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Research Article

Formulation and Evaluation of Floating Matrix Tablets of Sacubitril and Valsartan

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ABSTRACT

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. These floating tablets mainly prepared for reduction of lag time and release the drug up to 12 hours and may also increase the bioavailability of the drugs by utilizing the drug to full extent avoiding unnecessary frequency of dosing. The purpose of this research was to develop and evaluated floating matrix tablets of sacubitril and valsartan. The floating matrix tablets of sacubitril and valsartan were prepared by direct compression method using altered concentrations of HPMC K4M, HPMC K100M, sodium alginate as polymers and sodium bicarbonate, citric acid as gas generating agent. FTIR, DSC studies conformed that there was no incompatibility between the polymers and the drug. Tablet preformulation parameters were within the pharmacopoeias limit. Tablets were evaluated by different parameters such as weight uniformity, content uniformity, thickness, hardness, *in vitro* release studies, buoyancy determination and kinetic analysis of dissolution data. The varying concentration of gas generating agent and polymers was found to affect on *in-vitro* drug release and floating lag time. Tablet showed ≤ 1min lag time, continuance of buoyancy for >12 h. The *in-vitro* drug release pattern of sacubitril and valsartan optimized floating tablets (F16) was fitted to different kinetic models which showed highest regression (r^2 = 0.9838) for Higuchi model. The Optimized formulation (F16) showed no significant change in physical appearance, drug content, floating lag time, *in vitro* dissolution studies after 75%±5% RH at 40±20C relative humidity for 6 months. Prepared floating tablets of sacubitril and valsartan may prove to be a potential candidate for safe and effective controlled drug delivery over an extended period of time for gastro retentive drug delivery system.

Keywords: Sacubitril, Valsartan, Floating drug delivery system, HPMC, *In vitro* release study, Buoyancy determination.

INTRODUCTION

Drugs which are easily absorbed from the gastrointestinal tract and those with short half-lives are quickly eliminated from the systemic circulation due to which frequent dosing is required. To overcome this problem, gastro retentive drug delivery systems[1]. Which provide effective plasma drug concentration for longer periods thereby reducing the dosing frequency are being formulated[2-4]. It also has an advantage of minimizing the fluctuations in plasma drug concentration by delivering the drug in a controlled and reproducible manner. Floating drug delivery system or hydrodynamically[5,6] balanced systems has been reported for prolonging the residence time of drug delivery system in a particular region of the gastrointestinal tract, were first described by Davis (1968)[7]. The floating of FDDS occurs due to their lower bulk density than the gastric contents or due to gaseous phase formed inside in the environment. It is applicable for those drugs which (i) act locally; (ii) have a narrow absorption window in the small intestinal region;

and (iii) unstable in the intestinal environment[8,9]. Sacubitril is an antihypertensive drug used in combination with valsartan[10].The combination drug valsartan/sacubitril, marketed under the brand name Entresto, is a treatment for heart failure[11]. Sacubitril is a prodrug that is activated to sacubitril at by de-ethylation via esterases[12]. Sacubitrilat inhibits the enzyme neprilysin. The most common adverse reactions with sacubitril plus valsartan included hypotension, hyperkalemia, cough, dizziness, and renal failure. Sacubitrilis chemically (S)-5-[(4- phenylphenyl) methyl] pyrrolidin-2-one. Sacubitril Slightly soluble in water, sparingly soluble in dehydrated alcohol, freely soluble in methanol. Valsartan is used to treat high blood pressure, congestive heart failure, and to reduce death for people with left ventricular dysfunction after having had a heart attack[13]. Valsartan blocks the actions of angiotensin II, which include constricting blood vessels and activating aldosterone, to reduce blood pressure[14]. The drug binds to angiotensin type I receptors (AT1), working as an antagonist. This mechanism of action is different than the ACE inhibitor drugs, which

block the conversion of angiotensin I to angiotensin II. Since valsartan acts at the receptor, it can provide more complete angiotensin II antagonism since angiotensin II is generated by other enzymes as well as ACE. Most common side effects include dizziness, low blood pressure, and diarrhea. Valsartan is chemically (2S)-3-methyl-2-(N-{[2'-(2H- 1,2,3,4-tetrazole-5-yl)biphenyl-4-yl]methyl}pentanamid o) butanoic acid. Valsartan soluble in acetonitrile, practically insoluble in water also soluble in methanol. The present study aims in designing floating tablets of sacubitril and valsartan using HPMC K4M, HPMC K100M, sodium alginate, sodium bicarbonate, citric acid and evaluating the prepared tablets.

MATERIALS AND METHODS

Materials

Sacubitril, Valsartan was obtained as a gift sample from Torrent Research Centre, Ahmedabad. HPMC K4M, HPMC K100M, sodium alginate, sodium bicarbonate, citric acid was obtained from ACS Chemicals, Ahmedabad. Magnesium stearate, DCP, Talc, were received from S D fine Chemicals, Mumbai. India. All other solvents and reagents were purchased from Merck (Germany) and were of analytical grade. All the studies were carried in distilled water.

Methods

Determination of absorption maxima

A solution of containing the concentration 15and 40μg/ml was prepared in 0.1N HCl (1.2 pH). UV spectrum was taken using Double beam UV/VIS spectrophotometer (Shimdzu Jappan). The solution was scanned in the range of 200-400nm.

Preparation calibration curve of Valsartan

100mg of drug was accurately weighed and dissolved in 100ml 0.1N HCl (1.2 pH) in 10 ml volumetric flask, to make (1000 μg/ml) standard stock solution (1). Then 10 ml stock solution (1) was taken in another 100 ml volumetric flask to make (100μg/ml) standard stock solution (2), then again 0.5, 1, 1.5, 2, 2.5,3 and 3.5 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 5, 10, 15, 20, 25,30 and 35μg/ml with 0.1N HCl (1.2 pH). The absorbance of standard solution was determined using UV/ VIS spectrophotometer (Shimdzu Jappan) at 238nm. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which determined by least-square linear regression analysis.

