ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue X October 2025

Development and Evaluation Valsartan Containing Controlled Release Pellets

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DOI: https://doi.org/10.51244/IJRSI.2025.1210000130

Received: 20 August 2025; Accepted: 27 August 2025; Published: 07 Novenber 2025

ABSTRACT:

The concept of controlled drug delivery has been explored for the delivery of drugs for prolong period of time for the past few years. This type of drug delivery has proved to provide a solution to several problems encountered in the repeated administration of such drugs. Utilizing the concept of incorporating drug in to the polymer matrices and extend the drug release for prolong period of time. The present study is an attempt to formulate and evaluate sustained release pellets of valsartan, in view to improve patient compliance and therapeutic action. To increase therapeutic efficacy, reduce frequency of administration and for better patient compliance once daily sustained release valsartan pellets proposed for extended-release dosage forms as it offers several manufacturing and biopharmaceutical advantages. The spherical shape and low surface area to volume ratio of pellets are advantageous for uniform film coating. Ethylcellulose in combination with Eudragit NE 30D was employed in this research to sustain the drug release for 24 hours by using layering technology. Here, Ethylcellulose acts as a release retarding polymer and Eudragit NE 30D acts as a film forming agent.

Keywords: Controlled release, Pellets, Valsartan, Coating pellets, Multiperticulate system

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form. The concept of multiple unit dosage form was initially introducedintheearly1950's [1]. These forms play a major role in the design of solid dosage form processes because of their unique properties and the flexibility found in their manufacture. These forms can be defined as oral dosage forms consisting of a multiplicity of small discrete units, each exhibiting some desired characteristics [2]. Together, these characteristics units provide the overall desired controlled release of the dose. These multiple units are also referred to as pellets, spherical granules or spheroids. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free- flowing, spherical or semi spherical units, referred to as pellets. Pellets or spherical granules are produced by agglomerating fine powders with a binder solution [3]. These pellets usually range in size from 0.5 1.5mm and in applications may be as large as 3mm. Multiparticulate drug delivery systems (MDDS), mostly used for oral route, consist of multiplicity of small discrete units that exhibit different characteristics. It is based on subunits such as granules, beads, microspheres, pellets, spheroids and Minitab. These sub units show various advantages over monolithic devices (non-divided forms) [4]. Pulsatile drug delivery systems are characterized by a rapid drug release after a predetermined lag time. These can be classified as single unit (e.g. tablet or capsule) or multiparticulate (e.g. pellets) systems. Multiparticulate also known as multiple unit dosage forms appear to be more reliable for a time controlled adjustment in drug release due to their smaller variation in gastric transit time. Hence multiparticulate dosage forms are gaining considerable importance over single-unit dosage forms [5]. Valsartan contains not less than 90% and not more than 110% of C24H29N5O3 calculated with reference to the dried sample. Valsartan undergoes almost complete metabolism. Metabolites are excreted principally in the urine as conjugates, and also in the faeces.

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MATERIAL AND METHODS:

UV spectroscopy: An accurately weighed amount of valsartan (10 mg) was dissolved in 25 mL of 0.1 N HCl in 100 mL volumetric flask and then volume was made up to the mark with 0.1 N HCl which gives 100 µg/mL stock solution. The aliquots 1.0 mL of stock solution pipetted out into 10 mL volumetric flask. These dilution produced 10 µg/mL concentration of Valsartan. The λmax was found by scanning at 400 to 200 nm.

IR spectroscopy: Infrared spectrophotometer is a useful analytical technique utilized to check the conformation drug functional group. The valsartan (1 mg) was powdered and mixed with 10 mg of dry powdered potassium bromide. The powdered mixture was taken in a sampler and the spectrum was recorded by scanning in the wavelength region of 4000- 400 cm-1 using IR spectrophotometer. The interpretation of IR was done.

Melting point determination: Melting point of Valsartan was determined by thieles tube method (Capillary method). Observed value was compared with the reported value [7].

