Formulation and Evaluation of Gastroretentive Floating Beads of Valsartan

Nilesh Chitte*[1], Shivraj Jadhav[2], Sachin Shinde[1], Amol Deshmukh[3], Chandrashekhar Patil[2]

[1]R G Sapkal College of Pharmacy, Anjaneri, Nashik, Maharshtra, 422213

[2]Divine College of Pharmacy, Satana, Nashik, Maharshtra, 423301

[3]Concord Biotech Ltd., Ahemadabad, Gujrat,

*Corresponding Author: Nilesh Chitte, nileshchitte.761@gmail.com, 9503728404

Abstract:

Background: This study focuses on the formulation and optimization of floating calcium pectinate beads encapsulating valsartan, a BCS Class II drug with poor aqueous solubility and low oral bioavailability. **Method**: Floating drug delivery systems were developed using the inotropic gelation technique, incorporating low methoxy pectin (primary polymer), gellan gum (release modifier), sodium bicarbonate (gas-generating agent), and calcium chloride (cross-linking agent). A 2^3 factorial design was employed to optimize three independent variables: the ratio of pectin to gellan gum, sodium bicarbonate concentration, and calcium chloride concentration, with the goal of achieving prolonged gastric retention, high drug entrapment efficiency, and controlled drug release. **Result:** The optimized batch (G6) demonstrated a floating time of 12.25 ± 0.77 hours with a buoyancy percentage of over 90%, ensuring prolonged gastric retention. The beads exhibited an entrapment efficiency of 91.94 ± 3.18%, indicating effective drug loading. In vitro drug release studies in simulated gastric fluid (pH 1.2) showed a sustained release profile, with 92.96 ± 2.30% of valsartan released over 12 hours from optimized batch, following Higuchi diffusion-controlled kinetics. Morphological characterization confirmed spherical beads with a porous surface, contributing to their floating properties. Stability studies conducted over three months revealed no significant changes in floating behavior, entrapment efficiency (>90%), or drug release (90.45 ± 1.89%). **Conclusion:** The results confirm that the developed floating calcium pectinate beads provide an effective gastroretentive platform for valsartan, improving its bioavailability and enabling sustained drug release over 12 hours, which could enhance patient compliance and therapeutic efficacy in hypertension management.

Keywords: Floating Drug Delivery System, Floating Beads, Inotropic gelatin method, Valsartan, Hypertension.

1. Introduction

The concept of gastroretentive drug delivery systems (GRDDS) has gained significant attention in pharmaceutical research due to their ability to prolong gastric residence time and enable controlled and site-specific drug release. These systems are particularly advantageous for drugs that exhibit narrow absorption windows in the upper

gastrointestinal (GI) tract, are unstable in the intestinal environment, or have poor solubility in alkaline pH conditions. GRDDS can enhance bioavailability, reduce dosing frequency, and improve patient compliance, making them a versatile solution for a wide range of therapeutic applications**.** (1, 2)

Valsartan, an angiotensin II receptor blocker widely prescribed for the treatment of hypertension and heart failure, is a BCS Class II drug characterized by poor aqueous solubility and low oral bioavailability. Its absorption is limited to the upper GI tract, and its short half-life necessitates frequent dosing, which can lead to reduced patient adherence. Developing a GRDDS for valsartan offers the potential to overcome these limitations by maintaining the drug in the stomach for a prolonged duration, thus enhancing its solubility in the acidic gastric environment and allowing for sustained and controlled release. (3, 4)

Floating drug delivery systems (FDDS), a subclass of GRDDS, achieve gastric retention by employing buoyancy mechanisms. These systems typically incorporate gas-generating agents, such as sodium bicarbonate, which release carbon dioxide upon contact with gastric fluids, enabling the dosage form to float on the gastric contents. FDDS are particularly suited for drugs like valsartan, where prolonged gastric residence can significantly improve therapeutic outcomes. (5)

Ionotropic gelation is a widely used technique for the preparation of floating beads due to its simplicity, cost-effectiveness, and ability to encapsulate both hydrophilic and hydrophobic drugs. Calcium pectinate, a biodegradable and biocompatible polymer derived from natural sources, has been extensively used in ionotropic gelation for its ability to form stable gels in the presence of divalent cations such as calcium ions. Additionally, the incorporation of gellan gum as a drug release modifier can further enhance the mechanical strength and modulate the release profile of the beads. (6)

This study focuses on the formulation and optimization of floating calcium pectinate beads loaded with valsartan. The formulation strategy involved the use of low methoxy pectin as the primary polymer, gellan gum to modulate drug release, sodium bicarbonate as a gas-generating agent, and calcium chloride as a cross-linking agent. A 2^3 factorial design was employed to optimize key formulation parameters, including the pectin-to-

gellan gum ratio, sodium bicarbonate concentration, and calcium chloride concentration, to achieve the desired floating properties, entrapment efficiency, and sustained drug release profile.

By leveraging a systematic approach to formulation design and optimization, this study aims to address the challenges associated with valsartan's poor solubility and bioavailability. The findings of this research have the potential to contribute to the development of an effective GRDDS for valsartan, providing a platform for future in vivo evaluations and clinical applications.

2. Materials and Methods

2.1 Materials

Valsartan was procured as a gift sample from Taj Pharma, Mumbai. Sodium bicarbonate, serving as a gas-generating agent, and calcium chloride, acting as a cross-linking agent were procured form Sudarshan Scientific, Nandgaon. Low methoxy pectin (LMP) and gellan gum, used as primary and secondary polymers respectively, were obtained from Krishna Pectin Pvt. Ltd, Jalgaon and CP KELCO Pvt. Ltd., Mumbai respectively. All other reagents and solvents were of analytical grade and used without further purification.