Preparation calibration curve of Sacubitril

100mg of drug was accurately weighed and dissolved in 100ml 0.1N HCl (1.2 pH) in 10 ml volumetric flask, to make (1000 μg/ml) standard stock solution (1). Then 10 ml stock solution (1) was taken in another 100 ml volumetric flask to make (100μg/ml) standard stock solution (2), then again 1,2,3,4,5,6 and7ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 10,20,30,40,50,60 and 70μg/ml with 0.1N HCl (1.2 pH). The absorbance of standard solution was determined using UV/ VIS spectrophotometer (Shimdzu Jappan) at 266nm. Linearity of standard curve was assessed from the square of correlation coefficient (r^2) which determined by least-square linear regression analysis.

Drug -excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

Before formulating a dosage form it is very necessary to confirm that drug is not interacting with the polymer under certain experimental studies. Interacting among drug and

polymer may affect the efficacy of final dosage form. The infrared spectra of pure drug and with excipients (1:1) was recorded between 600 and 4000 cm−1 by Fourier-transform infrared (FT-IR) spectrometer (Bruker, USA) using the potassium bromide pellet technique.

DSC Study

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the Preformulation stage during the development of dosage form. Differential Scanning Calorimeter allows the fast evaluation of possible incompatibilities, because it shows changes in the appearance, shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug, other excipients and optimized batch were recorded.

Pre compression evaluation

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, carr's index, and hausner ratio.

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation. $θ = \tan^{-1}(h/r)$

Where, h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing
TBD = Powder weight /tapped volume of the packing

Compressibility index

The compressibility index of the granules was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = [(TBD – LBD)/TBD] \times 100.$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula[15,16].

$$\text{Hausner's ratio} = \text{Tapped density/Bulk density}.$$

Formulation development of Tablets

Direct compression method

Preliminary Trials (For selection of polymer)

Composition of preliminary trials for selection of polymer was shown in Table 1. Tablets containing different matrix forming agent were prepared by direct compression technique. All the powders were passed through 40 mesh sieves. Required quantity of drug and various ingredients like matrix forming agent, gas generating agent and diluents were mixed thoroughly. Talc and magnesium stearate were finally added as glidant and lubricant respectively. The blend was compressed using tablet press machine.

Table 1 Selection of polymer						
Ingredients (mg)	F1	F2	F3	F4	F5	F6
Sacubitril	24	24	24	24	24	24
Valsartan	26	26	26	26	26	26
HPC K4M	80	-	-	30	-	-
HPMC K100M	-	80	-	-	30	-
Sod. Alginate	-	-	80	-	-	30
Sod. Bicarbonate	20	20	20	20	20	20
Citric Acid	10	10	10	10	10	10
DCP	64	64	64	114	114	114
Talc	2	2	2	2	2	2
Mg. stearate	4	4	4	4	4	4
Total weight	230	230	230	230	230	230

Optimization of concentration of HPMC K100M as matrixing agent

The result of preliminary trials revealed that HPMC K100M as a matrixing agent gives satisfactory results. Hence HPMC K100M was used in different concentrations of 25-10%, along with drug. Composition of different batches is shown in Table 2

Table 2 Determination of polymer (HPMC K100M) concentration				
Ingredients (mg)	F7	F8	F9	F10
Sacubitril	24	24	24	24
Valsartan	26	26	26	26
HPMC K100 M	50	40	30	20
Sod. Bicarbonate	20	20	20	20
Citric Acid	10	10	10	10
DCP	94	104	114	124
Talc	2	2	2	2
Mg. stearate	4	4	4	4
Total weight	230	230	230	230

Selection of Gas generating agent using HPMC K100M as matrixing agent

Composition for selection of gas generating agent was shown in Table 3. In this formula two different gas generating agents like sodium bicarbonate and calcium carbonate were selected in same concentration.

Table 3 Effect of different gas generating agents on drug release profile		
Ingredients (mg)	F11	F12
Sacubitril	24	24
Valsartan	26	26
HPMC K100M	30	30
Sod. Bicarbonate	20	-
Ca. carbonate	-	20
Citric Acid	10	10
DCP	114	114
Talc	2	2
Mg. stearate	4	4
Total weight	230	230

Table 4 Optimized the concentration of Gas generating agent			
Ingredients (mg)	F13	F14	F15
Sacubitril	24	24	24
Valsartan	26	26	26
HPMC K100 M	30	30	30
Sod. Bicarbonate	15	20	25
Citric Acid	10	10	10
DCP	129	114	119
Talc	2	2	2
Mg. stearate	4	4	4
Total weight	230	230	230

Optimization of the concentration of sodium bicarbonate as a Gas generating agent

For optimization of gas generating agent, different concentration of sodium bicarbonate 7.5%, 10% and 12.5% should be taken which is shown in Table 4. The effect of concentration of gas generating agent was to be evaluated.

Selection of diluents using release profile of HPMC K100M floating matrix tablets

To selection of diluents using the release profile of floating matrix tablet from different formulation batches containing lactose (water soluble) and dicalcium phosphate (DCP) (water insoluble) were formulated Table 5.

Table 5 Selection of diluents		
Ingredients (mg)	F16	F17
Sacubitril	24	24
Valsartan	26	26
HPMC K100M	30	30
Sod. Bicarbonate	20	20
Citric Acid	10	10
DCP	114	-
Lactose	-	114
Talc	2	2
Mg. stearate	4	4
Total weight	230	230

Evaluation of tablets

All the tablets were evaluated for following various parameters which includes.

Weight variation test

To study weight variation 20 tablets of the formulation were weighed using a Sartorius electronic balance.

Hardness

The hardness of five tablets was determined using the Monsanto hardness tester and the average values were calculated.

Thickness

The thickness of the tables was determined by using Vernier calipers. Five tablets were used, and average values were calculated.

Tablet friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 10 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\%Friability= W0\text{-}W/\ W \times 100$$

Drug content

Five tablets were weighed individually, and the drug was extracted in 0.1 N HCl, filter through 0.45μ membrane. The absorbance was measured at 238 and 266 nm after suitable dilution using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer.

In vitro buoyancy studies

The in vitro buoyancy was determined by using dissolution testing apparatus USP type-1. The tablets were placed in 900 ml 0.1 N HCL at 100 rpm basket rotation at $37\pm0.5^\circ$c. The time require for tablets to ascend to the surface of dissolution medium and time taken by tablet to buoyant on surface of medium was recorded as floating lag time and total floating time.

