Formulation, Development & Evaluation of Valsartan Tablet

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Abstract

Osmotically regulated Valsartan drug distribution was the study's major goal. BCS class I medication Valsartan treats hypertension. This system seeks zero-order Valsartan release. This study also established a mechanism to reduce dose frequency, interpatient variability, adverse effects, and patient compliance. HPMC K100M polymer and Mannitol osmotic agent were drug-compatible. FTIR spectra of the physical combination demonstrate drug-polymer compatibility. This technique was created in two steps: formulation of core tablet and coating/drilling of orifice. Coated tablets were examined for in-vitro release research and hardness, thickness, friability, weight variation, and content consistency. All formulations dispersed well. Valsartan had 99.99% drug release in 12 hours. Direct compression produced Valsartan osmotic tablets. Polymeric HPMC K100M with osmotic Mannitol. Pre-compression characteristics such bulk density, tapped density, angle of repose, hausner ratio, and carr`s index were tested. Direct compression formed valsartan osmotic tablets. Different osmogen concentrations were tested on osmotic tablets. The osmotic tablet was made by coating the core tablet containing medicine and osmogen with a semipermeable membrane to allow water penetration and drilling an aperture to release drug after adequate osmotic pressure. First, drug solubility, melting point, and IR were studied. F1, F2, F3, F4, and F5 release drug at 12 hours. The stability research formulations were tested for physical appearance, hardness, thickness, and in-vitro dissolution for three months. The formulation parameters remained steady, indicating stability.

Keywords: Valsartan, Formulation, Development, Microcrystalline cellulose, Talc, Magnesium stearate.

Introduction

Valsartan, a strong, oral nonpeptide tetrazole derivative, specifically inhibits Angiotensin II Receptor type 1 to lower blood pressure and treat hypertension [1]. Novartis created it and sells it worldwide. It can be taken with other antihypertensive medicines. Lipophilic and moderately fast-acting, it is a medication in the same class. Generic companies target the medicine well [2]. It's neutral pH-soluble. Low-permeability, high-solubility BCS class III medication. Acetonitrile and methanol dissolve valsartan. Oral absorption is fast and plasma protein binding is high. Valsartan (F3) is mostly eliminated non-renally. Valsartan treats mild-to-moderate hypertension in children, adolescents, and the elderly [3]. Valsartan monotherapy with 80 mg as the starting dose has been effective in patients with CHF, renal impairment, and hypertension, and add-on therapy helped control BP in a large population of patients with severe hypertension not responding to β-blockers, ACE inhibitors, or diuretics [4]. End-organ protection is increasingly considered as important as aggressive blood

pressure management [5]. Thus, ARBs like Valsartan can decrease kidney damage caused by high blood pressure or diabetes, which has medical and commercial benefits. Valsartan administration has been studied in VALUE, VALIANT, VAL-Heft, PREVAIL, and others. These studies extensively compared valsartan to various antihypertensives. Valsartan was well-tolerated in clinical trials, with most treatment-associated side effects attributable to similar medications including ACE inhibitors. Many analytical methods have been developed to quantify and determine valsartan in biological fluids and pharmacological dose form [6, 7].