2. 2 Methods:

a. Preformulation Studies:

Preformulation studies were conducted to evaluate the physicochemical characteristics of valsartan and its compatibility with excipients, as described below:

Determination of absorption maxima and preparation of calibration curve:

Valsartan was dissolved in 0.1 N HCl, appropriately diluted and UV spectrum was recorded in the region of 200 to 400 nm. Similarly, 10 to 50 ppm solutions of valsartan were prepared in 0.1 HCl and absorbances were recorded in UV spectrophotometer at absorption maxima by use of UV spectrophotometer (1800, Schimadzu). (7)

Fourier Transfer Infrared Spectrum (FTIR):

Pellet of KBr and API was created in 1:1 ratio. The FTIR spectrum was obtained using a Jasco FT/IR-4600, Japan, FTIR spectrophotometer in 4000 to 400 cm^{-1} wavelengths. (8)

Differential Scanning Calorimetry (DSC):

Valsartan was analyzed by DSC (Mettler, DSC 8000, Switzerland). 5 mg of API was carefully weighed and sealed in an aluminum pan and heat was applied from room temperature to 300 ℃ at 10 ℃/min. To create an inert atmosphere, 100 ml/min pure nitrogen gas was injected. (9)

Drug-Excipient Compatibility Studies:

The interaction between valsartan and the excipients was analysed using FTIR and DSC. Physical mixtures of valsartan and excipients were scanned over a wavelength range of 4000 to 400 cm^{-1}. Significant shifts or changes in characteristic peaks were used to identify potential interactions. Thermograms of valsartan and physical mixture with excipients were recorded to detect any exothermic or endothermic changes, indicating interactions.

b. Preparation of Floating Beads:

Materials Preparation:

Low methoxy pectin was used as the primary polymer, and gellan gum was added as a release modifier. Sodium bicarbonate acted as a gas-generating agent, and calcium chloride served as a cross-linking agent.

Bead Formation by Ionotropic Gelation:

Calcium pectinate beads were prepared by ionotropic gelation method. Pectin and gellan gum were weighed and mixed in a required ratio. The polymers were dissolved in distilled water under gentle heating (~60–70°C) with continuous stirring until a clear, homogeneous solution was obtained. The solution was then allowed to cool to room temperature. The required amount of sodium bicarbonate was weighed and gradually added to the polymer solution. Continuous stirring was performed to ensure the uniform dispersion of the floating agent. Valsartan was dissolved into the polymer solution and stirred until homogeneity was achieved. Using a syringe, the polymer solution was dropped into a calcium chloride solution while stirring the solution gently. As the sodium bicarbonate reacted with the slightly acidic calcium chloride solution, carbon dioxide gas was released, forming pores in the beads and enabling them to float. The beads were allowed to remain in the calcium chloride solution for 20 minutes to complete the ionotropic gelation and ensure proper crosslinking. The beads were collected using a

sieve and washed with distilled water to remove any residual calcium ions and unreacted floating agents. The beads were dried in a hot air oven at 40 ℃ until they reached the desired consistency. (10)

Optimization:

A 2^3 factorial design was employed to evaluate the effect of three independent variables on the formulation parameters as indicated in table 1. Ratio of pectin to gellan gum concentration (X_1), concentration of sodium bicarbonate (X_2) and concentration of calcium chloride (X_3) were selected as three independent variables at two different levels. Effect of these variables on floating time, entrapment efficiency, and cumulative drug release was studied. Statistical analysis was conducted using Design-Expert software to identify the significance of the main effects and interactions. Graphs were plotted to visualize the relationships between the variables and responses.

Tabel 1: 2^3 Factorial Design for optimization.

Formulation Code	Ratio of pectin to gellan gum X_1	Concentration of Sodium Bicarbonate (% w/w of polymer) X_2	Concentration of Calcium Chloride X_3
G1	1:2	5 %	1%
G2	2:1	5 %	1%
G3	1:2	15 %	1%
G4	2:1	15%	1%
G5	1:2	5 %	3%
G6	2:1	5 %	3%
G7	1:2	15 %	3%
G8	2:1	15%	3%

c. Evaluation of Floating Beads:

Particle Size Analysis:

The average particle size of the beads was measured using an optical microscope fitted

with a calibrated eyepiece micrometer (B3, Motic, China). For each formulation, 50 beads were randomly selected, and the mean particle size was calculated.

Morphological Characterization:

The surface morphology of the beads was examined using Scanning Electron Microscopy (SEM) (FEI Quanta 200, Netherland). Images were captured to assess surface smoothness, porosity, and overall bead structure. (11)

Floating Behaviour:

To evaluate the floating time of the beads, approximately 50 beads were immersed in simulated gastric fluid (pH 1.2) maintained at 37°C ± 0.5°C to mimic gastric conditions. The time taken for the beads to remain buoyant was recorded using a stopwatch, and observations were made to differentiate between floating and sinking beads. The buoyancy percentage was calculated as the ratio of the number of floating beads to the total number of beads used, multiplied by 100. The test was repeated in triplicate to ensure consistency and reliability of the results. (12) The percentage of floating beads was calculated using the following formula:

$$\% \text{ of Floating beads} = \frac{Number\ of\ floating\ beads}{Total\ number\ of\ beads} * 100$$

Determination of bulk density:

The bulk density was calculated by first weighing a known volume of the beads using an analytical balance. A graduated cylinder or a similar measuring device was filled with the beads, ensuring no packing occurred, and the volume was recorded. The beads were gently tapped to settle them into the cylinder, but not compressed. The mass of the beads was divided by the volume they occupied to determine the bulk density, using the formula:

$$\text{Bulk Density} = \frac{Mass\ of\ beads}{Bulk\ desntiy\ of\ beads} * 100$$

The result was expressed in g/cm³.