Swelling index

The swelling index of tablets was in 0.1 N HCL. Tablets were weighed individually named as W_0 and then it is placed in separately in glass beaker containing 200 ml 0.1N HCL at $37\pm0.\ 5^\circ$C. At periodical time interval tablets were removed from beaker and extra amount of surface water discarded by blotting paper and then tablets were weighed and it is

referred as W_t and swelling index was calculated using following formula:

$$Swelling\ index = \frac{W_t - W_0}{W_0}$$

where $W_{t\ =}$ weight after swelling

W_0 = weight before swelling

Where, W_0 is the initial weight of tablet, and W_t is the weight of the tablet at time t.

Content uniformity

Randomly selected 10 tablets were weighed and make powdered individually. Take powder of individual tablet which is equivalent to 500 mg was weighed and dissolve in 100 ml of methanol, then the solution was sonicated for 15 min, then undissolved matter was removed by filtration. The absorbance of the diluted solutions is measured at 238 and 266 nm.

In Vitro dissolution studies

USP apparatus II was used to test the dissolution profile using 900 ml of 0.1N HCl as dissolution medium at 50 rpm and $37 \cdot C \pm 0.5 \cdot C$. six tablets from each batch were placed into respective basket containing HCl. 10ml of the sample was withdrawn hourly for 8h. The sample was filtered and from the filtrate 3ml was withdrawn. The volume was adjusted to 100ml with 0.1N HCl in the 100 ml to prepare 10 mcg/ml solutions. Absorbance of the solution was measured using UV spectrophotometer at 238 and 266 nm.

Drug release kinetic study

Data obtained form in vitro drug release studies were fitted to disso calculation software. The kinetic models used are zero order, first order, Korshmers and papps, Hexon crowell, and Higuchi equation.

The rate and mechanism of release of Drug from the prepared tablets were analyzed by fitting the dissolution data into the zero-order equation:

$Q = k0t$

Where, Q is the amount of drug released at time t, k0 is the release rate constant. The dissolution data fitted to the first order equation:

$\ln (100-Q) = \ln 100 - K1\ t$

Where, k1 is the release rate constant. The dissolution data was fitted to the Higuchi's equation:

$Q = k2\ t1/2$

Where, k2 is the diffusion rate constant.

The dissolution data was also fitted to Korsmeyer equation, which is often used to describe the drug release behavior from polymeric systems:

$Log (Mt/M\infty) = log\ k + n\ log\ t$

Where Mt is the amount of drug released at time t, M∞ is the amount of drug release after infinite time, K is a release rate constant incorporating structural and geometric characteristics of the tablet, n is the diffusion exponent indicative of the mechanism of drug release[17-19].

Stability study

Optimized batch of prepared floating tablet subjected to accelerated stability studies at 40 °C and 75% RH for 1 month in a humidity chamber. The tablets of best batch were

packed in aluminum foil pouch and analyzed for floating behavior and in-vitro drug release study.

RESULTS AND DISCUSSION

Sacubitril was found to be White to off-white solid powder in appearance, Characteristic odour and tasteless. Sacubitril was freely soluble in 0.1N HCL and distilled water. Valsartan was found to be white to practically white fine powder in appearance, Characteristic odour and was freely soluble in 0.1N HCL and distilled water. The IR spectra of the pure drug and the optimized formulation showed in figure 1 and 2. From the figure, it concluded that there was no any interaction between drug and excipients found.
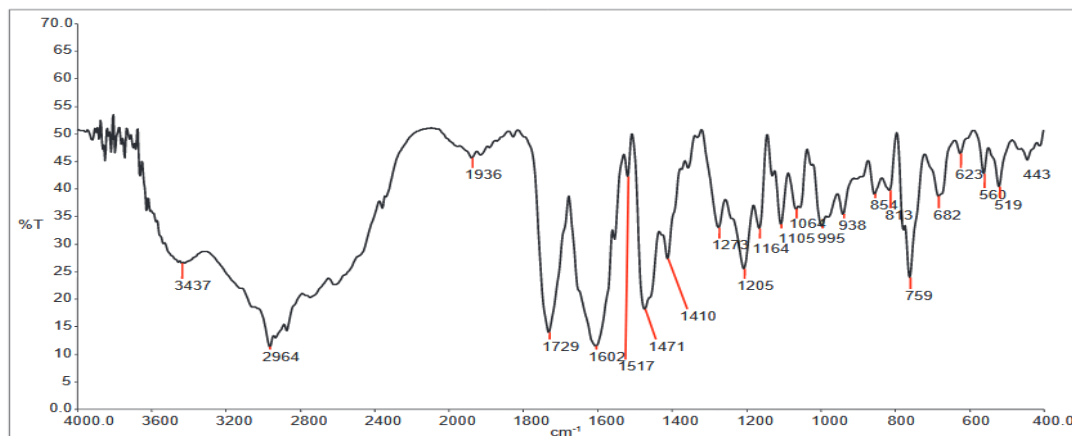
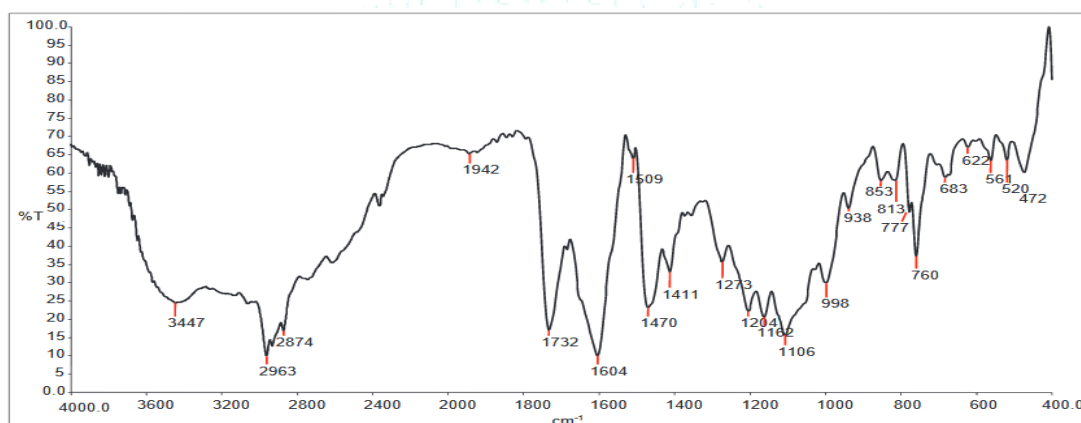**Figure 1 FT-IR Spectrum of Sacubitril and Valsartan**

