World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Research Article
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2025
Volume: 4; Issue: 5
Page: 940-954

DESIGN AND DEVELOPMENT OF VALSARTAN AN ANTI-HYPERTENSIVE DRUG FORMULATED AS FLOATING PULSATILE RELEASE FORMULATION

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Article Received: 24 September 2025 | | ***Article Revised: 14 October 2025*** | | ***Article Accepted: 05 November 2025***

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DOI: https://doi.org/10.5281/zenodo.17617468

How to cite this Article: Dr. J. Ramesh Babu, S. Meraj Sultana and Dr. S. Vidyadhara (2025). DESIGN AND DEVELOPMENT OF VALSARTAN AN ANTI-HYPERTENSIVE DRUG FORMULATED AS FLOATING PULSATILE RELEASE FORMULATION. World Journal of Pharmaceutical Science and Research, 4(5), 940-954. https://doi.org/10.5281/zenodo.17617468

ABSTRACT

The objective of the present study was to develop a pulsatile drug delivery system for valsartan, designed to align drug release with the body's circadian rhythm. Initial investigations indicated that β-cyclodextrin significantly enhanced the solubility of valsartan, demonstrating an AL-type solubility curve. Phase solubility studies confirmed a 1:1 molar ratio for the valsartan-β-cyclodextrin inclusion complex, which exhibited markedly improved dissolution efficiency compared to the pure drug, likely due to complex formation. A pulsatile delivery system was formulated using a "tablet-in-capsule" approach, incorporating both a floating tablet and an enteric-coated tablet. The optimized core tablets were placed inside capsules and coated with 4% Eudragit S-100. *In-vitro* release studies were conducted in 0.1 N HCl for 4 hours, followed by phosphate buffer (pH 6.8) for an additional 3 hours. The coated capsules exhibited minimal drug release in acidic medium and released the majority of the drug in the buffer medium. Among the formulation components, HPMC K4M played a crucial role in modulating the lag time. The final formulation demonstrated a 4-hour lag phase followed by rapid and complete drug release within the next 2 hours. This approach successfully achieved a pulsatile release profile for valsartan with enhanced dissolution performance.

KEYWORDS: Valsartan, β-Cyclodextrin, Directcompression, HPMCK4M, Tablet in capsule, Pulsatile drug delivery system.

INTRODUCTION

Pulsatile drug delivery systems (PDDS) are designed to align drug release with the body's biological rhythms and are particularly effective in managing conditions such as hypercholesterolemia, peptic ulcers, asthma, cardiovascular diseases, and arthritis. In the context of cardiovascular disorders, blood pressure typically rises during the early morning hours and fluctuates during sleep. Therefore, synchronizing drug release with these circadian variations could enhance therapeutic outcomes.[1]

Valsartan, an angiotensin II receptor blocker (ARB), was selected as the model drug for developing a PDDS. It is commonly used to manage hypertension, diabetic nephropathy, left ventricular hypertrophy, and isolated systolic hypertension. Additionally, it serves as an alternative treatment for coronary artery disease, myocardial infarction, systolic dysfunction, and heart failure. Valsartan lowers blood pressure by antagonizing the renin-angiotensin-aldosterone system. Specifically, it blocks the effects of angiotensin II by selectively inhibiting its binding to the angiotensin II type 1 (AT1) receptor subtype.[2,3]

Valsartan is classified as a BCS Class II drug, characterized by low solubility and high permeability, with a recommended daily dose ranging from 40 to 320 mg. It exhibits approximately 50% oral bioavailability and demonstrates high plasma protein binding, ranging from 94% to 97%. The drug has a pKa of 4.37 and a biological half-life of 4 to 6 hours, making it a suitable candidate for time-controlled, pulsatile delivery to optimize its therapeutic efficacy.[4]

MATERIALS AND METHODS

Valsartan was a kind gift sample received from FD Climited., Goa. β-Cyclodextrin was acquired from SD finechemicals, Mumbai, India. Crospovidone was purchased from FMC Biopolymers, Mumbai, India. EudragitS-100 was obtained from Lupin Pharmaceuticals, Mumbai, India. HPMC K4M was procured from Colorcon Asian Pvt. Ltd, India. All other reagents used were of analytical grade.

Methodology

1. Determination of λ_{max} of Valsartan

A diluted solution of valsartan in phosphate buffer solution (pH 6.8) was scanned for absorption maxima against blank between 200-400 nm using UV-visible spectrophotometer (UV-1601, Shimadzu, Japan).

2. Construction of Calibration curve of valsartan

An accurately weighed quantity of valsartan (100 mg) was placed into a 100 ml volumetric flask, dissolved, and the volume was brought up to 100 ml using phosphate buffer solution (pH 6.8) to prepare stock solution A. From this, 10 ml was transferred into another 100 ml volumetric flask and diluted to the mark with the same buffer to obtain stock solution B. Various volumes from stock solution B were then pipetted into 10 ml volumetric flasks and diluted with phosphate buffer (pH 6.8) to prepare solutions with concentrations ranging from 3 to 30 µg/ml. The absorbance of these solutions was measured at 251 nm using a UV-visible spectrophotometer (UV-1601, Shimadzu, Japan).

3. Solubility studies[5,6]

The solubility studies were performed in phosphate buffer solution (pH 6.8), 0.1Nhydrochloricacid and water. Drug (50 mg) was placed in 10 ml volumetric flask and added with different medias. The volumetric flasks were placed on rotary

shaker for 24 h at 100 rpm. At the end of the studies, the solutions were filtered through What man filter paper, suitably diluted and finally analyzed using UV spectrophotometer (UV1601, Shimadzu, Japan) using suitable blank at251 nm.

