between various levels of concentration of independent variables on weight gain



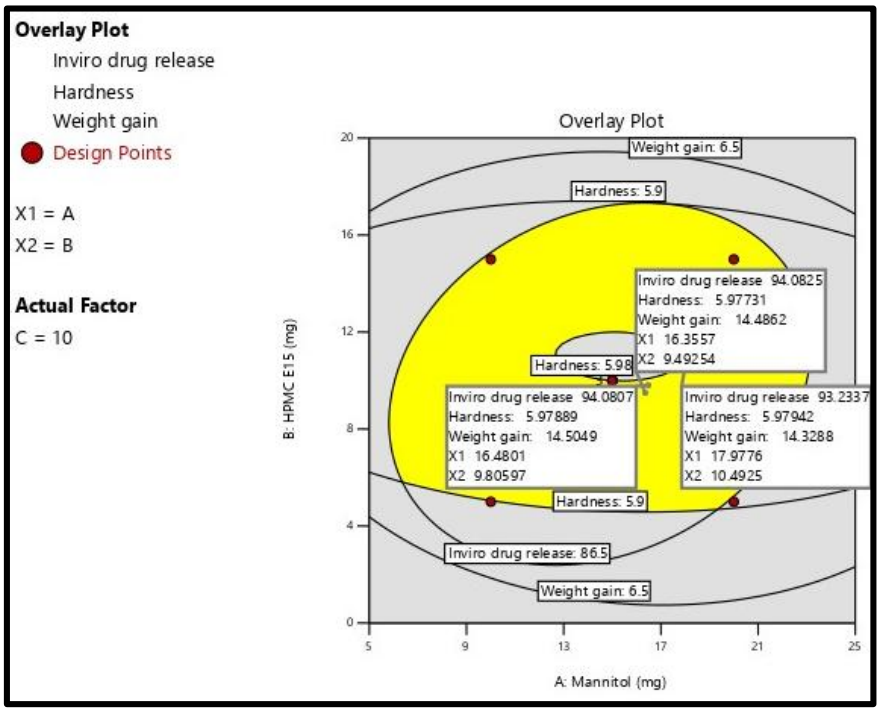
Weight gain = 14.50 + 0.315 A+ 0.1250B+3.19 C -0.2500AB+0.3750BC+0.0000AC - 0.9375A^2 – 2.31 B^2 – 2.19C^2

From the Figure 9, it was observed that ethyl cellulose has significant effect as weight gain. However, mannitol also have significant effect on coating as concentration of mannitol increases coating decreases, and increase in concentration of ethyl cellulose weight gain is also increased.

Table No. 5: Result of ANOVA

Response model	**Sum of square**	**Degree of freedom**	**Mean square**	**F value**	**P value**	**R^2**	**Ade. Precision**
% drug release	158.15	9	17.57	15.96	0.0035	0.9954	30.086
Hardness	0.0253	9	0.0028	16.04	0.0035	0.9880	18.2842
Weight gain	119.16	9	13.42	22.54	0.0016	0.9375	7.7243

Figure 10: Overlay plot of optimized batch



3.5 Evaluation of Optimal Formulation

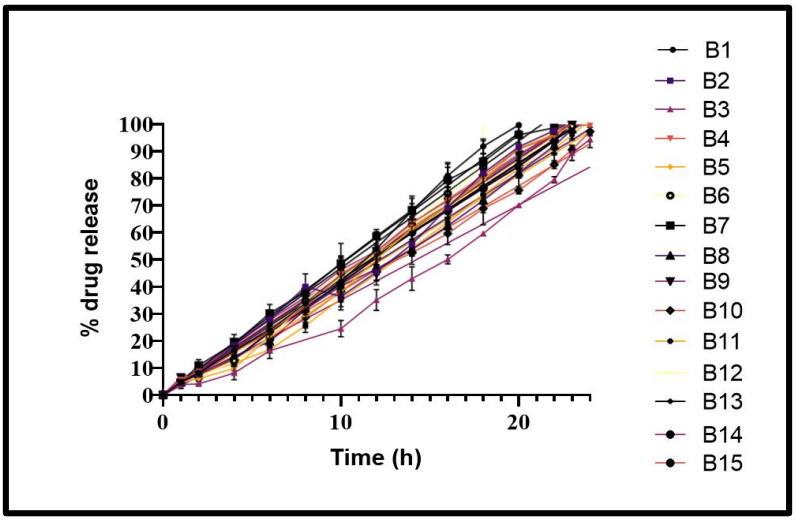
Evaluation tests for powder blend and formulated tablets (bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose of powder blend ,and hardness, drug content , thickness and weight variation of tablet) were performed to optimize the formulated osmotic controlled floating tablets. The batch 8 was selected as optimized batch , results of which are listed in table .

Table No. 6: % Drug release for dissolution

Sr .No	Parameters	Results
1.	% Drug content	97.63±0.37%
2.	Buoyancy time	56.88 ±0.34sec
3.	*In vitro* drug release	94.08 ± 1.27%
4.	Hardness	5.97±0.3%
5.	Weight gain	14.3 ±0.27%
6.	Angle of Repose	25.25 ±1.52
7.	Carr's index	9.84 ±1.16
8.	Hausner's ratio	1.12 ±1.18
9.	Tapped density	0.63 ±0.3g/cm3
10.	Bulk density	0.568 ±0.32 g/ml

3.6 In-vitro drug release profile

Figure 11: In-vitro drug release profile of all batches



In in-vitro dissolution study, polymer concentration had an effect on drug release. As the concentration of HPMC E15 were increased, the drug release was retarded, B8 batch gave drug release up to 24 h (99.33%). In batch F9 to F15, the concentration of both the polymers HPMC E15 and ethyl cellulose were more, so retards the drug for more than 24 h. Mannitol play important role in in-vitro drug as osmotic agent, increase in concentration of mannitol leads faster rate drug release of drug.