Figure 2 FT-IR Spectrum of optimized Formulation (F16)

The DSC thermograms of the Sacubitril and Valsartan are shown in below figure 3 and 4 individually. Figure 5 shows DSC thermogram of the final formulation (F16). From the DSC Thermogram it concluded that no any drug excipients interaction observed and formulation excipients found compatible with drugs.
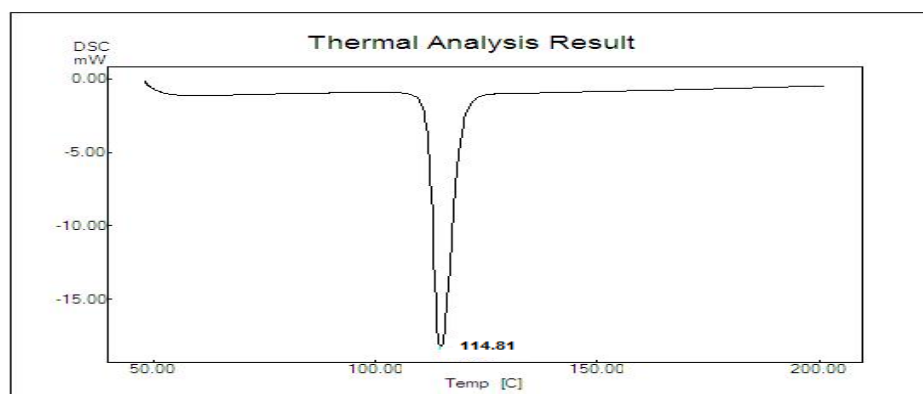

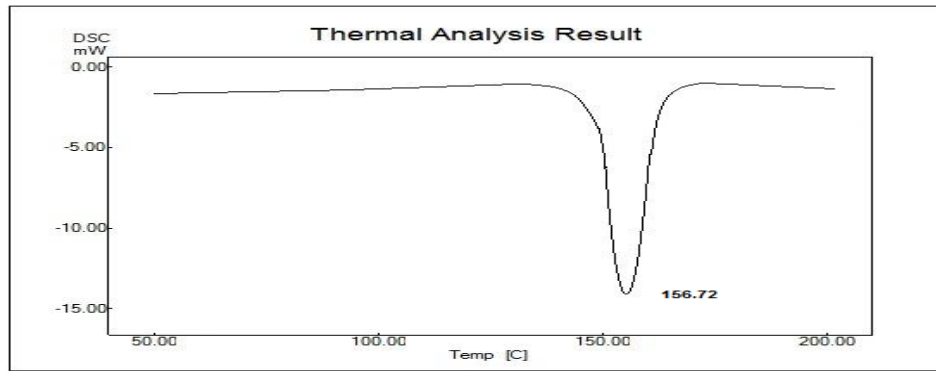
Figure 3 DSC Thermogram of Valsartan

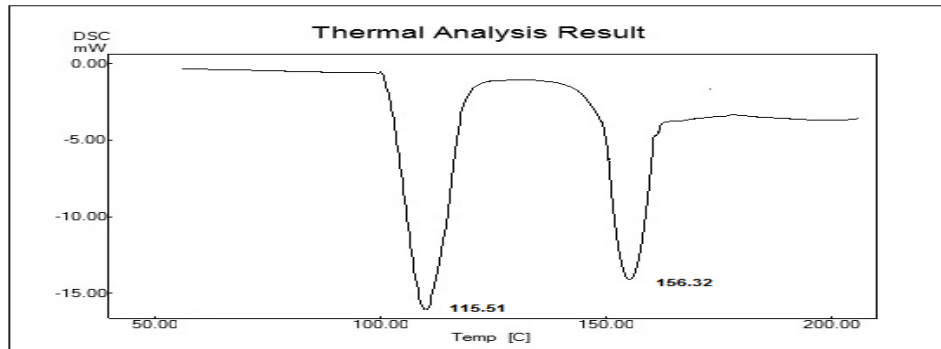**Figure 4 DSC Thermogram of Sacubitril**

Figure 5 DSC Thermogram of Final Formulation (F16)

The calibration curve of **Sacubitril and Valsartan** was found to be linear in the concentration range of 10-70 and 5-35µg/ml at 266 and 238nm respectively figure 6, 7.
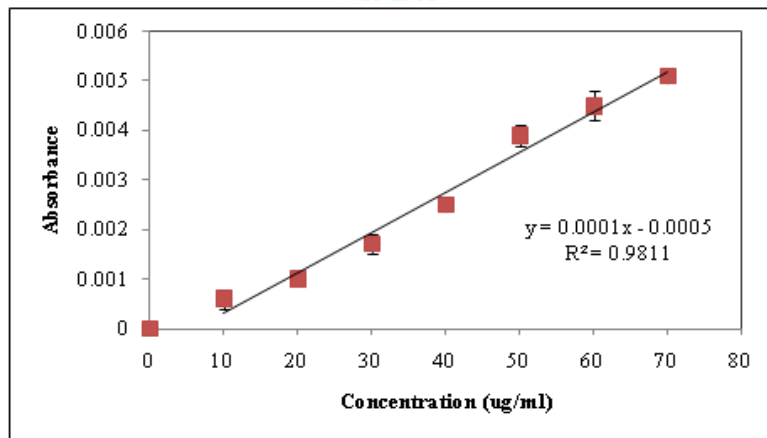

Figure 6 Calibration curve of Sacubitril in 0.1 N HCl at 266 nm
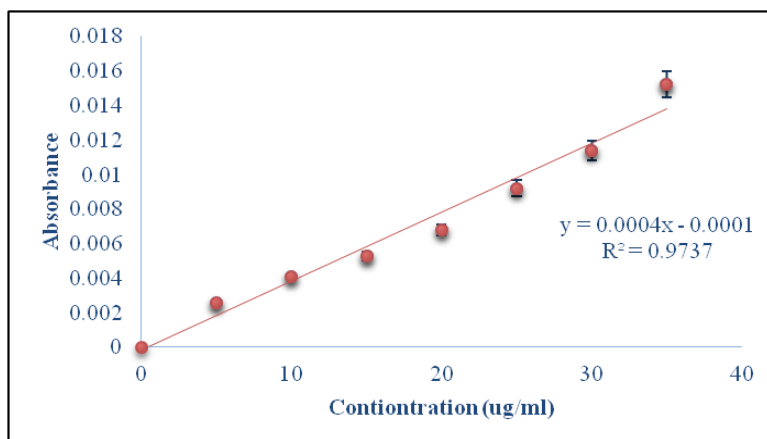