4. Phase solubility studies[7,8]

Phase solubility studies are a widely accepted method for evaluating the effect of cyclodextrin complexation on the drug solubility. Phase solubility studies were performed nun buffered water, according to the Higuchi and Connors method. An excess amount of valsartan was added to β-cyclodextrin aqueous solutions (0, 2, 4, 6, 8, 10 ml) in volumetric flasks. The resulting suspensions were shaken for 24 hours at 100 rpm. At the end of the studies, the solutions were filtered through what man filter paper, suitably diluted and finally analyzed using UV spectrophotometer (UV1601, Shimadzu, Japan) using suitable blank at 251 nm.

3. Drug-Excipient compatibility studies[9]

FTIR spectra were recorded using FTIR spectrum in a range of 4000-400cm^{-1}. FTIR spectra were used for the investigation of interaction in the physical mixture of API and excipient through shifting of peaks to lower or higher wave numbers and appearance or disappearance of characteristic peaks of functional groups for pure API in physical mixture. FTIR spectroscopic study was performed to check the compatibility between API, and different excipients. The FTIR spectra of an API alone and API with excipients were obtained by KBr method and compared with the standard FTIR spectrum of the pure API. Infrared spectrophotometer is not only used for determining the compatibility of excipients with the APIs, but also for API identification.

4. Methodology for the preparation of Pulsatile drug delivery system[10-15]

Table No.1: Composition of Tablet and Capsule Formulations.

Formulation	Drug (mg)	DCP (mg)	MCC (mg)	Lactose (mg)	HPMC K4M (mg)	Cross povidone (%)	SSG	Magnesium Stearate (mg)	Talc (mg)
F1	40	60		-	-	-	-	6	4
F2	40	-	60	-	-	-	-	6	4
F3	40	-	-	60	-	-	-	6	4
F4	40	60	-	-	-	-	-	6	4
F5	40	60	-	-	-	-	-	6	4
F6	40	60	-	-	-	-	-	6	4
F7	40	60	-	-	-		2	6	4
F8	40	60	-	-	-	2	-	6	4
F9	40	60	-	-	-	4	-	6	4
C1	40	60	-	-	200	4	-	6	4
C2*	40	60	-	-	200	4	-	6	4
C3	40	60	-	-	200	4	-	6	4
C4*	40	60	-	-	200	4	-	6	4
C5	40	60	-	-	200	4	-	6	4
C6*	40	60	-	-	200	4	-	6	4
C7	40	60	-	-	200	4	-	6	4
C8*	40	60	-	-	200	4	-	6	4
C9	40	60	-	-	200	4	-	6	4
C10*	40	60	-	-	200	4	-	6	4
C11	40	60	-	-	200	4	-	6	4
C12*	40	60	-	-	200	4		6	4

- Formulation F1 to F3 contains pure drug.
- Formulation F4 to F6 contain drug-carrier complex in different ratios. (1:0.5, 1:1, 1:1.5)
- Formulation F7 to F9 contain 1:1 ratio of drug-carrier complex along with different concentrations of SSG and CP

(2 and 4%)

- Formulation F7 to F9 and C1 to C12containacoretabletcompressioncoated with mixture of HPMCK4 M(150 mg) and sodium bicarbonate (50 mg).
- C1 and C2 coated with Eudragit S-100 coating solution(2%w/v). All other formulations C3 to C12 coated with Eudragit S-100 (4%w/v).
- *Indicates cap of capsule is uncoated and remaining formulations both cap and body coated.

4.a. Preparation of Drug-Carrier Mixture[16]

The drug–carrier mixture was prepared by the solvent evaporation method. In this method, an accurately weighed amount of drug and carrier (β-cyclodextrin) was taken in a china dish, and 10 mL of ethanol:water (6:4) was added slowly with constant stirring until the solvent evaporated. The obtained powder was packed in an airtight container and stored in a desiccator until further use.

4.b. Preparation of core and coated tablets

Drug and β-cyclodextrin complex mixture was accurately weighed equivalent to 40mg of the drug valsartan, to this 60 mg of dicalcium phosphate, 4% of crospovidone was added, lubricated with talc and magnesium stearate. The homogeneous mixture was compressed on a single-station tableting machine (Cadmach Machinery, Ahmedabad) using 6.05 mm punches.

A set of core tablets were compression coated with HPMC K4M layer containing 75mg mixture of calcium carbonate and sodium bicarbonate (0.5:1) using 7.25 mm punches.

4.c. Preparation of plug tablet

200 mg of the polymer (HPMC K4M) was accurately weighed and mixed with gas generating agents like sodium bicarbonate and citric acid in the ratio of 1:1(100 mg)in a mortar and pestle. The homogenous powder mixture was compressed into tablet on a single station tableting machine using7.25 mm punches.

4.d. Preparation of coating solution

The body portion of the hard gelatin capsule was coated with 4% Eudragit S-100 to achieve pH-dependent release. The coating solution was prepared by dissolving Eudragit S-100 in isopropyl alcohol with acetone in a 1:1 ratio.

4.e. Coating of capsule

A dip coating method was used for coating the body portion of the capsule separately. In a beaker, 50 mL of coating solution was taken, into which the capsule (body or whole capsule) was dipped to obtain the coating. After each coating, the capsule was subjected to drying by placing it in a hot air oven maintained at 40 ± 1 °C for a predetermined time to ensure complete removal of the solvent used to dissolve the coating polymer. The process was repeated until the desired thickness (weight gain) was achieved.

4.f. Assembly of capsule delivery system and mechanical drilling of aperture

100 mg of sodium alginate was weighed into the pre-coated capsule body and lightly compacted. One core tablet was placed onto the compacted sodium alginate layer, above which a plug tablet (HPMC K4M) was placed. Finally, another core tablet containing HPMC K4M with a gas-generating agent was inserted into the mouth of the capsule. The capsule body was closed with a water-soluble cap. An orifice was mechanically drilled into the top center of each capsule cap

for formulations coated with enteric polymers. The coating thickness was measured with the help of a digital Vernier caliper using empty shells obtained after complete coating.