Entrapment Efficiency:

The entrapment efficiency of the beads was determined by crushing a specific weight of beads, dissolving them in 0.1N HCl, and analyzing the solution spectrophotometrically at 248 nm. Entrapment efficiency was calculated using the formula:

$$\% \text{ of entrapment efficiency} = \frac{Actual\ Drug\ Content}{Theorotical\ Drug\ Content} * 100$$

***In Vitro* Drug Release Studies:**

Drug release studies were conducted using a USP Type II dissolution apparatus containing 900 mL of 0.1N HCl (pH 1.2) maintained at 37±0.5°C and stirred at 50 rpm. Samples were withdrawn at predetermined time intervals, filtered, and analysed spectrophotometrically at 248 nm. The release kinetics were fitted to mathematical models, including Zero Order, First Order, Higuchi, and Korsmeyer-Peppas, to determine the mechanism of drug release.

Stability Studies:

The optimized formulation was subjected to accelerated stability testing as per ICH guidelines. Samples were stored at 40±2°C and 75±5% RH for three months. At regular intervals, the beads were analysed for floating behaviour, entrapment efficiency and drug release to assess any changes in formulation performance. (12)

3. Result and Discussion:

a. Preformulation Studies

Determination of absorption maxima and preparation of calibration curve:

UV spectrum for valsartan is shown in Figure 1. It shows absorbance maxima at 248 nm in 0.1N HCl. UV spectrum shows peak at 248 nm which matches with the reported value.

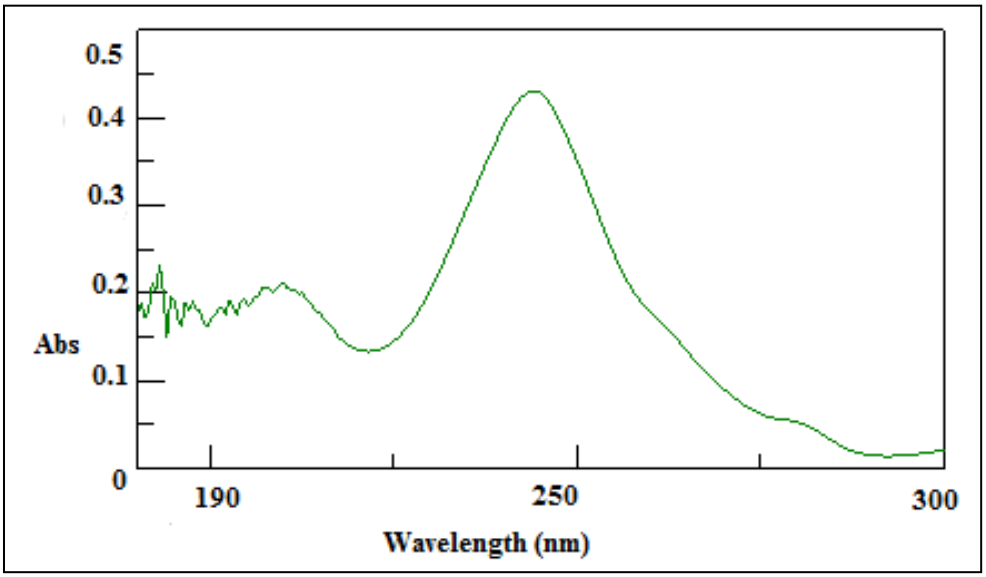

Figure 1: UV Absorption maxima of Valsartan.

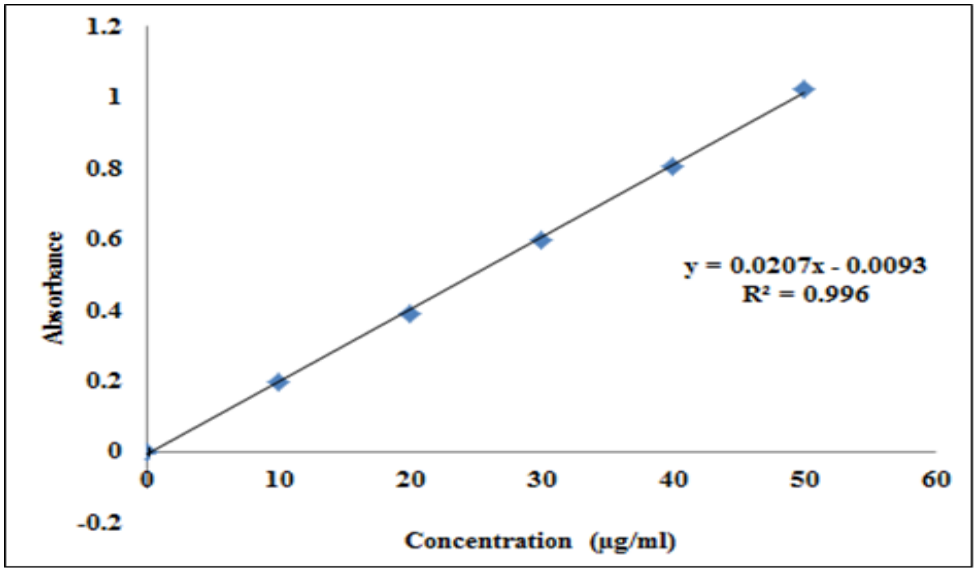

Figure 2: Calibration curve of Valsartan in 0.1 N HCl at 248 nm

Valsartan was found to obey Beer's Lambert's law in the concentration range of 10-50 µg/mL at 248 nm. The graph of the standard calibration curve of Valsartan in 0.1 N HCl is shown in Figure 2.