Figure 7 Calibration curve of Valsartan in 0.1 N HCl at 238 nm

Tablet powder blend was subjected to various pre-formulation parameters Table 6. From the below table we found that bulk density found between 0.42-0.57g/ml and tapped density found between 0.49-0.64 g/ml. Hausner's ratio value is less than 1.25 for all formulation means all the formulation has good flow properties. And it favors to do with direct compression method for tablet preparation.

Table 6 Pre-Compression Parameters of Formulation F1-F17

Formulation	Bulk density (g /ml) (n=3)	Tapped density (g /ml) (n=3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ°) (n=3)
F1	0.54 ± 0.02	0.61 ± 0.03	11.48 ± 0.01	1.13 ± 0.02	17.25 ± 0.05
F2	0.48 ± 0.03	0.52 ± 0.05	7.69 ± 0.02	1.08 ± 0.01	19.22 ± 0.08
F3	0.47 ± 0.05	0.55 ± 0.03	14.55 ± 0.04	1.17 ± 0.02	21.12 ± 0.07
F4	0.57 ± 0.07	0.60 ± 0.04	5.00 ± 0.07	1.05 ± 0.01	19.26 ± 0.08
F5	0.47 ± 0.04	0.54 ± 0.04	12.96 ± 0.05	1.15 ± 0.02	25.15 ± 0.07
F6	0.42 ± 0.05	0.54 ± 0.02	16.00 ± 0.06	1.19 ± 0.02	21.15 ± 0.05
F7	0.51 ± 0.08	0.56 ± 0.05	8.93 ± 0.04	1.10 ± 0.01	19.56 ± 0.04
F8	0.52 ± 0.02	0.58 ± 0.04	10.34 ± 0.05	1.12 ± 0.01	18.75 ± 0.03
F9	0.47 ± 0.04	0.54 ± 0.02	12.96 ± 0.05	1.15 ± 0.01	17.84 ± 0.03
F10	0.58 ± 0.03	0.65 ± 0.03	10.77 ± 0.02	1.12 ± 0.01	19.29 ± 0.05
F11	0.49 ± 0.04	0.58 ± 0.08	15.52 ± 0.03	1.18 ± 0.02	22.14 ± 0.08
F12	0.47 ± 0.05	0.54 ± 0.08	12.96 ± 0.04	1.15 ± 0.02	21.04 ± 0.07
F13	0.48 ± 0.06	0.59 ± 0.07	18.64 ± 0.02	1.23 ± 0.01	18.56 ± 0.05
F14	0.58 ± 0.05	0.64 ± 0.05	9.38 ± 0.03	1.10 ± 0.01	17.45 ± 0.06
F15	0.48 ± 0.04	0.53 ± 0.06	9.43 ± 0.05	1.10 ± 0.02	16.84 ± 0.04
F16	0.43 ± 0.03	0.49 ± 0.04	12.24 ± 0.06	1.14 ± 0.01	19.84 ± 0.06
F17	0.46 ± 0.07	0.52 ± 0.07	11.54 ± 0.02	1.13 ± 0.01	21.54 ± 0.04

In process test for tablets should be performed for acceptance of batches. All batches were performed IPQC test like weight variation, Drug content, Hardness and Thickness. Optimized batch F16 passed all the specified range of parameter. F16 batch was shown weight variation in the range of 230 ± 3.5 mg. It had also sufficient hardness to stand mechanical shock. Friability of batch F16 was 0.65±0.17 % which was desirable for our formulation Table 7, 8.

Table 7 Evaluation parameter of tablets				
Batch	Weight variation test (mg)	Thickness (mm) (n=3)	Hardness (kg/cm²)	Friability (%)
F1	235 ± 2.82	4.51±0.09	4.8 ± 0.12	0.84 ± 0.14
F2	230 ± 2.57	4.49±0.11	4.5 ± 0.05	0.70 ± 0.29
F3	230 ± 3.51	4.50±0.12	4.5 ± 0.06	0.73 ± 0.18
F4	230 ± 2.54	4.52±0.11	5 ± 0.15	0.61 ± 0.24
F5	225 ± 2.74	4.51±0.11	5 ± 0.13	0.62 ± 0.24
F6	230 ± 2.62	4.48±0.13	5.5 ± 0.05	0.77 ± 0.16
F7	230 ± 3.59	4.52±0.14	5 ± 0.15	0.82 ± 0.11
F8	235 ± 2.88	4.51±0.12	6 ± 0.11	0.84 ± 0.15
F9	230 ± 2.56	4.51±0.10	5 ± 0.14	0.70 ± 0.29
F10	225 ± 2.86	4.50±0.13	4.5 ± 0.03	0.73 ± 0.18
F11	233 ± 2.34	4.49±0.14	5 ± 0.16	0.61 ± 0.24
F12	231 ± 3.51	4.47±0.08	6 ± 0.19	0.68 ± 0.14
F13	229 ± 3.88	4.51±0.09	4.5 ± 0.06	0.65 ± 0.13
F14	230 ± 2.54	4.48±0.11	6 ± 0.11	0.54 ± 0.21
F15	226 ± 2.88	4.47±0.06	5 ± 0.12	0.81 ± 0.15
F16	**230 ± 3.54**	**4.49±0.11**	**5.6 ± 0.2**	**0.65 ± 0.17**
F17	231 ± 2.46	4.52±0.14	4.5 ± 0.06	0.73 ± 0.16