Oral osmotic medication delivery is the most prevalent systemic drug delivery route. Oral administration is the oldest and most used method.Controlled drug delivery dosage forms provide desired drug release pattern for longer period of time, although typical controlled release systems like matrix or reservoir type may display bioavailability variation due to gastric pH and hydrodynamic condition of body [8]. Human and veterinary pharmaceuticals use osmotic systems for controlled drug delivery. Oral osmotic medication delivery systems have compressed tablet cores coated with semipermeable membranes. These systems release drugs under osmotic pressure from osmogen. Osmotic pressure prevents solvent passage on the higher concentration side. Osmotic pressure applies to concentrated solutions. Drug release is unaffected by stomach pH or hydrodynamics [9]. That treats hypertension alone or in combination. Antiarrhythmic valsartan is angiotensine ll receptar antagonist. Angiotensin II blockers' vasoconstrictor and aldosterone-secreting effects are blocked by losartan. Radiolabeled losartan is well absorbed and undergoes significant first-pass metabolism. Strategic drug distribution by osmotic devices is most promising [10]. They might be oral or implanted controlled medication delivery systems [11]. Osmosis, a noble bio phenomena, is used to produce regulated medication delivery systems with all the desirable properties. Drug distribution uses osmotic pressure. Antihypertensive valsartan blocks angiotensin II receptors. It is BCS class 1. Oral absorption is good, but first-pass metabolism reduces bioavailability to 33%. Peak plasma concentration occurs 1 hour after an oral dose and terminal elimination half-life is 1.5 to 2 hours, requiring two to three times daily treatment in many individuals, which often leads to noncompliance [12]. Thus, there is a considerable clinical need and market opportunity for a regulated Valsartan dosage form that improves patient compliance. This study developed osmotic-based extended-release Valsartan formulations. This work created Valsartan osmotic medication delivery tablets. Mannitol and HPMC K100M were added to Valsartan pills to make them osmotic. Ethyl Cellulose and PEG-4000 Dichloromthane coated core pills. Optimized coated tablets use a needle on the upper face to get 0.5µm aperture diameter to release the medicine slowly. This study examined how formulation variables such swellable polymer, Mannitol concentration, and SPM coating solution ratios affected drug release from tablet formulations [13, 14].

Material And Method

As a gift sample, Losartan was provided by Ranbaxy Pharma India. HPMC K100M (Hydroxy propyl Methyl Cellulose) was provided by M/S colorcon Asia in Mumbai. Mannitol and Microcystalline Celulose were also provided by M/S Matrix Pharma in Hyderabad. Talc and Magnesium Stearate were provided by Loba Chemical in Mumbai [15].

Electronic weighing balance, Dissolution test apparatus, UV-Spectrophotometer, pH meter, FTIR 200 Spectrometer [16].

To examine the interaction between the drug and the polymers, the FTIR spectra of the physical mixture of polymer and Valsartan were recorded. In the spectrum of the mixture, the typical peak of valsartan occurred without a noticeable shift in position. This shows that Valsartan and the physical composition of polymer did not interact [17].

Preparation of Valsartan Tablet:

The Valsartan osmotic core tablet was made using a direct compression process.In a double cone blend, valsartan and HPMC K100M were combined for 10 minutes. A 30 mesh sieve was used to filter the mixture. After adding the osmotic agent MCC, the mixture was continued for another 10 minutes after geometric dilution. Talc and magnesium stearate that had been blended for five more minutes

after passing through a 60-mesh screen were added. Utilizing a Clit 10 station mini press, the mixture was compressed into tablets. The same process was used to prepare many batches of tablets with different mannitol concentrations to minimize processing variables. All batches of tablets were compressed under the same circumstances [18].
The Valsartan core pill was coated in a coating pan with three baffles set at 1200 and a 10 cm outside diameter. When adding components of the coating solution to the solvent combination, the first component was given time to dissolve before the next was added. The coating temperature ranged from 38°C to 42°C. Spraying and coating were done at a rate of 4-5 ml/min. The amount of coating solution used during the coating process determined the coat's weight and thickness. Before further analysis, all coated tables were dried at 500 for six hours. the makeup of the coating solution applied to the tablets' cores. Use a needle with a suitable aperture size (0.5um) on one face of all coated tablets [19, 20].

Table 1: Valsartan tablet Formulation

Excipients	F1	F2	F3	F4	F5
Valsartan	80mg	80mg	80mg	80mg	80mg
HPMC	50mg	50mg	50mg	50mg	50mg
Mannitol	30mg	40mg	50mg	60mg	70mg
Talc	3mg	3mg	3mg	3mg	3mg
Magnesium stearate	2mg	2mg	2mg	2mg	2mg
Microcrystalline cellulose	170mg	160mg	150mg	140mg	130mg

Table 2: Tablet Coating composition:

Excipient	F1	F2	F3	F4	F5
Ethyl cellulose (gm)	1.2	1.2	1.2	1.2	1.2
PEG -4000 (mg)	0.8	0.8	0.8	0.8	0.8
Dichloromethane (ml)	20	20	20	20	20

Evaluation parameters of Valsartan tablet:
Thickness: A vernier caliper was used to measure the tablet's thickness. Five tablets from each formulation type were used to get the average value. It is written in millimeters.
Hardness: Monsato tester was used to measure the hardness. And the weight of this test was in kilos [18].
Weight variation test: To perform the USP weight variation test, weigh each of the 20 tablets separately, compute their average weight, and then compare their weights [18].
Friability: The test for friability In the Roche friabilitor, 10 tablets were placed with their initial weights recorded and rotated for 100 revolutions at a speed of 25 rpm. The formulae shown below can be used to calculate this test.
Friability is equal to (W1-W2)/W1 100.
Uniformity of drug content: A Valsartan osmotic tablet from a batch was taken at randoom and ground into a fine powder. The powder substance was transferred into a 100 ml volumetric flask, 70 ml of distilled water was added, and the mixture was agitated occasionally for 30 minutes before being filled to the required 100 ml level. The volumetric flask's solution was taken out, and 10 ml of it was centrifuged. The centrifuge tube's supernatant solution was removed, and Millipore filter 16 was used to filter it once more. The absorbance at 250 nm was then measured after the filtrate had been diluted. Six times (N=6) for each batch of tablets were used in this test. the predicted Valsartan dosages from various batches [18].

Dissolution is the process by which a medication is released from a solid dosage form and immediately enters a solution of molecules.

Procedure: For Valsartan controlled release osmotic tablets, dissolving studies were carried out for both the core formulations and coated formulations using calibrated eight station dissolution equipment equipped with paddles and 900 ml of phosphate buffer over the course of 12 hours. The medium's temperature was held constant at 37 to 100 °C throughout the studies while the paddles were operated at 100 revolutions per minute. To keep the dissolution medium's volume constant throughout the investigations, dissolution samples were regularly taken at intervals of up to 12 hours and replaced with an equivalent volume. By measuring, the samples' drug content was identified. Following appropriate sample dilution, the absorbance at 234 nm using an ELICO double beam UV spectrophotometer. According to the I.P. dissolution approval criteria, in vitro dissolution tests were carried out six times for each batch of formulation, and the average of six results was selected for the studies (n=6) [19-21].

Studies on accelerated stability: The osmotic tablet (F3) sample formulation was kept at 40 20 and 75 % RH for three months consecutively. Samples were taken out and examined for hardness and dissolution [22-27].

Result And Discussion

IR SPECTRA OF VALSARTAN OF PURE DRUG:

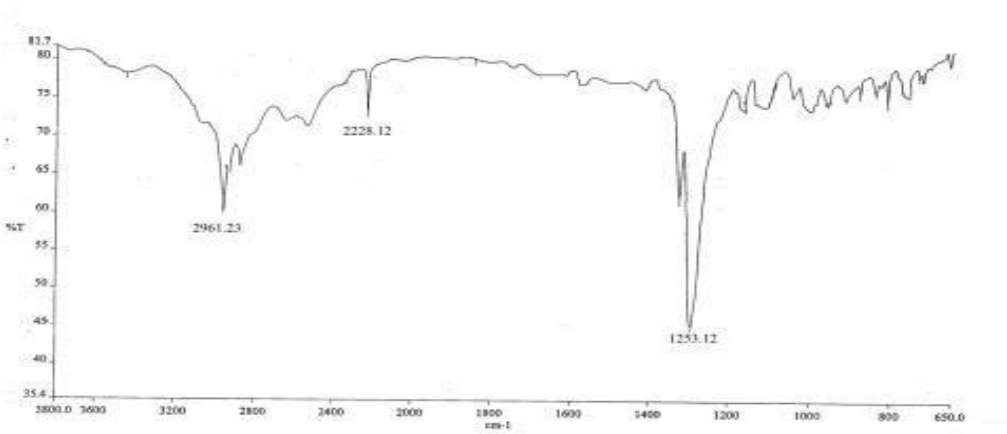

Figure 1: IR Spectra of Valsartan API

Table 3: Characteristic peak of Valsartan

Functional group	Characteristic peak	Observed peak
C-H stretching	3000-2800	2961.23
N-H bending	1640-1430	1620
OH-stretching	2400-2000	2228.12
Stretching C-Cl	500-1000	994.63