FTIR:

IR spectrum was taken by KBR disc technique and graph is shown in Figure 3, shows peaks as following that gives conformity of structure of drug. IR spectrum shows various peaks corresponding to different functional groups present in API. Peaks at 2964.36 cm^{-1}, 2874.61 cm^{-1}, represents C-H stretching (alkane); 1732.16 cm^{-1}, represents ketone stretching which represents acyclic saturated compound; 2613.05, 2595.55 cm^{-1} which represents hydroxyl stretching (bonded); 1602.16 cm^{-1}, 1512.50 cm^{-1}, N-H bending represents aromatic tertiary amine. C-N vibration shows peaks 1206.39 cm^{-1}, 1198.42 cm^{-1}, 1106.04 cm^{-1} and at 1410.82 cm^{-1} shows aliphatic tertiary amine.

DSC:

DSC thermograph of Valsartan has showed sharp endothermic peak around 112 ^{0}C, which corresponds to the melting point of the API as indicated in figure 4.

Drug-Excipient Compatibility Studies:

Drug excipient compatibility study indicated no major interaction in between Valsartan and selected excipients as shown in figure 3. All characterization peaks of valsartan like 3427.23 cm^{-1}, 1327 cm^{-1} were observed in FTIR spectra of drug in combination with

pectin and gellan gum. There was no shifting of peaks were observed as shown in figure 3.

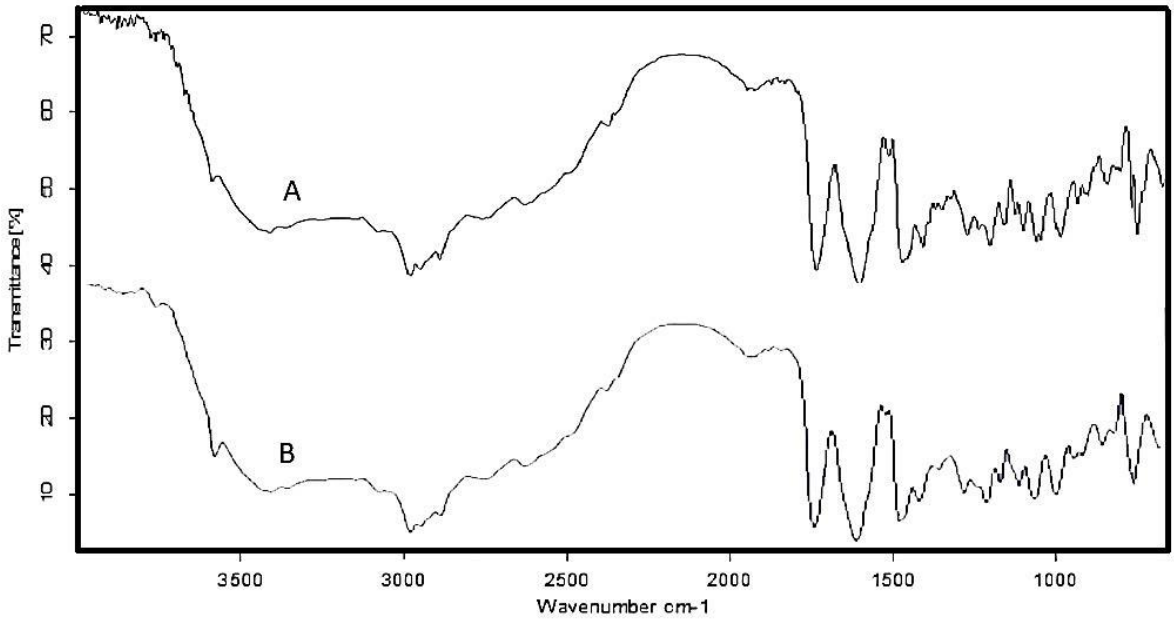

Figure 3: IR spectrum of Valsartan (A), IR spectrum of Valsartan: Pectin: Gellan gum (B)

The DSC analysis of the valsartan, gellan gum, and pectin mixture did not show any shift in the endothermic peak, indicating no incompatibility between the drug and the polymers. Furthermore, FTIR and DSC studies confirmed the absence of any chemical interactions between the drug and the excipients as shown in figure 4. Therefore, the drug and polymers were deemed compatible for further experimental studies.

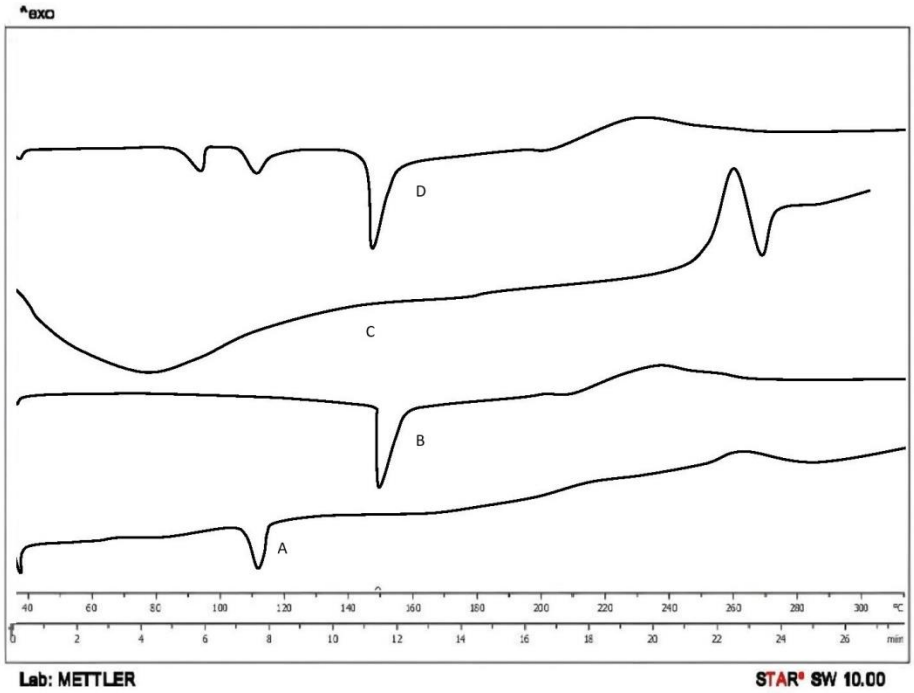

Figure 4: DSC spectra of Valsartan (A), Pectin (B), Gellan gum (C), Physical mixture of valsartan, pectin and gellan gum (D).

b. Optimization:

Table 1: Results of optimization.