5. Evaluation of tablets

The prepared tablets were evaluated for various physicochemical properties, as discussed below:

a. Thickness and Diameter[17]

The thickness and diameter of the final tablets of all prepared formulations were determined using a dial micrometer and Vernier calipers, respectively. The average of their readings was taken, and the results were tabulated as mean ± SD.

b. Hardness of tablets[18]

Hardness of tablets was tested using Monsanto hardness tester. Scale was adjusted to zero and the tablet held between the moving jaw and pressure was applied by these jaws until the tablet braked. Hardness of tablets is measured in terms of Kg/cm^2 and noted as an average(± SD).

c. Friability of tablets[19]

Pre-weighed tablets (n = 10) were subjected to 100 revolutions using a Roche friabilator. The weight loss was calculated, and the % friability was then determined by:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

d. Weight variation test

The tablet weight test was carried out using an electronic weighing balance. Ten tablets were weighed individually, and the average weight was noted. The % deviation of each tablet weight was determined using the following equation:

$$Percentdeviation(PD) = \frac{W_{avg} - W_{initial}}{W_{initial}} x\ 100$$

Where,

W avg=Average weight of tablet

W initial=individual weight of tablet

e. *In-vitro* disintegration time[20]

In-vitro disintegration time was determined using disintegration test apparatus. The tablets were placed in each of the six tubes of the apparatus and one disc was placed on each tablet of each tube. The test was carried out using phosphate buffer saline, pH 6.8 as medium maintained at 37 ± 0.5^0 C. Time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured.

f. Drug content study[21]

One tablet from each formulation of core tablets was taken in a mortar and powdered using a pestle. The weighed quantity of powder was transferred into a 100 mL volumetric flask containing 50 mL of phosphate buffer (pH 6.8). The flasks were allowed to rotate in a rotary shaker for 24 h, and the final volume was made up with phosphate buffer (pH 6.8). The solution was filtered, and the amount of valsartan present was estimated using a UV–Visible spectrophotometer at 251 nm.

6.1. *In-vitro* drug release study[22]

The drug release studies of prepared formulations were carried out using USP paddle dissolution test apparatus at 50 rpm and 37±1°C using 900 ml of 0.1N HCl(pH 1.2) as a dissolution medium for first 4 h, followed by phosphate buffer (pH6.8) up to 7 h. An aliquot of 5 ml was withdrawn at predetermined time intervals and were replaced with fresh medium. Amount of drug in each aliquot was assayed on a UV- Spectrophotometer (Shimadzu 1601, Japan) at 251 nm using a suitable blank. All trails were conducted in triplicate and the average (± SD) reading was noted. Cumulative drug release was plotted as a function of time.

6.2. Model Independent Analysis[23-25]

a. Dissolutionefficiency: Dissolution efficiency (DE) is used to translate the dissolution profile difference into a single quantitative value. It was calculated using the following equation:

$$DE\ \% = \frac{\int_0^t y\ dt}{y_{100}} t \times 100$$

Where, y is the drug present dissolved at time.

b. Mean dissolution time: Mean dissolution time represents the mean time for drug molecules to completely dissolve. It is used to characterize the drug release rate from a dosage form and indicates the drug release retarding efficiency of the polymer.MDT was calculated by using the following equation.

$$MDT = \frac{\sum_{i=1}^{i=n} t_{mid} \times \Delta M}{\sum_{i=1}^{i=n} \Delta M}$$

Where *'i'* is the dissolution sample number, *'n'* is the number of dissolution sample time, *'t mid'* is the time at the midpoint between '*i'* and *'i-1'*, and *'ΔM'* is the amount of drug dissolved between *'i'* and *'i-1'*.

RESULTS AND DISCUSSIONS

1. Determination of λ_{max} of drug

A diluted solution of valsartan prepared in phosphate buffer (pH 6.8) was scanned in the wavelength range of 200–400 nm against a blank using a UV-visible spectrophotometer (UV-1601, Shimadzu, Japan). The wavelength corresponding to maximum absorbance (λmax) was observed at 251 nm.

2. Construction of Calibration curve of valsartan

A calibration curve for valsartan was constructed over the concentration range of 3–30 µg/ml at a wavelength of 251 nm. The curve exhibited excellent linearity with a regression coefficient (R^2) of 0.9998, (shown in figure no.1.) indicating strong correlation. The selected concentration range complied with Beer-Lambert's law.

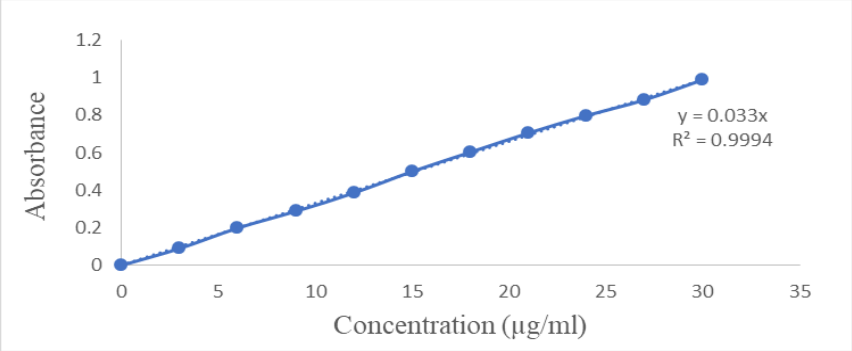

Figure No. 1: Calibration curve of valsartan in phosphate buffer (pH 6.8).