Standard Calibration Curve of Valsartan in 0.1N HCl at 248 nm: An accurately weighed amount of Valsartan (10 mg) was dissolved in 25 mL of 0.1N HCl in 100 mL volumetric flask and then volume was made up to the mark with same 0.1N HCl which gives 100 µg/mL stock solution. The aliquots 1.0, 2.0, 3.0, 4.0 and 5.0 mL of stock solution were pipetted out into 10 mL volumetric flask. The volume was made up to the mark with 0.1N HCl. These dilutions produced 10, 20, 30, 40 and 50 µg/mL concentration of Valsartan respectively. The absorbance of these solutions was measured at 248 nm (λmax) using 0.1N HCl as a blank.

Preparation of pellets by extrusion method:

The pellets of valsartan were prepared by using extruder and he compositions of core pellets are given in Table 1. The dry blend of drug valsartan was prepared by mixing of drug with lactose, and Avicel PH-101 in double cone blender. The binder solution containing polyvinyl pyrolidone (PVP K-30) solution prepared by dissolving weighed quantity in distilled water under stirring. The granulating fluid/ binder solution was added in small increments to dry blend until a desirable end point was obtained. The wet mass was passed through the extruder equipped with screw and screen with 0.5 mm aperture at 50 rpm. The extrudate was prepared by varying the speed of extruder to get extrudate with good appearance. The extruded material was transferred to a spheronizer having plate diameter 2.0 mm and spheronized for 1 min at 800 rpm. The effect of spheronization speed and time were studied to get spherical pellets. The spheronized pellets were then dried in a vacuum oven at 40°C for 24 h. The sieving analysis was performed using standard sieves. The pellets passed through sieve # 20 and retained on sieve # 40 (0.42–0.84 mm) were used for enteric coating [8].

Table 1. Composition of pellets

Ingredients (%)	**VP1**	**VP2**	**VP3**	**VP4**	**VP5**
Valsartan	20	20	20	20	20
Avicel pH 101	25	30	35	40	45
Lactose	45	35	25	15	5
PVP K-30	5	10	15	20	25
Talc	5	5	5	5	5
Water	q.s	q.s	q.s	q.s	q.s

Coating of the pellets: Dried pellets were weighed accurately and lubricated with 0.1% talc. The composition of coating solutions is given in Table 5.4. Eudragit® and talc were dispersed/ dissolved separately in solvent mixture and then mixed together. The triethyl citrate solution was mixed with Eudragit®-talc dispersion using

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overhead stirrer for 30 min. The coating solution was passed through sieve # 100 to get a clear dispersion and was used for coating. Pellets were coated in a pharma R&D coater (Model: delux, Ideal Cures Pvt. Ltd [9],

Table 2. Trials for the selection of process parameters for drug layering

Process parameters	
Spray rate (gm/ml)	2-2.5 g /min
Air flow (bar)	0.2-0.3
Atomizing air pressure (bar)	1.5 bar
Inlet air temperature (ºC)	40-50
Product temperature (ºC)	25-30

Evaluation of the drug layered pellets

Sieve analysis: The average particle size of the pellets was analyzed by simple sieve analysis method. The sample collector and sieves arranged as per specification. Hundred gms of the pellets are shifted in to sieve shaker where a series of sieves was placed (14 #, 16 #, 18 #, 20 # and 25#). The machine was run for 5 minutes, all the meshes/sieves were taken out and retained pellets were collected by respective mesh and the % retention of pellets by that mesh was calculated. The retains collected on the larger dia sieve (A) and from the sample collector separately passes through the smaller dia sieve (B)

Particle size distribution and determination: This practice was done for the pellets obtained after functional coating to check average size of the pellets. Hundred gms of the pellets are shifted in to sieve shaker where a series of sieves was placed (14 #, 16 #, 18#, 20 # and 25 #). The machine was run for 5 minutes, all the meshes were taken out and retained pellets were collected by respective mesh and the % retention of pellets by that mesh was calculated. Average particle size was determined. A graph was plotted taking mean size opening on X- axis and percent weight retained on smaller sieve on Y - axis.