Sr. No.	Formulation Code	floating time (Hours)	Entrapment efficiency (%)
1	G1	06.10 ± 0.13	86.54 ± 2.61%
2	G2	11.34 ± 0.57	88.56 ± 1.55%
3	G3	08.49 ± 0.54	83.14 ± 1.70%
4	G4	12.81 ± 1.00	86.49 ± 2.08%
5	G5	06.82 ± 0.22	90.93 ± 1.37%
6	G6	12.25 ± 0.77	91.94 ± 3.18%
7	G7	07.59 ± 0.45	89.68 ± 0.85%
8	G8	11.62 ± 0.44	89.77 ± 2.59%

(Mean ± SD, n=3)

2^3 factorial design was used for optimization of floating beads. Three independent factors under consideration were ratio of pectin to gellan gum (X1), concentration of sodium

bicarbonate (X2) and concentration of calcium chloride (X3) at two different levels. Effect of these factors was studied on two dependant variable namely floating time and entrapment efficiency. Formulation that provides best result will be considered as optimised. The results of optimization are provided in table 1.

Figure 5 indicates the effect of ratio of pectin to gellan gum concentration of sodium bicarbonate and on floating time of prepared beads. As indicated in figure, higher amount of pectin favours more floating time. Higher amounts of pectin favour more floating time due to its gel-forming ability, porous matrix formation, low-density gel structure, and efficient gas retention. Pectin, a natural polysaccharide, forms a robust gel matrix upon hydration, trapping air or gases (e.g., CO_2 from sodium bicarbonate reaction) that enhance buoyancy. The porous structure created by higher pectin concentrations allows gas to remain trapped longer, contributing to prolonged floating. Additionally, pectin gels have lower density compared to gellan gum, further aiding buoyancy by keeping the beads less dense than gastric fluid. These combined properties ensure a prolonged floating time by reducing water penetration, retaining gas, and maintaining structural integrity. Also as there is increase in concentration of sodium bicarbonate there is increase in floating time. Higher concentrations of sodium bicarbonate lead to an increase in floating time due to its role as a gas-generating agent. Sodium bicarbonate reacts with gastric fluid (or acidic medium) to produce carbon dioxide gas, which becomes trapped within the bead matrix, enhancing buoyancy. As the concentration of sodium bicarbonate increases, more gas is generated, resulting in greater buoyant force and prolonged floating time. However, excessively high concentrations might compromise the structural integrity of the beads, so an optimal concentration is essential to balance gas generation and bead stability.

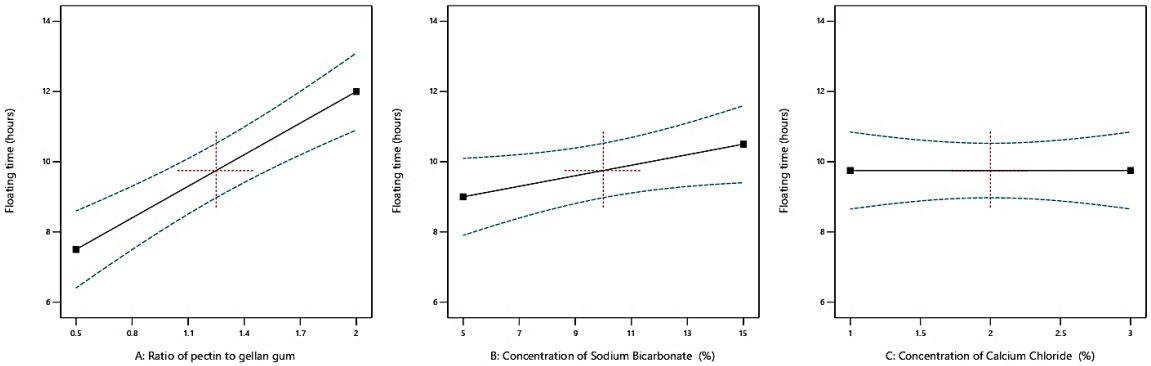

Figure 5: Effect of ratio of pectin to gellan gum, concentration of sodium bicarbonate and, concentration of calcium chloride on floating time.

However concentration of calcium chloride doesn't affect much on floating time. The concentration of calcium chloride does not significantly affect floating time because its primary role is to act as a cross-linking agent, strengthening the bead matrix by forming ionic bonds with polymers like pectin and gellan gum. While higher concentrations of calcium chloride can increase the structural integrity and rigidity of the beads, these changes do not directly influence buoyancy or gas generation. Since floating time primarily depends on the amount of gas trapped within the bead matrix (influenced by factors like sodium bicarbonate and polymer properties), variations in calcium chloride concentration have a minimal effect on this parameter.