3. Solubility studies

a. Solubility of Pure Drug

The solubility profile of valsartan in different media-water, 0.1 N HCl, and phosphate buffer (pH 6.8)is presented in Table 5. The solubility values were found to be 86.15 ± 1.12 µg/ml in water, 59.33 ± 1.44 µg/ml in 0.1 N HCl, and 384.53 ± 2.01 µg/ml in phosphate buffer (pH 6.8). Valsartan belongs to Biopharmaceutics Classification System (BCS) Class II, characterized by poor aqueous solubility and low oral bioavailability (~23%). Additionally, its solubility is limited in the acidic environment of the gastrointestinal tract, highlighting the need for solubility enhancement strategies.

b. Solubility of Drug-Complex

The solubility of the valsartan-β-cyclodextrin complex was evaluated in the same media as the pure drug. The complex showed significantly improved solubility, with values of 286.15 ± 2.11 µg/ml in water, 152.33 ± 1.54 µg/ml in 0.1 N HCl, and 594.53 ± 1.92 µg/ml in phosphate buffer (pH 6.8). These results (figure no.2) demonstrate a marked enhancement in solubility compared to the pure drug, confirming the effectiveness of complexation in improving valsartan's dissolution profile.

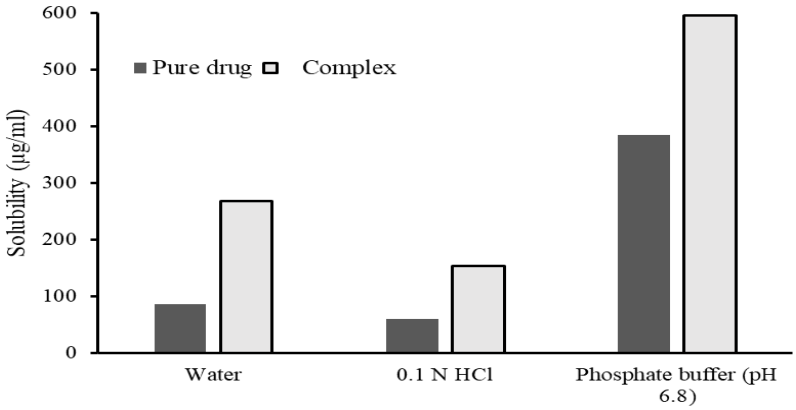

Figure No. 2: Solubility of complex in water, 0.1 N HCl, and phosphate buffer (pH 6.8).

4. Phase solubility studies

Phase solubility studies were carried out to evaluate the efficacy of β-cyclodextrin in improving the solubility of valsartan. The phase solubility diagram revealed a linear increase in valsartan solubility with increasing β-cyclodextrin concentration, as shown in Figure No. 3. The slope was less than unity over the entire concentration range studied, indicating an AL-type diagram and the formation of a complex with 1:1 stoichiometry.

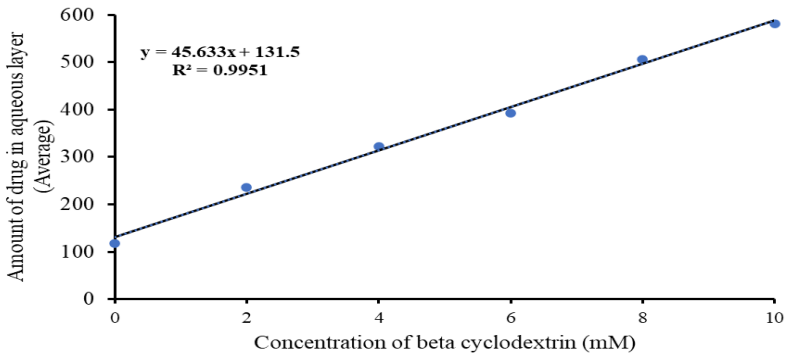

Figure No. 3: Phase solubility studies for β-cyclodextrin in unbuffered water to enhance solubility of Valsartan.

5. Fourier Transform Infrared Spectroscopy (FTIR) analysis

FTIR studies were carried out to evaluate the interaction of valsartan with β-cyclodextrin. The infrared spectra of valsartan, β-cyclodextrin, and the valsartan–β-cyclodextrin complex are shown in Figures 4, 5, and 6, respectively. Valsartan alone showed two carbonyl absorption bands at 1733.89 cm^{-1} and 1600.63 cm^{-1}, assigned to the carboxyl carbonyl and amide carbonyl stretching, respectively. These bands are diagnostically valuable for explaining drug–cyclodextrin interactions.

In the FTIR spectra of the inclusion complex, the amide carbonyl band shifted from 1600.63 cm^{-1} to 1637.10 cm^{-1}, which falls within the typical range for amide groups (1600–1695 cm^{-1}), indicating that no chemical changes occurred. The slight shift of the absorption band for the carbonyl group of amides to a lower frequency can be attributed to the breakdown of intermolecular hydrogen bonds associated with the crystalline drug molecule and the formation of hydrogen bonding between the drug and β-cyclodextrin.

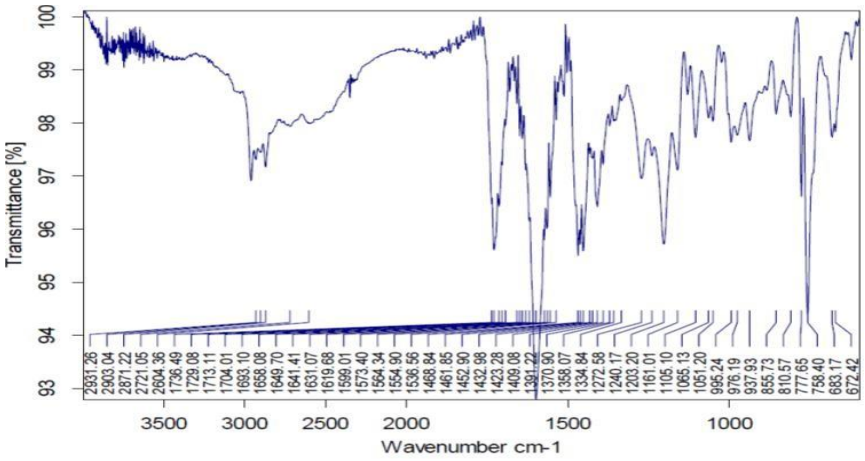

Figure No.4: FTIR spectra of pure drug.