Micromeritics properties: The micromeritics properties of prepared peelts was characterized in terms of Carr's index, hausner's ratio and Angle of repose.

Drug content: Accurately weighed samples of the coated pellets (1 gm) were subjected for extraction using 100 ml of phosphate buffer pH (6.8) for 10 min. The mixture was stirred overnight to ensure a complete extraction. The solution was filtered through a filter paper, diluted with appropriate amount of phosphate buffer pH (6.8) and analyzed spectrophotometrically for valsartan content at 250 nm. A calibration curve was used based on standard solutions in phosphate buffer pH (6.8). The other excipients used in the coating did not interfere with the analysis at this wavelength. All experiments were performed in triplicate [10].

Water content by KF method: Around 50ml of methanol was taken in titration vessel of Karl Fischer titrator and titrated with Karl Fischer reagent to end point. In a dry mortar the pellets grinded to fine powder. Accurately about 0.5 g of the sample, weighed and transferred quickly to the titration vessel, stirred to dissolve and titrated with Karl Fischer reagent to end point.

Percentage Yield: All the sustained release valsartan pellets prepared by fluid bed coating were evaluated for percentage yield of pellets. The actual percentage yield of pellets was calculated.

Friability: About 6.5g pellets were weighed collectively and placed in the chamber of the friabilator rotated at 25rpm for 4min. In the friabilator, the pellets were exposed to rolling, resulting from free fall of pellets within the chamber of the friabilator. After 100 rotations (4 minutes), the pellets were taken out from the friabilator and

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intact pellets were again weighed collectively after removing fines using sieve # 44 sieve. Friability values below 0.8% are generally acceptable. The percentage friability was calculated according to the following formula.

% F = W1-W2/W1 × 100

Where, W1 = weight of the pellets before test, W2 = weight of the pellets after test.

Morphology of drug loaded pellets: The topography of pellets was analyzed with help of scanning electron microscopy (SEM). Few pellets were spread on glass stub. Afterwards, the stub containing the sample was placed the scanning electron microscope chamber. The scanning electron photomicrograph was taken at the acceleration voltage of 20 kv, chamber pressure of 0.6 mm Hg, with original magnification of 90X. surface of drug layered pellets were examined [11].

Filling of capsules: The empty hard gelatin capsules size '0' were used and capsules were filled with pellets using a hand filling machine (ProFill 100 System, Torpac Inc., NJ, USA). Unit formulae for 80 mg valsartan capsule filled with coated pellets

Evaluation of Capsules:

Weight variation test: Individual weights of 20 capsules were taken and the average weight was calculated.

Weight variation should not be more than 10%.

Limits: Less than 300 mg ±10%, more than 300 mg ± 7.5%

Content uniformity: The amount of drug determined by assay is within the range of 85- 105% of the label claim for 9 out of 10 dosage forms and no formulation outside the range of 70 -125% of label claim.

Disintegration: The capsules are placed in the basket rack assembly which is repeatedly immersed about 30 times per minute into a thermostatically controlled fluid at 37±2oC and observed.

In vitro drug release studies: In-vitro release of valsartan from pellet formulations was investigated by the USP apparatus II (Paddle method). The release medium was 900 mL of (0.1N HCL, phosphate buffer pH 6.8, phosphate buffer pH 7.4) for the period of 24 h, at 37 ± 0.5 ºC and the rotating speed of the apparatus was set to 50 rpm for all formulation (pellets). At certain time intervals, 5 ml of sample was withdrawn and immediately same amount of fresh medium (37 ± 0.5 ºC) was replaced. For the determination of valsartan amount, the UV absorbances of the samples were measured at 250 nm by UV spectrophotometer and the amount of valsartan released was calculated [12].

RESULTS AND DISCUSSION

UV spectroscopic studies: The solutions containing 10 µg/mL and 100 µg/mL of Valsartan in 0.1 N HCl (pH1.2) were scanned. Wavelength (λmax) was found to be 248 nm.