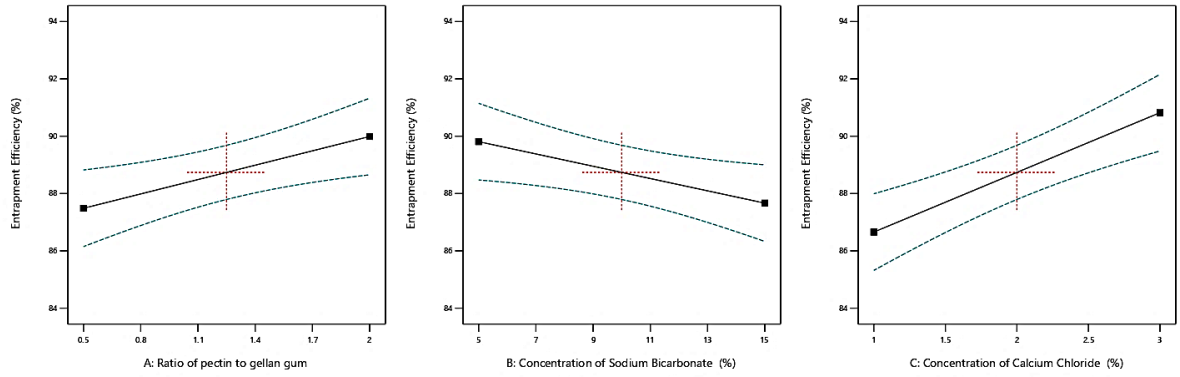

Figure 6: Effect of ratio of pectin to gellan gum, concentration of sodium bicarbonate, and concentration of calcium chloride on entrapment efficiency.

As indicated in figure 6, as ratio of pectin to gallan gum increases there is increase in entrapment efficiency of floating beads. It is due to due to pectin's superior gel-forming ability, efficient cross-linking with calcium ions, and hydrophilic nature. Pectin forms a

dense and cohesive matrix that effectively traps drug molecules, reducing their diffusion out of the beads during the formulation process. Additionally, higher pectin concentrations result in a less porous bead structure, further minimizing drug leakage. These combined factors lead to enhanced entrapment efficiency with an increased pectin-to-gellan gum ratio. Increase in concentration of sodium bicarbonate decreases the entrapment efficiency because higher gas generation leads to increased porosity in the bead structure, which allows the drug to diffuse out more easily. Additionally, excessive gas production weakens the structural integrity of the beads, making it harder for the polymer matrix to retain the drug. The increased porosity and weakened matrix result in a reduction of entrapment efficiency as the concentration of sodium bicarbonate rises. Increase in concentration of calcium chloride increases entrapment efficiency. An increase in the concentration of calcium chloride increases entrapment efficiency due to its role as a cross-linking agent. Calcium chloride facilitates the formation of a more rigid and stable gel network by interacting with the polymer chains (such as pectin and gellan gum), which enhances the structural integrity of the beads. This stronger matrix helps trap and retain the drug molecules more effectively. As calcium chloride concentration increases, the cross-linking density also increases, reducing the leakage of the drug from the beads and thereby improving the entrapment efficiency.

Statistical validity of the polynomials was established on the basis of analysis of variance (ANOVA) provision in the Design Expert® software. Level of significance was considered at $p < 0.05$. Design expert-13 software predicted following polynomial equations for floating time and entrapment efficiency over the range of independent variables.

$$\text{Floating time} = 9.75 + 2.25X_1 + 0.75X_2 + 3.92^{-16}X_3$$

$$\text{Entrapment Efficiency} = 88.73 + 1.2525X_1 - 1.0725X_2 + 2.0825X_3$$

From the obtained results batch G6 is found to be optimized with floating time of 12 hours and drug entrapment efficiency of 93.30 %.

c. Evaluation of Floating Beads:

Particle Size Analysis:

Particle size analysis of optimized batch G6 beads was performed by use of Motic microscope. The average particle size of beads was found to be 1.53 ± 0.24 mm (n=50).

Morphological Characterization:

The beads of batch G6 exhibited a spherical shape with a combination of smooth and rough surface morphological characteristics. The rough surfaces, along with ridges, were attributed to the diffusion of pectin during interaction with the cross-linking agent as observed in figure 7.