Table 8 Post Compression Parameters of Formulation F1-F17

Formulation	Drug Content of Sacubitril (%) (n=3)	Drug Content of Valsartan (%) (n=3)	Swelling Index (%) (n=3)	Floating Lag Time (sec)	Total Floating Time (hr)
F1	99.2 ± 0.3	99.4 ± 0.4	58.2 ± 4.4	840 sec	> 10 hrs.
F2	99.8 ± 0.4	98.5 ± 0.5	62.5 ± 2.2	35 sec	> 12 hrs.
F3	98.5 ± 0.5	99.5 ± 0.7	54.6 ± 5.3	30 sec	> 6 hrs.
F4	97.8 ± 0.7	97.8 ± 0.5	51.6 ± 6.2	45 sec	> 8 hrs.
F5	99.5 ± 0.5	99.8 ± 0.6	62.4 ± 4.3	19 sec	> 12 hrs.
F6	99.4 ± 0.4	99.4 ± 0.5	68.5 ± 5.2	105 sec	> 6 hrs.
F7	99.5 ± 0.5	98.4 ± 0.4	72.1 ± 1.6	35 sec	> 12 hrs.
F8	99.7 ± 0.6	99.4 ± 0.2	68.6 ± 3.2	43 sec	> 12 hrs.
F9	98.4 ± 0.4	98.8 ± 0.4	69.4 ± 2.5	40 sec	> 12 hrs.
F10	100.5 ± 0.5	99.7 ± 0.2	68.5 ± 3.2	50 sec	> 12 hrs.
F11	100.8 ± 0.4	99.9 ± 0.6	67.4 ± 3.6	20 sec	> 12 hrs.
F12	98.7 ± 0.2	99.8 ± 0.4	66.5 ± 5.6	22 sec	> 12 hrs.
F13	99.5 ± 0.3	99.4 ± 0.5	69.7 ± 3.9	25 sec	> 12 hrs.
F14	98.6 ± 0.4	99.7 ± 0.7	78.5 ± 2.9	20 sec	> 12 hrs.
F15	99.7 ± 0.5	98.7 ± 0.5	71.5 ± 3.4	19 sec	> 12 hrs.
F16	**99.8 ± 0.5**	**99.6 ± 0.8**	**85.6 ± 5.6**	**17 sec**	**> 12 hrs.**
F17	98.7 ± 0.4	98.9 ± 0.4	74.1 ± 4.5	20 sec	> 12 hrs.

In Vitro drug release study

Preliminary Trials (For selection of polymer)

For preliminary trial, three different matrixing agents were used, at different concentration level as indicated in Table 1. The polymers were taken HPC HXF (Klucel) (F1), HPMC K100M (F2) and Sodium alginate (F3) as matrixing agent and sodium bicarbonate as gas generating agent. In all among these batches, when 40% concentration of polymer was used then drug release from matrix was much sustained. Drug release after 12 hours in HPC HXF (Klucel), HPMC K100M and Sodium alginate is 46.27%, 84.23% and 72.32% respectively. Therefore, it was required to decrease the concentration of each of the polymers. Decreasing concentration up to 15% of each matrixing agent, drug release was evaluated. Batches F4 - F6 were prepared and

dissolution was taken in 0.1N HCl in Type II dissolution apparatus in 50 RPM at 37.5°C. From these batches, HPMC K100M matrix shows best release profile which is more similar to the calculated theoretical profile as compare to other polymers. Drug release after 12 hours was 93.46% which was suitable for our formulation. Effect of different matrixing agent on floating lag time also determined. Tablets containing HPC polymer lost their shape due to their more swelling property. And in case of sodium alginate floating lag time was higher as compared to HPMC K100M batches therefore; they were not suitable for our formulation. F5 batch which has matrixing agent HPMC K100M gives floating lag time of only 15 sec., which is lower as compared to other and desirable for best formulation. So, from the preliminary study, we selected HPMC K100M as a matrixing agent for our formulation Figure 8, 9.
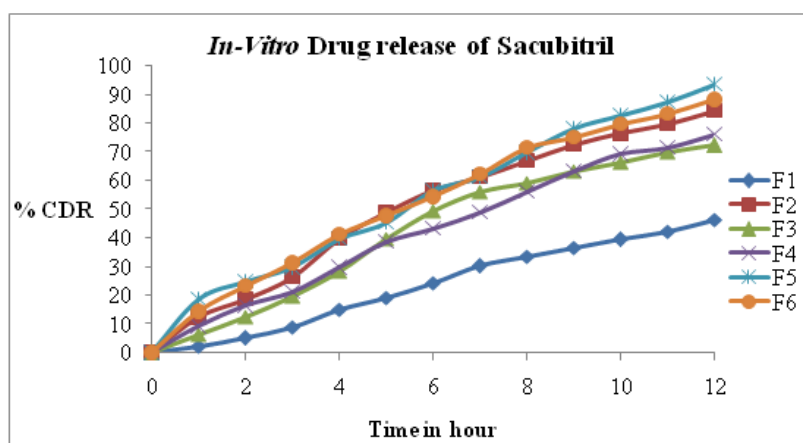

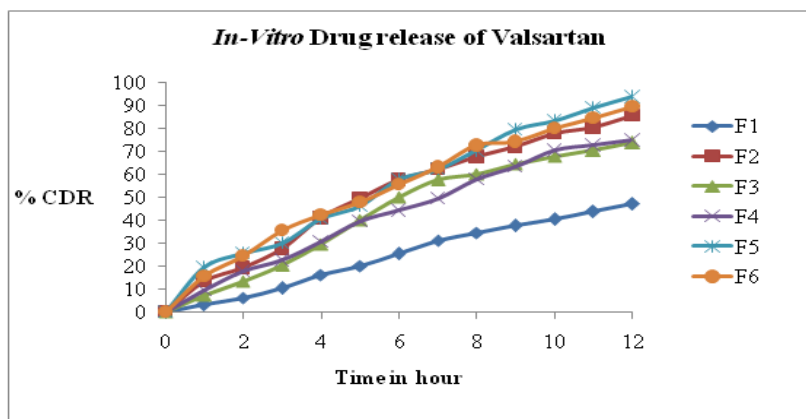**Figure 8 In-Vitro Drug release of Sacubitril in Preliminary Trials**