Ir Spectrum Of Valsartan With Other Excipients

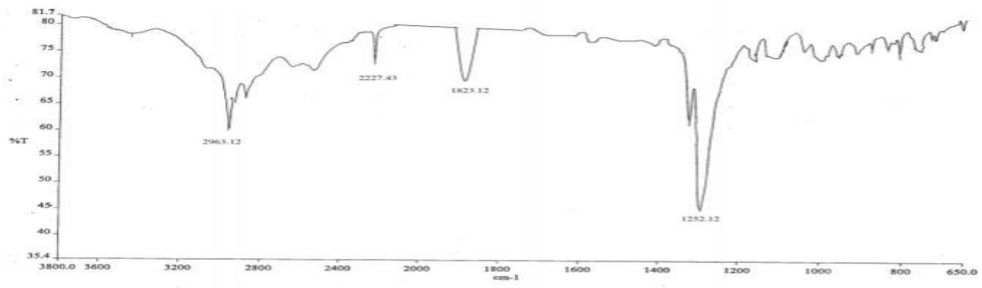

Figure 2: IR Spectra of Valsartan with other excipient

Table 4: Characteristic of Valsartan with other excipient

Functional group	Characteristic peak	Observed peak
C-H stretching	3200-2800	2963.12
OH-stretching	2400-2000	2227.12
C-N amine	1400-1200	1251.21
C-Cl stretching	1000-800	920.21

Table 5: Evaluation parameters of pre-compression studies

Formulation	Bulk density	Tapped density	Carr`s index	Housner ratio	Angle of repose
F1	0.48 ± 0.2	0.58 ± 0.2	15.99	0.83 ± 0.3	30.96 ± 0.96
F2	0.49 ± 0.2	0.57 ± 0.2	16.03	0.83 ± 0.2	30.14 ± 0.87
F3	0.48 ± 0.2	0.57 ± 0.3	14.99	0.84 ± 0.2	29.33 ± 0.70
F4	0.46 ± 0.3	0.56 ± 03.	20.54	0.78 ± 0.2	30.37 ± 0.66
F5	0.48 ± 0.2	0.56 ± 0.3	14.28	1.04 ± 0.2	29.88 ± 0.78

Table 6: Evaluation parameters of post compression studies

formulation	Weight uniformity (mg)	Hardness (kg/cm2)	Thickness (mm)	Diameter (mm)	Initial weight (mg)
F1	348 ± 5.0	5.8 ± 0.2	2 ± 0.38	10 ± 0.28	348
F2	350 ± 2.0	5.4 ± 0.4	2 ± 0.40	10 ± 0.18	350
F3	349 ± 2.0	6.2 ± 0.2	2 ± 0.24	10 ± 0.34	349
F4	347 ± 2.0	5.6 ± 0.2	2 ± 0.12	10 ± 0.15	347
F5	350 ± 5.0	5.5 ± 0.2	2 ± 0.23	10 ± 0.24	350

Table 7: Evaluation parameters of post compression studies (Friability and Drug Content)

formulation	Final weight (mg)	% weight gain	Friability (%)	Drug content (mg/tablet)

F1	365	8.22	0.18	78.8 ± 0.4
F2	378	8.42	0.15	80.2 ± 0.3
F3	379	8.62	0.15	79.42 ± 0.4
F4	381	9.13	0.17	79.5 ± 0.2
F5	380	8.92	0.13	80.4 ± 0.2

The aforementioned table clearly shows that every trial formulation complies with the requirements listed in the Indian Pharmacopoeia for average weight, weight variation, and friability.