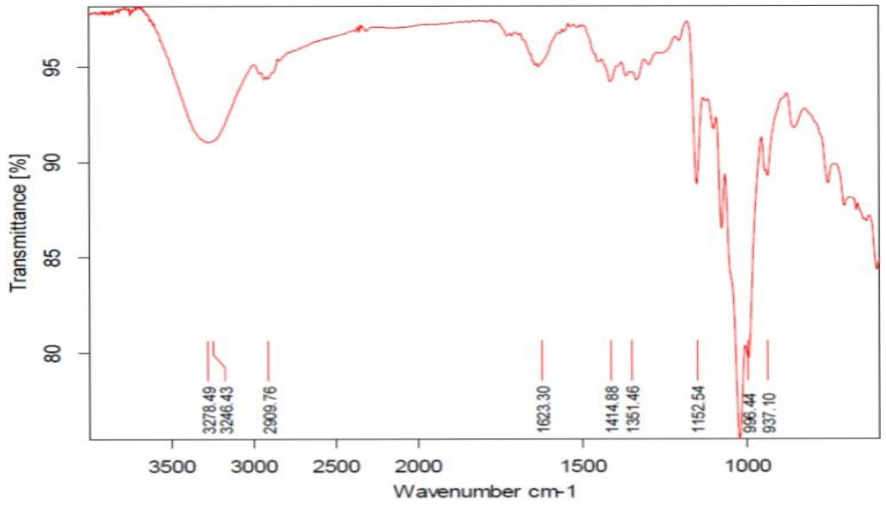

Figure No. 5: FTIR spectra of β-cyclodextrin.

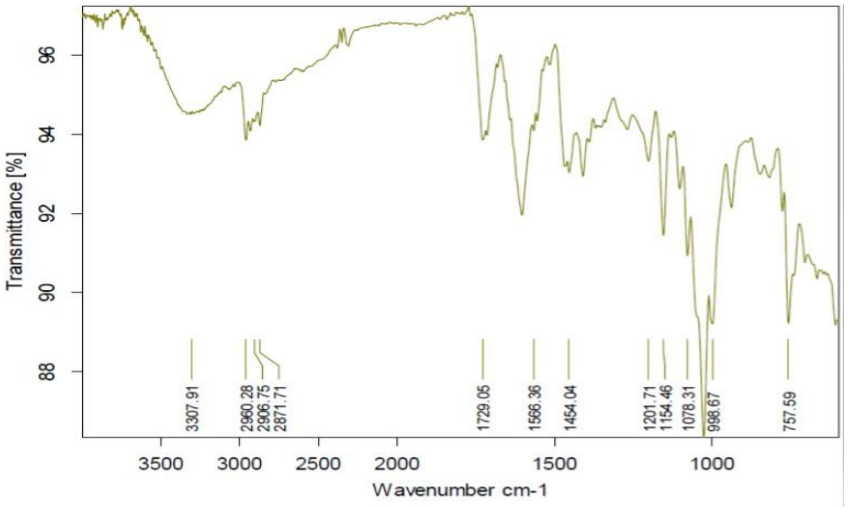

Figure No. 6: FTIR spectra of valsartan ß-cyclodextrin inclusion complex.

5. Physical Evaluation

The prepared tablets were evaluated for various physico-mechanical properties. The results of the tests are shown in table no.2.

Table No.2: Physical properties of prepared tablets.

Formulation	Thickness (mm)	Diameter (mm)	Hardness(kg/cm^2)	Friability (%)	Weight of the tablets (mg)	Drug content (%)
F1	1.82±0.01	6.03±0.01	2.80±0.01	0.25±0.03	131±1.50	99.66±1.52
F2	1.82±0.01	6.01±0.01	2.81±0.01	0.67±0.03	129±1.23	99.33±1.52
F3	1.80±0.01	6.02±0.02	2.81±0.01	0.95±0.02	130±2.11	98.56±1.32
F4	1.83±0.01	6.01±0.04	2.80±0.01	0.34±0.04	130±1.15	98.66±2.08
F5	1.81±0.01	6.02±0.04	2.80±0.01	0.69±0.02	129±1.73	98.66±0.57
F6	1.81±0.03	6.03±0.02	2.81±0.01	0.96±0.04	131±0.52	98.66±1.15
F7	1.82±0.02	6.03±0.03	2.82±0.02	0.66±0.01	137±1.15	98.66±1.15
F8	1.85±0.04	6.04±0.02	2.82±0.02	0.33±0.02	136±1.50	99.00±1.12
F9	1.81±0.03	6.03±0.03	2.82±0.02	0.95±0.03	137±1.10	98.66±2.08

Values are mean±SD, n=3

The thickness of the tablets was found in the range of 1.80±0.01 mm to 1.84±0.02mm and for core tablets of all batches of formulation prepared ranges in between2.06±0.15mm and 2.93±0.05 mm.

The diameter of the tablets was found in the range of 6.01±0.01 mm to6.04±0.04mm.

The hardness of core tablets was found to be in the range of 2.80 ± 0.01 kg/cm² to 2.84 ± 0.04 kg/cm², indicating that the hardness of the tablets was within acceptable limits.

The percentage friability of all the formulations of prepared tablets was found to be in the range of $0.25 \pm 0.03\%$ to $0.96 \pm 0.04\%$, indicating that the friability is within acceptable limits and the tablets were mechanically stable.

The percentage drug content was found to be in the range of $98.85 \pm 0.35\%$ to $99.35 \pm 0.75\%$, indicating uniform drug dispersion within the tablets of all formulations.