Figure 9 In-Vitro Drug release of Valsartan in Preliminary Trials

Optimization of concentration of HPMC K100M as matrixing agent

From the Table 2, different concentrations of HPMC K100M were taken as matrixing agents. For optimizing the concentration of polymer, concentration of HPMC K100M taken were from 25% to 10% in decreasing order. In this study, it was observed that when decreasing the concentration of polymer drug release increased and

floating lag time decreased. Observed that when increasing concentration of matrixing agent drug release sustained. Thus, observed data show same result. From this data batch F9 shows 89.43% drug release after 12 hours and floating lag time is 20 sec. considering the similarity factor, batch F9 is best suitable for our preparation. Similarity factor f2 value of batch F9 was >>50 (i.e 64.02). Drug release profile of different concentrations of HPMC K100M is shown in figure 10, 11.
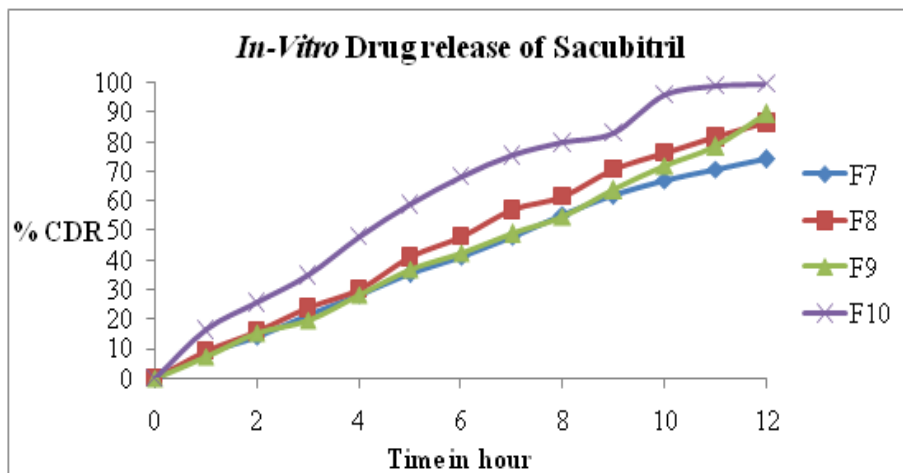

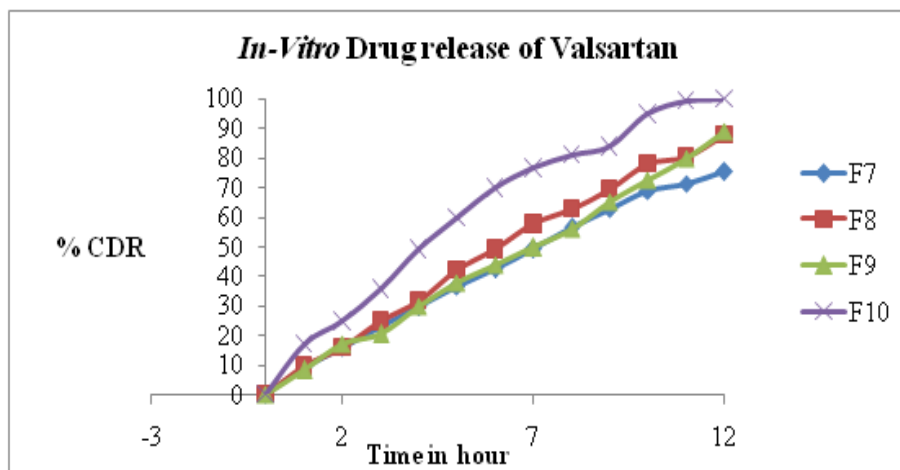**Figure 10 In-Vitro Drug release of Sacubitril**

Figure 11 In-Vitro Drug release of Valsartan

Selection of Gas generating agent using HPMC K100M as matrixing agent

The composition of formula for selection of gas generating agent in gastro retentive drug delivery system. The effect of gas generating agent on drug release profile was checked out by taking different gas generating agent like sodium bicarbonate and calcium carbonate in 10% concentration. There is no significant difference between the effect of sodium bicarbonate and calcium carbonate on release profile. However, this study observed that sodium bicarbonate has higher gas generating efficiency than calcium carbonate. The drug release profile of these batches showed that sodium bicarbonate (batch F11) release up to 92.13% drug whereas in calcium carbonate (batch F12) showed 84.27% drug release after 12 hours. There is no significant effect on floating lag time of optimized tablets. But when considering Similarity factor (f2) of F11 and F12 batches has 68.56 and 58.07 which showed that sodium bicarbonate is more suitable for our formulation. So, sodium bicarbonate is selected for our formulation.

Optimized the concentration of sodium bicarbonate as a Gas generating agent

The effect of concentration of sodium bicarbonate on drug release profile was checked out on formulations containing approximately 7.5%, 10 % and 12.5% of the gas generating agent. The drug release in the first hour for all the three batches F13, F14 and F15 was approx. near to 33 % and that after 12 hours was near to 95% (> 90%). The similarity factor for batches F13, F14 and F15 in ascending order of

batch numbers was 63.39, 67.86 and 58.03 respectively. During the in vitro buoyancy test, a significant change was observed in the floating lag time of the formulation with increased amount of sodium bicarbonate. With increase in concentration of sodium bicarbonate floating lag time decreased. Desired floating of the tablets was not achieved in lower concentrations of sodium bicarbonate. The FLT for formulation batch F14 was 20 seconds, which contained approx. 10% concentration of sodium bicarbonate. The FLT and drug release after 12 hours of batch F14 was very close to the desired objective and also to that of batch F15. Evaluating all these parameters, batch A14 was selected as the optimized batch since it gives best release profile as compare to theoretical profile (FLT: approximately 20 seconds) and having similarity factor greater than 50. Thus, from drug release profile, 10% concentration of sodium bicarbonate was optimum.