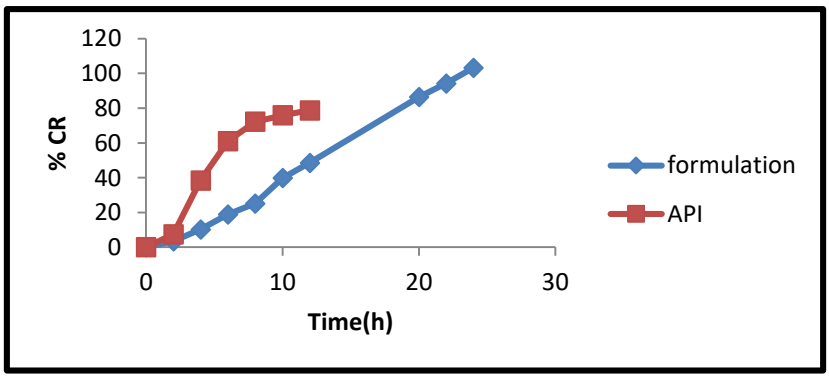
From the above result it was concluded that F8 batch was selected as optimized formulation based on best correlation with desired release profile i.e., 94.08% of bisoprolol fumarate . It was confirmed that the formulated tablets will release the medicament for longer period of time.

3.7 In-vitro release kinetics studies of optimal formulation

Table. No 7: In vitro release kinetic studies

Model	***In vitro* release kinetic study of optimized batch**			
	Zero order	**First order**	**Higuchi**	**Korsmeyer – peppas**
R^2	0.9924	0.8218	0.8957	0.5827
Slope (n)	4.4782	0.0613	24.294	0.7389
Intercept	5.2319	0.7772	29.892	1.0442

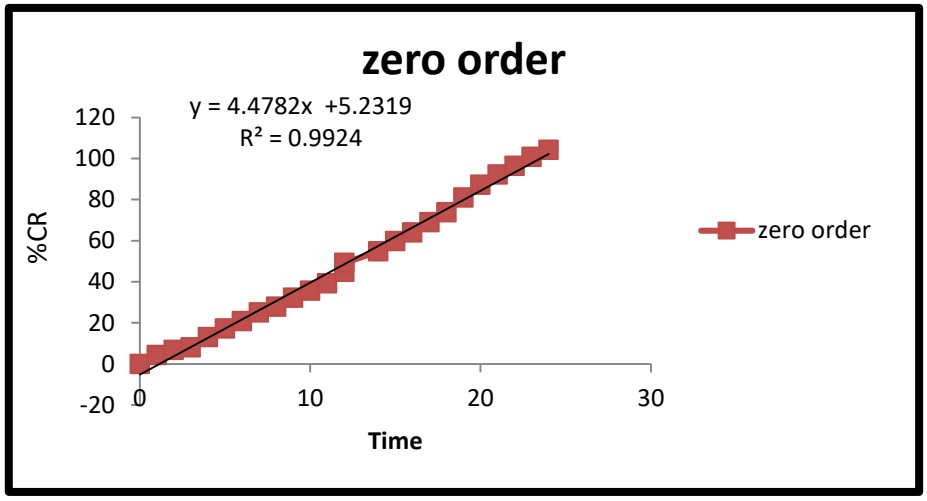
Figure 12: In-vitro drug release of API vs Formulation



Mean ±SD: n=3

In in-vitro drug release, release rate of drug of API is 92.88% upto 12 h which is sustained drug release less as compared to formulation which contain 94.08% upto 24 h and formed controlled release drug delivery system.

Figure 13 : zero order kinetic release graph



3.8 Stability Studies

Table No. 8: Stability studies evaluation parameters

Sr.No.	Parameters	Initial	15 days	30 days
1.	Drug content (%)	98.63±0.37	98.02±0.47	97.03±0.59
2.	Hardness (kg/cm$^{2)}$	5.97 ±0.3	5.98±0.45	5.98±0.58
3.	Floating lag time	56.88 sec	58.88 sec	59 sec
4.	Duration of floating	23h	24h	24h
5.	*In-vitro* drug release (%)	94.08 ±0.56	95.033±1.33	94.22±1.2

The result of drug content, hardness, floating lag time ,duration of floating, *in-vitro* drug release after 1 month stability in 40± 2˚C and 75 ± 5% RH was found in limit which indicates that there was no significant changes in the optimized formulation after 30 days ,and product was stable and well protected from environmental conditions.

4. Conclusion

Drug release from developed formulation was directly influenced by concentration of polymers in core and thickness of semipermeable membrane but remain unaffected by pH, hydrodynamic condition of release medium and amount of gas generating agent (SBC) in compression coat. All the formulation shows floating lag time of less than 2 min and floating log time up to 24 h. All the floating osmotic tablets prepared using HPMC E15(10%) and mannitol(20%) were of good quality with regard to drug content, hardness, and thickness. This study reports for the development of floating osmotic tablet for controlled release of Bisoprolol fumarate following oral administration. The results demonstrated that the release of the drug is dependent on rate controlling polymers used such as HPMC E15 and osmogene used such as mannitol**.** From the above result it was concluded that F8 batch was selected as optimized formulation based on best correlation with desired release profile i.e., 94.08% of Bisoprolol Fumarate. It was confirmed

that the formulated tablets will release the medicament for longer period of time. Optimized formulation was found to be stable in 40± 2˚C and 75 ± 5% RH for 1 month.

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