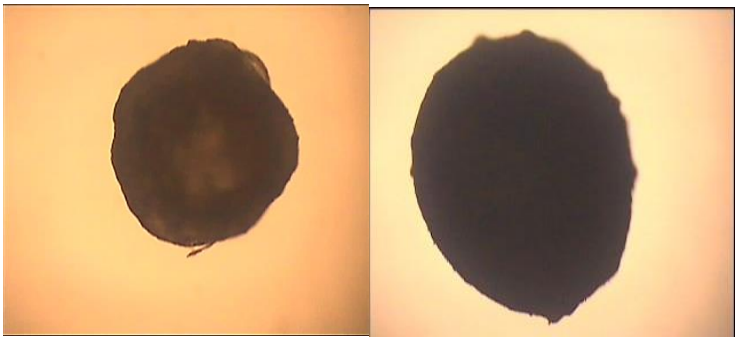

Figure 7: Optical microscopic images of drug loaded beads

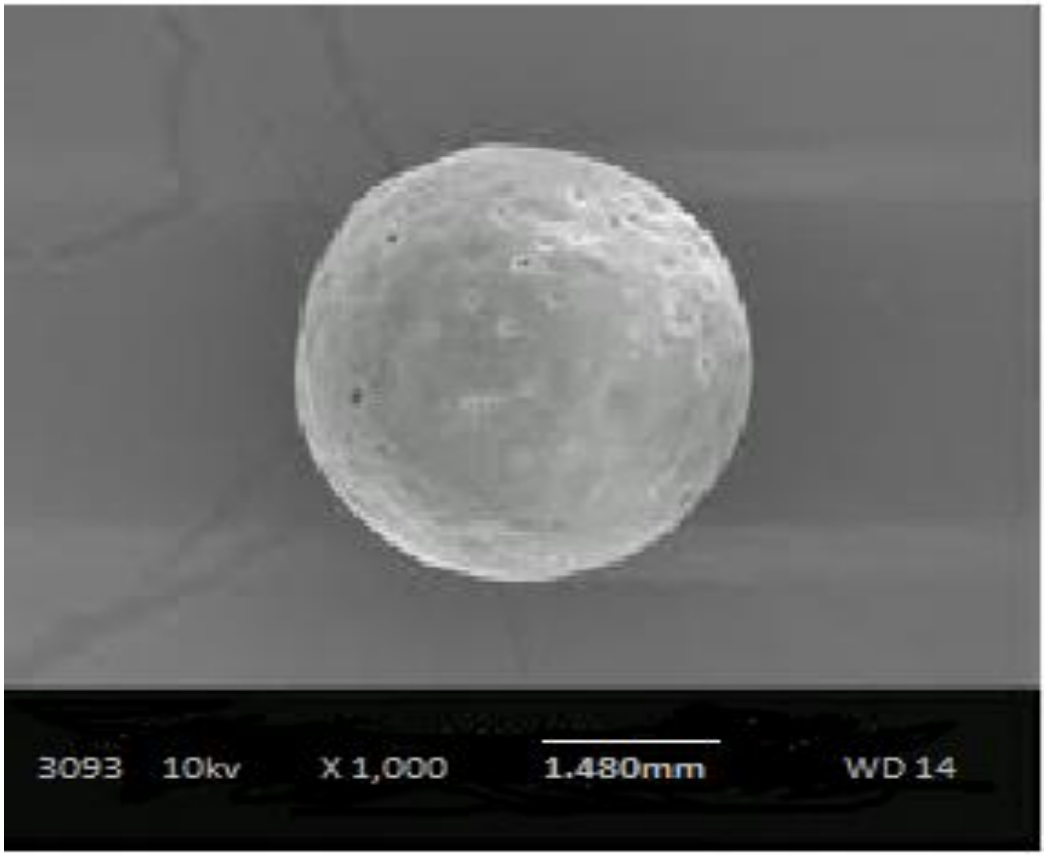

Figure 8: SEM photograph of valsartan drug loaded beads of batch G6.

The beads exhibited rough surfaces, attributed to the cross-linking interaction between calcium chloride and pectin. Additionally, the beads were observed to be porous in nature and spherical in shape as observed in figure 8.

Floating Behavior:

The floating time and buoyancy percentage of the beads were evaluated in simulated gastric fluid (pH 1.2). The beads from optimised batch demonstrated excellent floating properties, with a buoyancy percentage exceeding 90% and floating durations of more than 12 hours. These results indicate the formulation's ability to remain buoyant for extended periods, which is crucial for gastro-retentive drug delivery.

Determination of bulk density of beads:

The density of the beads was measured to ensure they remained less dense than gastric fluids, a critical factor for floating. All formulations exhibited densities below 1 g/cm³, ensuring effective buoyancy throughout the study as indicated in table 2.

Table 2: Bulk densities of different batches.

Batch	Bulk density (g/cm³)
G1	0.54 ± 0.02
G2	0.42 ± 0.03
G3	0.48 ± 0.02
G4	0.40 ± 0.04
G5	0.52 ± 0.01
G6	0.41 ± 0.03
G7	0.50 ± 0.02
G8	0.43 ± 0.02

The floating beads of calcium pectinase exhibited an inverse relationship between bulk density and floating time. Beads with lower bulk density, such as G4 (0.40 ± 0.04 g/cm³), showed the longest floating time (12.81 ± 1.00 hours), while beads with higher bulk density, like G1 and G5 (0.54 ± 0.02 g/cm³ and 0.52 ± 0.01 g/cm³), had shorter floating durations (6.10 ± 0.13 and 6.82 ± 0.22 hours, respectively). This indicates that reduced bulk density, achieved through higher void spaces, enhances buoyancy and floating time.

Entrapment Efficiency:

The entrapment efficiency ranged between 83% to 93%, depending on the polymer ratio and cross-linking conditions. Beads with a higher pectin-to-gellan gum ratio showed improved entrapment efficiency due to the stronger gel matrix formed by pectin, which effectively retained the drug. However, excessive sodium bicarbonate concentrations led to decreased entrapment efficiency due to increased porosity and drug diffusion during the cross-linking process.

In-Vitro Drug Release Studies:

Table 3: In vitro drug release study of formulated batches.

Time (h)	G1	G2	G3	G4	G5	G6	G7	G8
1	19.36 ± 0.82	17.00 ± 0.75	18.28 ± 0.92	20.17 ± 0.65	21.06 ± 0.95	16.77 ± 0.81	19.28 ± 0.79	17.35 ± 0.68
2	27.99 ± 0.95	24.75 ± 1.02	26.66 ± 0.88	24.80 ± 0.97	34.29 ± 1.10	24.41 ± 0.92	28.95 ± 1.05	26.87 ± 0.99
3	36.94 ± 1.15	33.71 ± 1.25	32.61 ± 1.10	33.00 ± 1.08	48.95 ± 1.42	31.60 ± 1.20	40.23 ± 1.32	33.20 ± 1.14
4	57.30 ± 1.25	39.45 ± 1.32	48.90 ± 1.38	36.86 ± 1.24	66.24 ± 1.50	38.38 ± 1.31	55.65 ± 1.45	42.04 ± 1.22
5	78.32 ± 1.38	45.24 ± 1.45	61.85 ± 1.52	44.17 ± 1.32	77.55 ± 1.65	44.52 ± 1.38	68.23 ± 1.58	49.33 ± 1.36
6	91.30 ± 1.52	53.46 ± 1.65	70.69 ± 1.72	53.02 ± 1.48	82.32 ± 1.78	52.18 ± 1.52	78.32 ± 1.70	55.18 ± 1.50
7	-	61.96 ± 1.80	82.56 ± 1.92	57.35 ± 1.60	91.23± 1.20	60.20 ± 1.68	88.41 ± 1.85	62.47 ± 1.65
8	-	65.71 ± 1.92	94.78 ± 2.05	64.89 ± 1.75	-	65.01 ± 1.80	96.56 ± 2.12	67.88 ± 1.78
9	-	73.10 ± 2.10	-	77.89 ± 1.90	-	73.20 ± 1.95	-	73.97 ± 1.85