Selection of diluents using release profile of HPMC K100M floating matrix tablets

For selection of diluents, water-soluble (lactose) (F17) and water-insoluble (DCP) (F16) fillers should be used. There were no differences between the two different fillers. But from the point of view of directly compressible method, DCP was best suitable because of their good flow property and compressibility. The slight increase in drug release in DCP can probably be explained by the less tight hydrogel structures upon swelling. There were same results predicted in our investigation. Thus, DCP should be taken as filler for further investigation due to their good flow property and compressibility Figure 12, 13.
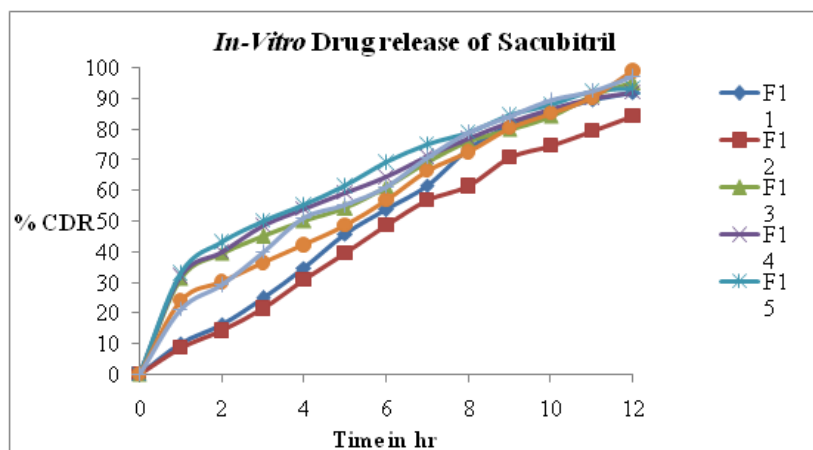

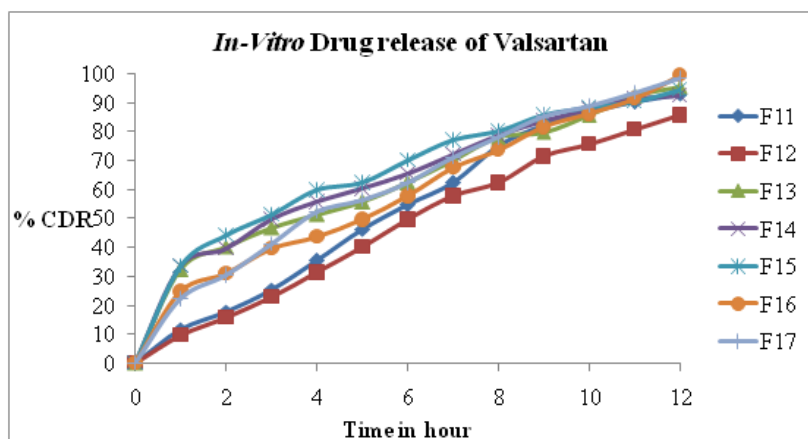**Figure 12 In-Vitro Drug release of Sacubitril**

Figure 13 In-Vitro Drug release of Valsartan

All the different formulation had floating lag time less than 2 minutes. The pictorial results of in vitro buoyancy study of the best batch are shown in figure 14, which clearly depicts the floating lag time, stable and persistent buoyancy and swelling characteristic of tablet.
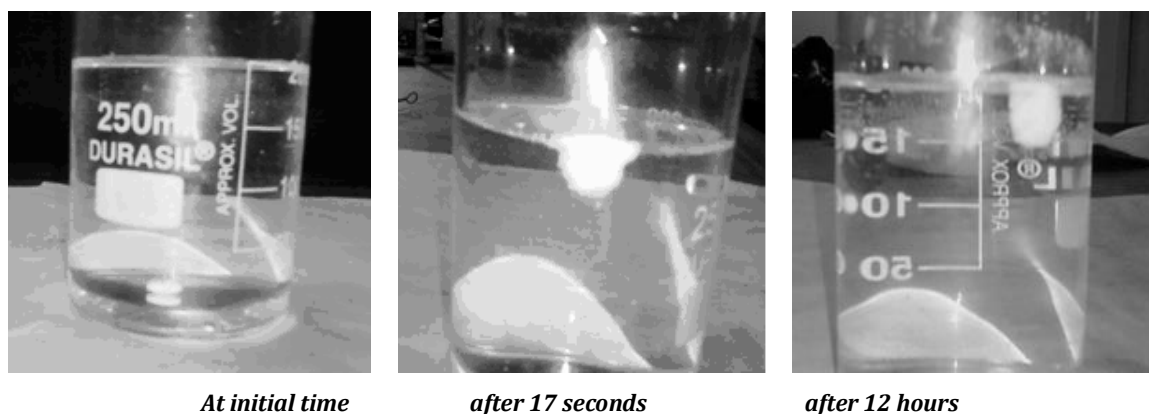

| At initial time | after 17 seconds | after 12 hours |

Figure 14 in vitro buoyancy studies of batch F16

The dissolution profile of the best batch (F16) was fitted to zero-order, first-order, Higuchi and korsmeyer models to ascertain the kinetic modeling of drug release. It may be concluded that the drug release from gastro retentive floating tablet is best explained by Higuchi model because R^2 value of Higuchi model has 0.9838. The values of slope and intercept for Higuchi model are 18.517 and 5.5844 respectively Table 9.

Table 9 Kinetic modeling data of batch F16				
Model	**Zero-order**	**First-order**	**Higuchi plot**	**Korsmeyer**
R^2	0.896	0.3542	0.9838	0.9636
Slope	3.2971	0.0399	18.517	0.3062
Intercept	25.81	1.2756	5.5844	1.4652

CONCLUSION

The present investigation aimed that preparation of twice daily formulation and for that the HPMC K100M was optimized as matrixing agent in hydrophilic matrix tablets. HPMC K100M has low density than release media i.e. 0.1N HCl. Incorporation of the gas generating agent like sodium bicarbonate helps to floating tablets. Tablets have floating behavior for 12 hrs. It is possible due to high viscosity of HPMC K100M. The drug release from the matrix is Biphasic. In this, immediate drug release from matrix for first hour and after that drug release is controlled by the HPMC matrix for 12 hours. HPMC swell and controlled drug release. By evaluating different concentration of HPMC K100M, 15% concentration gives more nearer to desired profile. Floating lag time of this batch has only 17 sec and tablet float for more than 12 hours. So, it is suitable for our formulation. Faster release of the drug during first hour was due to faster release of drug from the surface of the hydrophilic matrix tablet and after that drug release was diffusion controlled. Drug diffuses out from the hydrophilic matrix of HPMC K100M for 12 hours. So, finally obtained batch which is suitable for our experiment have 30 mg HPMC K100M, 20 mg Sodium bicarbonate, 114 mg DCP and required quantity of glidant and lubricant.

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