7. *In-vitro* disintegration Test

In vitro disintegration time was determined for the prepared tablets. It was observed that the tablet containing 40 mg of drug and 4.8 mg of sodium starch glycolate disintegrated completely within 4.5 ± 0.2 min. The disintegration time of the tablet containing 40 mg of drug and 4.8 mg of crospovidone was 1.4 ± 0.32 min. The tablets were designed to

disintegrate completely upon contact with GI fluid. Hence, the tablet containing 4.8 mg of crospovidone was selected for further studies.

8.a. *In-vitro* drug release studies for Tablet Formulations F1-F9

The pure drug tablet formulations were prepared by using DCP, MCC and Lactose. The release studies of pure drug tablets were conducted in 0.1 N HCl for 60 min shown in figure no.8.*In-vitro* release profile of these tablets was found to be26.18±5.12 %, 24.33±7.24 % and 23.84±1.83 % of drug released from F1, F2 and F3formulations respectively during 60 min of dissolution studies. Based upon result F1formulation was selected for further studies as it showed higher amount of drug release.

The core tablet formulations were prepared using different ratios of drug to β-cyclodextrin, namely 1:0.5, 1:1, and 1:1.5. Drug release studies of the core tablet formulations were conducted in 0.1 N HCl for 60 min. The in vitro release profile of these tablets showed 30.55 ± 5.12%, 39.37 ± 7.24%, and 36.11 ± 1.83% drug release from F4, F5, and F6 formulations, respectively. Based on the results, F5 was selected for further studies as it showed a higher amount of drug release compared to F4 and F6.

To the selected F5 formulation, super disintegrating agents such as SSG and crospovidone, and floating agents such as sodium bicarbonate and calcium carbonate, were added in different percentages: F7 contained 2% SSG, F8 contained 2% crospovidone, and F9 contained 4% crospovidone. The effect of different percentages of disintegrating and floating agents on the in vitro drug release profile of F7, F8, and F9 was investigated, as shown in Figure 12.

It was observed that 47.12 ± 5.12%, 54.45 ± 7.24%, and 57.60 ± 1.83% of the drug was released from F7, F8, and F9 formulations, respectively, and all formulations remained buoyant for more than 6 h. Based on these results, F9 was selected for further studies as it showed immediate and higher drug release along with buoyancy for 6 h compared to F7 and F8.

HPMC K4M plug tablet and the selected formulation F9 were placed in capsule and the capsule was coated with EudragitS-100 to achieve pulsatile release.

8.b. *In-vitro* drug release studies for Capsule Formulations C1-C12

The selected F9 tablet was placed in C1 and C2 capsules which is coated with 2 % Eudragit S-100. Both cap and body portion of C1 formulation is coated, whereas only body portion of C2 capsule is coated and small orifice is made manually. The drug release studies for C1-C6 shown in figure no.9. The drug release studies were conducted in 0.1 N HCl for about 6 h. *In-vitro* release profile of these capsule is shown in fig 13 and it was observed that 6.03±5.12 % and7.24±7.24% of drug released fromC1andC2formulationsrespectively.Basedupon result C2 formulation showed higher amount of drug release because only body portion of the capsule is coated.

The selected C2 formulation was further coated with 4% Eudragit S-100. In the C3 and C4 formulations, the core tablet was placed on top of the plug tablet. In C3, both the cap and body portions were coated, whereas in C4, only the body portion of the capsule was coated and a small orifice was made manually.

Drug release studies were conducted in 0.1 N HCl for approximately 6 h. The in vitro release profile of these capsules is shown in Figure 14. It was observed that 13.37 ± 3.21% and 18.58 ± 2.33% of the drug was released from C3 and C4

formulations, respectively. Based on these results, the C4 formulation showed a higher amount of drug release because only the body portion of the capsule was coated.

C5 and C6 formulations are similar to C3 and C4; the only difference is that the core tablet is placed at the bottom of the plug tablet. The in vitro release profile of these capsules showed that 8.31 ± 6.84% and 9.26 ± 3.42% of the drug was released from C5 and C6 formulations, respectively. Based on these results, the C6 formulation showed a higher amount of drug release because only the body portion of the capsule was coated.

The drug release studies for C7–C12 are shown in Figure No. 10. C7 and C8 are coated capsules with 4% Eudragit S-100. Two core tablets are placed between the plug tablet inside the capsule. Dissolution studies were carried out in 0.1 N HCl for approximately 7 h. In C7, both the cap and body portions are coated, whereas in C8, only the body portion of the capsule is coated and a small orifice is made manually. The in vitro release profile showed that 21.06 ± 5.10% and 27.72 ± 6.59% of the drug was released from C7 and C8 formulations, respectively.

C9 and C10 formulations are similar to C7 and C8, with the only difference being that dissolution studies were carried out in phosphate buffer solution (pH 6.8) for 7 h. The in vitro release profile showed that 86.40 ± 5.10% and 95.12 ± 6.59% of the drug was released from C9 and C10 formulations, respectively, indicating a higher amount of drug release in phosphate buffer (pH 6.8) compared to 0.1 N HCl.

Finally, dissolution studies of coated capsules C11 and C12 with 4% Eudragit S-100 were carried out in both 0.1 N HCl and phosphate buffer solution (pH 6.8) for approximately 7 h. Dissolution was initially conducted in 0.1 N HCl for 4 h, and the drug release was found to be 12.16 ± 5.12% and 12.14 ± 7.24%, respectively, at the end of the 4th hour. The dissolution medium was then replaced with phosphate buffer solution (pH 6.8), and the drug release was 92.38 ± 2.33% and 101.87 ± 1.12% at the end of 7 h. The in vitro release profile of these capsules demonstrates that the main aim of the coating is to retard initial drug release for a lag time and achieve pulsatile release thereafter.