Infrared spectroscopy: The IR spectrum of the Valsartan was recorded and the functional groups were interpreted as per the structure and were found to be appropriate and matching the structure of the drug. Figure 7.1 describes the IR spectrum of the pure drug.

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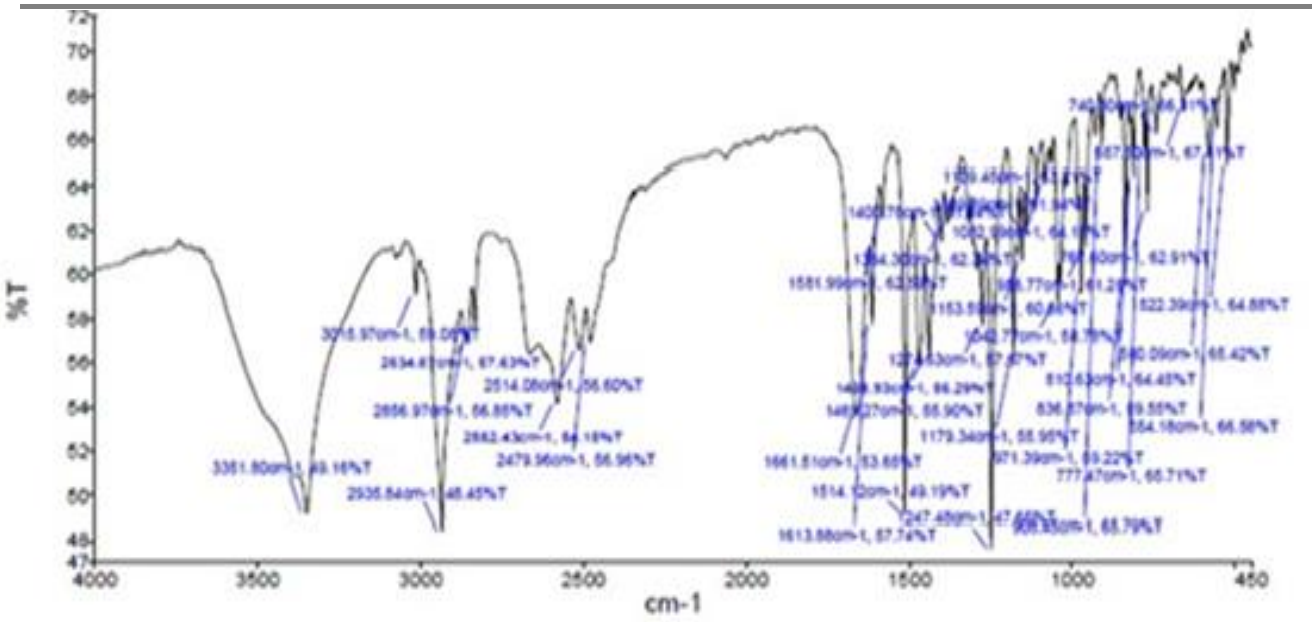

Figure 1: IR spectra of the Drug (Valsartan).

The IR spectra of Valsartan (Figure 7.1) exhibited sharp and strong bands at 3417.6 cm- 1 due to N-H stretching. A band at 2964.90 cm-1 showed C-H stretching superimposed upon O-H stretching indicating the presence of phenyl groups. A sharp band at 1733.12 cm-1 was due to C=O stretching. Near to the 1600 cm-1, a sharp peak appeared due to N=N which indicates the presence of azo group. A peak at 1567.23 cm-1 is due to N-N bending. Peaks at 1470.79 and 1458.25 cm-1 appeared due to C-O-H in plane band.\

Melting point determination: The melting point of the Valsartan was found to be 114 to 117ºC. Observed melting point was compared with the reference melting point available in Pharmacopoeia and as per certificate of analysis (COA) found to be accurate.