10	-	77.98 ± 2.15	-	79.37 ± 1.98	-	79.00 ± 2.00	-	80.98 ± 1.95
11	-	95.40 ± 2.50	-	86.23 ± 2.15	-	85.95 ± 2.20	-	87.00 ± 2.10
12	-	95.4	-	95.23 ± 2.35	-	92.96 ± 2.30	-	90.22 ± 2.25

The drug release profile indicated a sustained release pattern over 12 hours in simulated gastric fluid as indicated in table 3 and figure 9. Beads formulated with higher pectin content exhibited slower drug release, attributed to the denser matrix structure. The release kinetics followed the Higuchi model, suggesting a diffusion-controlled mechanism, with some formulations also showing alignment with the Korsmeyer-Peppas model, indicative of a combined diffusion and erosion mechanism. The optimise batch G6 has shown the drug release for more than 12 hours.

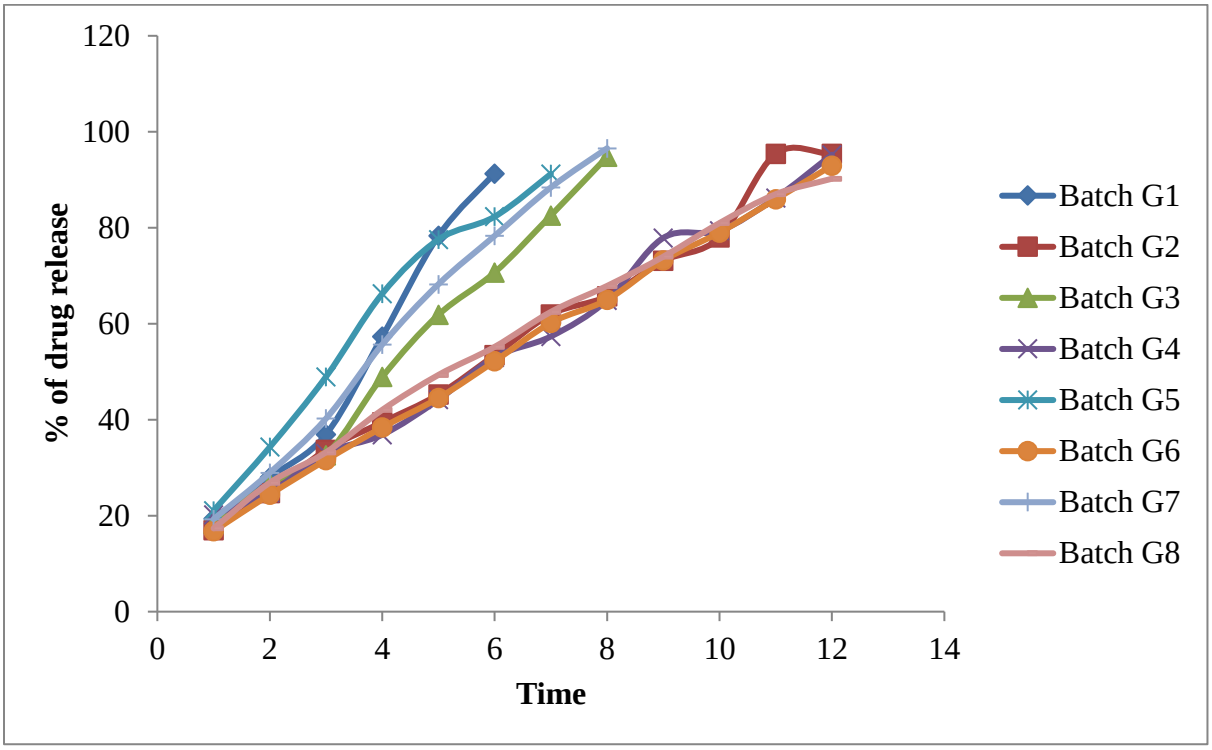

Figure 9: In-vitro drug release study of formulated batches.

Stability Studies:

The physical observation of the stability batch revealed no changes in color or other physical properties. Stability studies demonstrated that the floating time remained unchanged after three months, indicating the robustness of the formulation. Additionally, entrapment efficiency showed no significant variations, confirming the stability of the formulation. Furthermore, the in vitro drug release study exhibited no substantial alterations in the release pattern over the study period, with the drug release kinetics following the Peppas model. Table 4 indicates the results of different evaluation parameter after three months.

Table 4: Results of stability study

Time (months)	**Floating time* (h)**	**Entrapment Efficiency**	***In vitro* drug release in 12 hours**
0	More than 12 hours	More than 90 %	92.96 ± 2.30
1	More than 12 hours	More than 90 %	91.23 ± 1.40
2	More than 12 hours	More than 90 %	91.12 ± 0.45
3	More than 12 hours	More than 90 %	90.45 ± 1.89

4. Conclusion:

This study successfully developed and characterized floating beads of calcium pectinase loaded with valsartan, demonstrating their potential for prolonged gastric retention and controlled drug release. The optimized formulation exhibited excellent buoyancy, high drug entrapment efficiency, and sustained drug release, which could significantly enhance valsartan's bioavailability and therapeutic efficacy. The floating beads offer a promising approach to improving antihypertensive therapy by maintaining drug levels for an extended duration and reducing dosing frequency. Furthermore, this delivery system may minimize fluctuations in drug plasma concentration, potentially improving patient compliance and treatment outcomes. However, further in vivo and clinical studies are necessary to confirm their pharmacokinetic advantages, safety, and overall therapeutic potential.

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