The thickness of capsule was found in the range of 3.02±0.19 mm to 3.44±0.10 mm for all coated formulations. This varied based on the number of coatings given to the capsule.

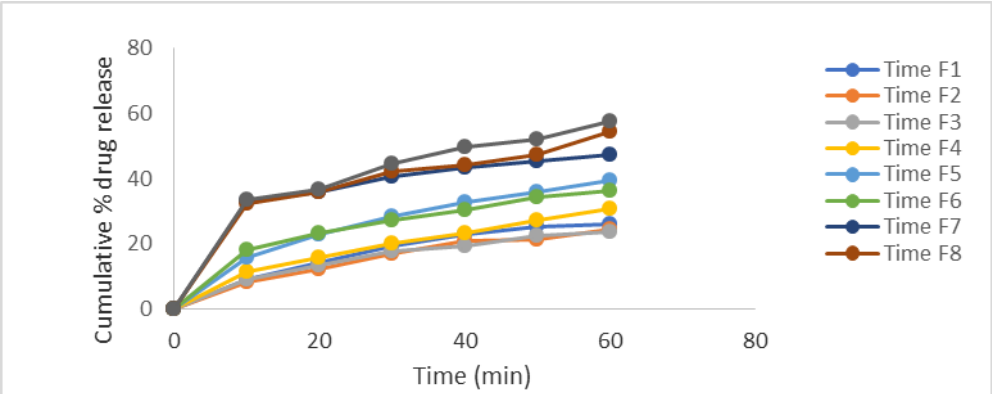

Figure No. 8: *In-vitro* drug release profiles for formulation F1-F9.

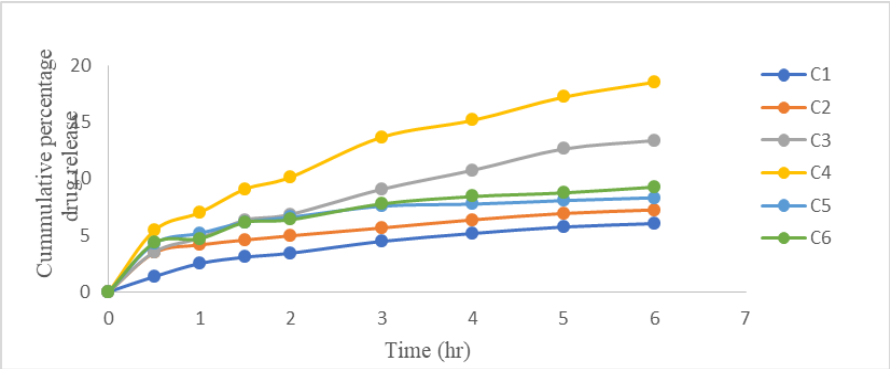

Figure No. 9: *In-vitro* drug release profiles of coated capsule in 0.1 N HCl (C1 to C6formulation).

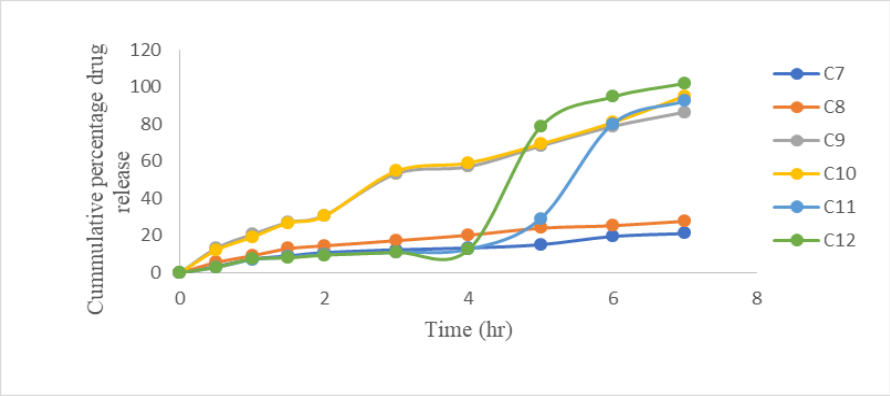

Figure No.10: *In-vitro* release profiles of coated capsule in 0.1 N HCl (C7-C10) and in Phosphate buffer solution (pH6.8) (C11-C12 formulations)

8.c. Model Independent Analysis

- The MDT and % DE values for all formulations are shown in Figure No. 11. In the prepared tablets, the MDT and % DE values varied between 2.05 to 3.97 h and 50.33% to 69.20%, respectively.
- In the prepared formulations, F7 was selected as the optimized formulation, as it showed better results with respect to percent drug release, MDT, and %DE when compared to the other formulations.
- In the case of coated capsules, MDT and %DE values varied between 4.21 to 4.89 h and 54.54% to 61.87%, respectively. The dissolution efficiency of the coated formulations decreased with an increase in the coating percentage, and the mean dissolution time varied accordingly.

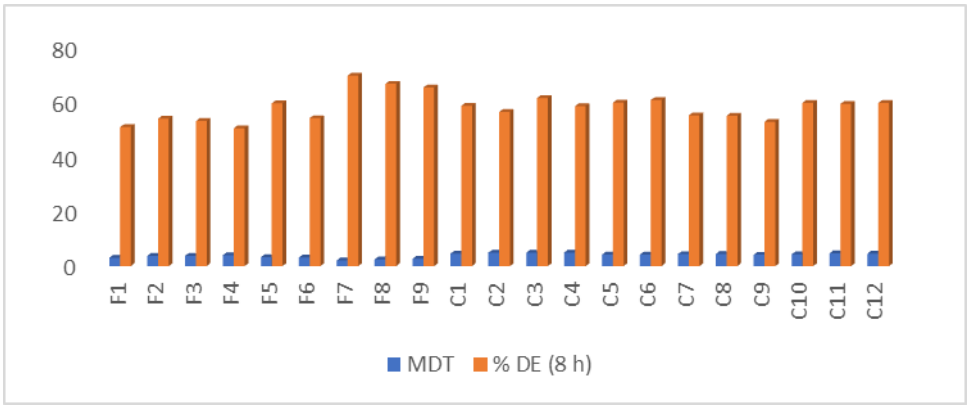

Figure No.11: Model Independent Analysis of MDT and %DE.