Table 8: Dissolution profile of various batches of osmotic tablet at 6.8 pH

Time in Hrs.	**% Drug release**				
	F1	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
1 Hrs	10.66	13.12	14.54	14.41	13.14
2 Hrs	28.66	21.66	20.36	20.89	20.50
3 Hrs	29.72	24.14	25.30	25.85	27.51
4 Hrs	30.63	29.79	29.91	29.66	29.92
5 Hrs	35.62	40.53	43.05	45.03	45.13
6 Hrs	36.7	44.58	52.25	52.2	52.35
7Hrs	38.45	54.02	57.95	57.97	58.05
8 Hrs	57.93	57.25	62.28	65	65.15
9 Hrs	75.35	68.15	76.74	76.56	75.36
10 Hrs	83.68	79.97	82.13	84.2	79.86
11 Hrs	87.54	86.34	91.82	91.34	90.25
12 Hrs	93.21	94.37	99.99	96.42	97.21

All of the formulations F1, F2, F3, F4, and F5's dissolving studies were successful. It was discovered that the drug release dates for formulations F1, F2, and F4 were 93.21, 94.37, and 99.99, respectively. For formulations F3, F5, the drug release data was determined to be 99.99 and 97.21, respectively. In this instance, the medication was released for 12 hours with a 99.99% dissolution profile. Consequently, formulation F3 has outstanding% drug release.

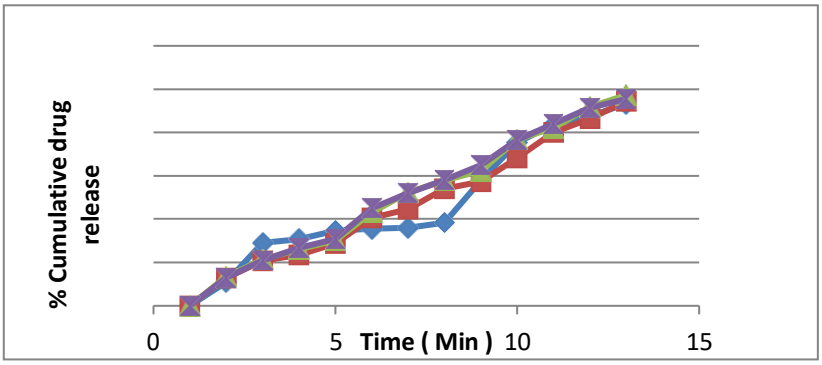

Figure 3: Cumulative Drug Release Curve

Table 9: value of rate constant (k) and correlation coefficient(R) for osmotic tablet

Formulation	Zero order	First order	Higuchi Model	Korsmeyers and peppas	
				r^2	n
F1	0.958	0.9917	0.9281	0.9477	0.7757
F2	0.990	0.9922	0.9691	0.9863	0.8207
F3	0.996	0.9910	0.9801	0.9912	0.8440
F4	0.996	0.9871	0.9835	0.9650	0.8235
F5	0.997	0.9026	0.9846	0.9933	0.8352