Standard Calibration Curve of Valsartan in 0.1 N HCl (pH 1.2) at 248 nm: It was found that the Valsartan shows absorbance in UV range 200 to 400 nm. The absorbance of serial dilution of Valsartan in 0.1 N HCl was taken and the absorbance vs. concentration curve was found at 248nm. It was found to be linear over the range 10 to 50 µg/mL indicating its compliance with Beer's and Lambert's law.

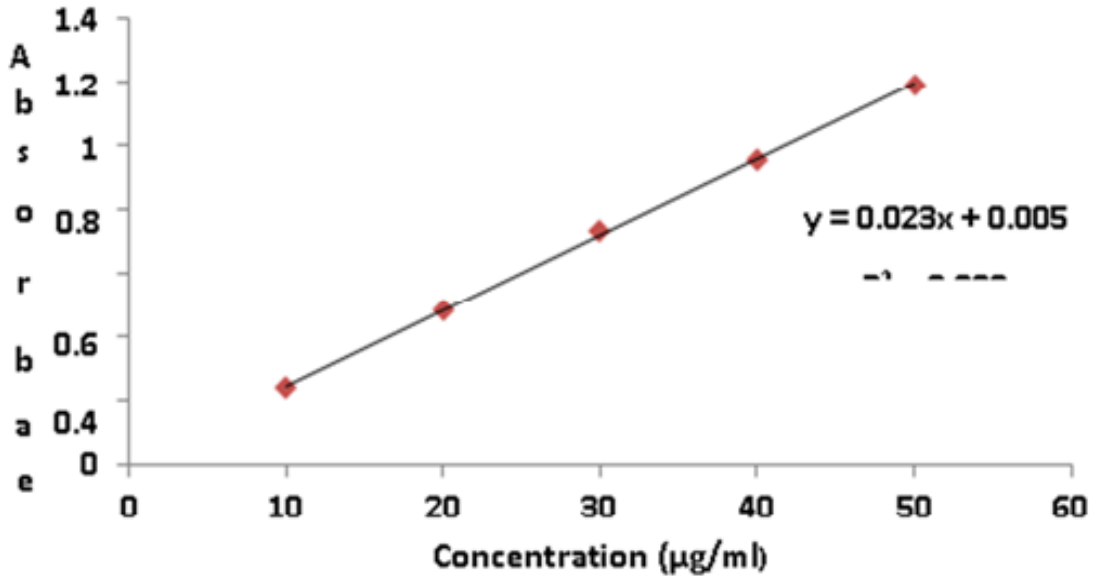

Figure 2: Graph of Standard Calibration Curve of Valsartan in 0.1N HCl at 248nm

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Table 3. Physicochemical properties of the pellets

Formulation code	Bulk density ± SD (gm/ml)	Tapped density	Angle of repose ±SD (Ɵ)	Haussner's ratio ±SD	Friability ±SD (%)	%water content ±SD
VP1	0.628±0.009	0.712±0.002	32.6±0.01	1.133±0.001	0.563±0.033	2.05±0.04
VP2	0.655±0.001	0.742±0.001	31.8±0.02	1.132±0.004	0.459±0.052	1.97±0.02
VP3	0.686±0.002	0.775±0.006	29.87±0.030	1.129±0.003	0.326±0.131	1.85±0.03
VP4	0.702±0.004	0.793±0.007	27.8±0.03	1.129±0.006	0.379±0.064	1.70±0.02
VP5	0.679±0.003	0.767±0.004	28.48±0.024	1.11±0.001	0.414±0.012	2.01±0.02

Filling of capsules:

The empty hard gelatin capsules size '1' were used and capsules were filled with pellets using a hand filling machine or by manually method. Capsules are evaluated for weight variation, content uniformity, and disintegration. The results were listed in Table 4.