9. *In-vitro* buoyancy Studies

The floating behavior of the prepared tablets was visually determined. The tablets were placed in a 250 mL beaker containing 200 mL of 0.1 N HCl. The time required for the tablet to rise to the surface and float was recorded as the floating lag time, and the duration for which the tablet remained buoyant was recorded as the total floating time.

The formulation containing sodium bicarbonate showed a lag time of 1.5 ± 1.22 min, calcium carbonate showed 6.1 ± 2.23 min, and the formulation containing a mixture of sodium bicarbonate and calcium carbonate showed a lag time of 2.5 ± 1.44 min.

All the tablets initially remained at the bottom of the beaker immediately after being added to the test solution. The shape, swelling, and buoyancy behavior are shown in Figure No. 12. The tablet containing sodium bicarbonate ruptured within 0.5 h. However, the other two tablets containing calcium carbonate and a mixture of sodium bicarbonate and calcium carbonate remained intact throughout the study period. Both formulations exhibited swelling and formed a hydrogel.

Therefore, for further studies, tablets containing 50 mg of sodium bicarbonate were selected, as they showed a shorter lag time compared to the formulations containing calcium carbonate and the mixture of sodium bicarbonate and calcium carbonate.

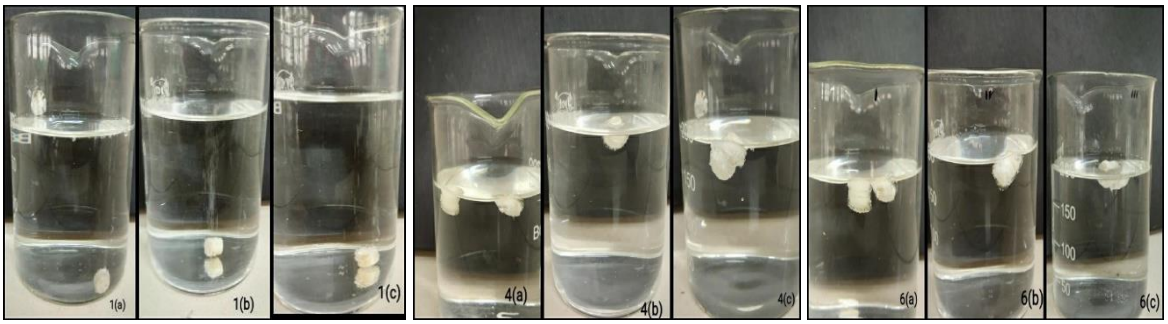

Figure No.12: Buoyancy studies at different time intervals (a), (b) and (c).

a) Buoyancy study at 0 Time

1(a) Sodium bicarbonate, 1(b) Calcium carbonate, 1(c) Mixture of sodium bicarbonate and calcium carbonate.

b) Buoyancy study at 2 h

4(a) Sodium bicarbonate, 4(b) Calcium carbonate, 4(c) Mixture of sodium bicarbonate and calcium carbonate.

c) Buoyancy study at 4 h

6(a) Sodium bicarbonate, 6(b) Calcium carbonate, 6(c) Mixture of sodium bicarbonate and calcium carbonate.

10. Physical evaluation of capsule formulations

The prepared capsules were evaluated for various Physico-mechanical properties. The results of the tests are shown in table no. 3.

Table No. 3: Physical Evaluation of Capsule.

Formulation	Weight(mg)	Weight gain After coating (mg)	Coating Thickness (mm)	Drug content (%)
C1	752±1.50	792±0.01	3.08±0.1587	98.66±1.52
C2	750±1.00	788±0.01	3.10±0.1006	98.33±1.52
C3	751±2.00	793±0.02	3.02±0.1928	97.94±1.00
C4	751±1.15	799±0.04	3.25±0.0115	98.66±2.08
C5	752±1.73	785±0.04	3.35±0.0264	97.66±0.57
C6	751±0.52	787±0.02	3.39±0.0057	98.66±1.15
C7	752±1.15	791±0.03	3.43±0.0416	97.66±1.15
C8	752±1.50	788±0.02	3.25±0.0152	99.00±1.00
C9	753±1.10	785±0.03	3.34±0.0115	98.66±2.08
C10	752±1.20	780±0.01	3.41±0.0110	98.23±1.00
C11	753±3.00	777±0.01	3.44±0.0378	98.66±1.52
C12	752±1.20	778±0.01	3.33±0.0161	98.66±3.05

Values are mean±SD, n=3

CONCLUSION

Valsartan is an angiotensin receptor blocker that may be used to treat a variety of cardiac conditions, including hypertension, diabetic nephropathy, and heart failure. The solubility of valsartan in an acidic medium is very low; therefore, to increase its solubility, an inclusion complex of valsartan with β-cyclodextrin was prepared. The inclusion complex showed significantly improved drug release as compared to the pure drug. Subsequently, tablets were prepared by the direct compression technique and placed in a coated capsule system. HPMC K4M, used as a plug tablet, had a significant effect on the lag time. The prepared formulation exhibited a lag time of 4 hours and released almost the entire drug within 2 hours after the lag phase. Thus, the pulsatile release of valsartan with improved dissolution characteristics could offer a superior drug delivery strategy and enhance patient compliance.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge to the Chebrolu Hanumaiah Institute of Pharmaceutical Sciences for providing the necessary facilities and infrastructure to carry out this research work.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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