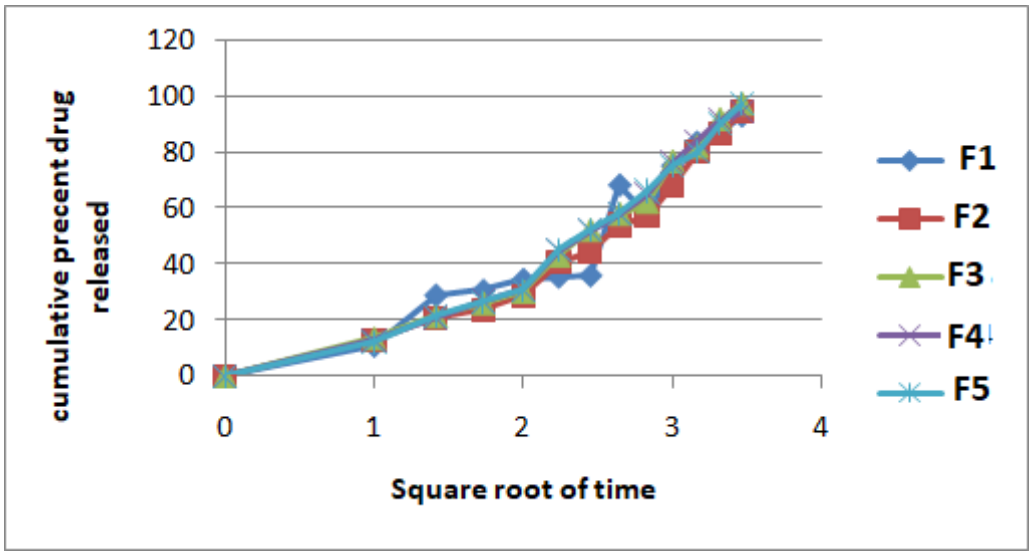

Figure 3: Higuchi plot

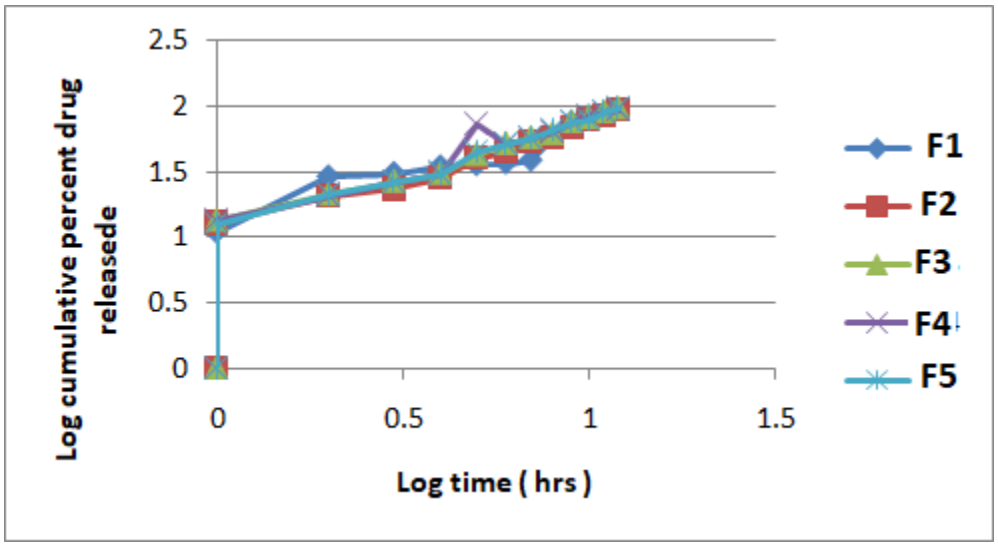

Figure 4: Korsmeyers and Peppas Plot

Figure 1 to 4 show graphs of cumulative drug release versus time, log% drug remaining versus time, drug release versus square root of time, and log% drug remaining versus log time. Respectively. In Table No. 9, the regression coefficient of determination (r2) was provided. The diffusion controlled release mechanism is explained by the Higuchi equation, whose coefficient of determination indicated that the release data was best fitted with zero order kinetics. Every formulation of the medicine through tablets indicates non-fickian.

Conclusion:

The goal of the current work was to create a zero order release system and a solid dosage form system for Valsartan using the principles of osmosis. This would reduce its dose frequency to once per day. It was intended to use mannitol as an osmotic agent in the formulation. Direct compression technique was successfully used to create Valsartan osmotic tablets utilizing Mannitol. FTIR analysis showed that the drug and excipient were compatible. The concentration of osmogen employed had an impact on how quickly Valsartan was released from the osmotic tablet. Additionally, it was determined that a higher osmogen concentration in the formulation improved the drug's release. For percentage drug release, formulation F3 performed better than the other formulations created for this trial. After 12 hours, it demonstrated an almost flawless zero order release and a nearly 100% release.

Declarations:

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

All the authors approved the manuscript for publication.

Availability of data and material:

All required data is available.

Competing interests:

All authors declare no competing interests.

Funding:

Not applicable.

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