Table. 4. Capsules Evaluation Parameters

Batch	Content Uniformity (%)	Wt. Variation (mg)	Disintegration Time (sec)
VCP1	94.5±0.6	352±0.1	201±1.52
VCP2	96.8±0.8	365±0.4	213±2.93
VCP3	95.9±0.7	354±0.3	215±3.56
VCP4	98.6±0.5	352±0.5	218±2.45
VCP5	98.5±0.4	355±0.1	221±1.42

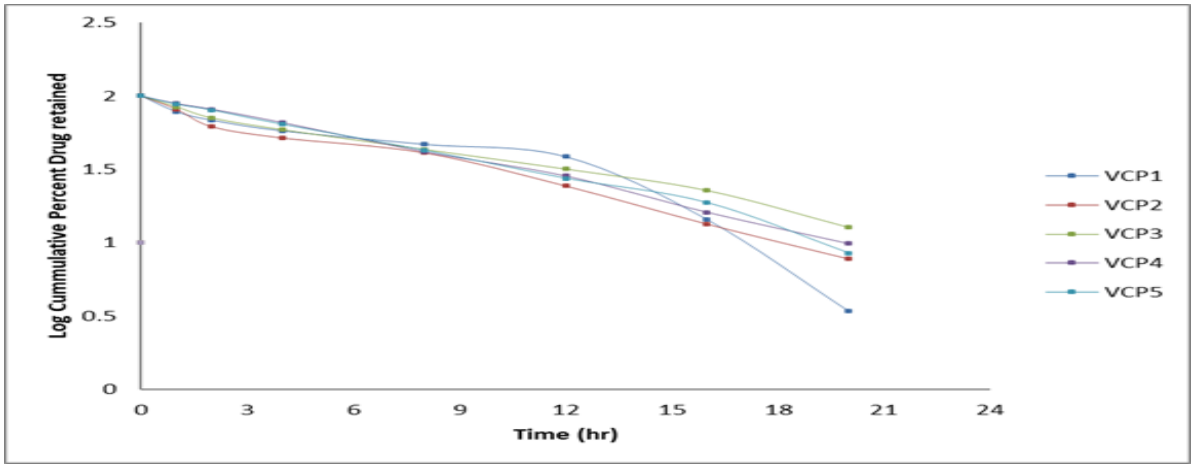

Figure 3: First-order kinetic plot of SR valsartan pellets

Pelletization can be defined as an agglomeration process that converts fine powders or particles of a bulk drug and excipients into small, free-flowing, more or less spherical units, called pellets. The usage of pellets provides novel approaches to the patients in providing accurate, and easy in administrating the dosage form. The use of

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polymer blends represents a valuable and under-utilized resource in addressing a diverse range of drug delivery challenges. Polymers are widely used in the formulation of pharmaceutical and healthcare products. Applications include controlling drug release, providing site specific delivery of active pharmaceutical ingredients (APIs) and improving drug stability. The goal of blending polymers from a functionality standpoint is to improve, customize, or maximize material performance. It is anticipated that new drug molecule development challenges such as bioavailability enhancement and the demand for enabling excipients will lead to increased applications of polymer blends in pharmaceutical products.

Summary and conclusion: The aim of the present study was to formulate and evaluate a stable valsartan sustained release pellet. The formulation process was carried out in FBP by wurster technique. The work was carried out to extend/prolong the release of Valsartan by using different polymers such as EC, Eudragit NE 30D. Based on the in vitro release studies, PS4 was considered as optimized formulation which extends the drug release upto 24hrs and showed 95.79% drug release. Different kinetic models were applied to optimized formulation PS4 and observed that it follows first order release kinetics and mechanism of drug release is by Higuchi model ($n > 1$), indicated that the drug transport mechanism by super case – II transport. The optimized PS4 formulation was found as pharmaceutically equivalent to innovator due to similarity ($f2 = 77.77$) in drug release profile. Stability studies were conducted on the optimized formulation PS4 at 40°C/ 75% RH (accelerated stability testing) for 3 months according to ICH guidelines. Dissolution release profile and physical appearance of optimized formulation PS4 showed that there was no significant difference in physicochemical parameters ($p < 0.05$) during the stability study. It was concluded that the order of extending the release of the drug increase with the increase in the coating concentration of the polymer. The dissolution data revealed that the level of coating and the ratio of polymers are very important to achieve optimum formulation.

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