The Journal of Multidisciplinary Research (TJMDR)

Content Available at www.saap.org.in ISSN: 2583-0317

FORMULATION, DESIGN, AND EVALUATION OF VALSARTAN SODIUM-SUSTAINED-RELEASE MATRIX TABLETS

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Received: 19 Apr 2023 Revised: 25 May 2023 Accepted: 10 June 2024

Abstract

Developing and evaluating sustain release matrix tablets of valsartan, a type 1 antagonist for the angiotensin II receptor, was the principal objective of this study. For a long period, the active components of pharmaceuticals in sustained-release forms are released topically or intravenously at regular intervals. A combination of various release retardant polymers, chitosan, and sodium alginate concentrations were used in the direct compression technique to create the matrix tablet. Before compression, the powder mixtures were evaluated for bulk density, angle of repose, and Carr's index. After compression, the compressed tablets were evaluated for weight variation, thickness, hardness, friability, drug content, in-vitro dissolution, and stability, among other post-compression parameters. The outcomes met expectations. According to in-vitro dissolve trials carried out for 24 hours using pH 6.8 phosphate buffers for the last 24 hours and 0.1N HCl for the first 2 hours, formulations F4 and F7 showed an effective dissolving profile for drug release control. Polymers, along with an increased concentration of chitosan and sodium alginate, were among the substances used to create a twenty-four-hour sustained-release formulation. The drug's compatibility with the polymers and other excipients was determined using Fourier Transform Infrared Spectroscopy. Polymers were among the excipients with which the medication was found to be compatible. Mathematical models such as Zero-order, First-order, the Higuchi equation, and the Korsmeyer-Peppas model were used to fit the release data in order to evaluate the kinetics and drug release. The drug release was first-order, and the mechanism was found to be non-Fickian. The two selected formulations, F4 and F7, were shown to be stable after three months of testing.

Keywords: Antihypertensive, Carbopol 934P, Chitosan, Sodium alginate, Sustain release matrix tablet, Valsartan.

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DOI: https://doi.org/10.37022/tjmdr.v4i2.577

Produced and Published by

South Asian Academic Publications

Introduction

Oral administration is preferred because it offers more dosage form, formulation, and patient adherence flexibility. In this scenario, one must consider the varied pH levels the dosage form will experience throughout transit, the gastrointestinal tract's motility, and the enzyme system's effect on the drug and dosage form. Most sustained release systems for oral drugs use dissolution, diffusion, or both to release the drug slowly into the gastrointestinal tract [1-3]. A sustained release delivery system should distribute the drug through a zero-order method, creating a blood level time profile similar to intravenous constant rate infusion. Plasma drug concentration profiles for conventional tablet or capsule, sustained release, and zero order sustained release formulations [4-8].

Any treatment that slowly releases the medication is sustained release. The system can provide excellent treatment control in duration, location, or both. Sustained release systems mimic zero-order release by slowly releasing the drug in a first-order pattern. Repeat action pills are sustained-release medications with multiple dosages. Regular doses are given [9].

Matrix tablets use dissolving and diffusion to continuously release medicine. Drugs with different solubility are dispersed within hydrophilic components that may expand or an insoluble matrix comprised of stiff hydrophobic or plastic materials to govern their release. Compressing a combination of drug release, retardant material, and additives into a tablet with the medicine imbedded in the release retardant is a simple and precise way to make sustained release dosage forms. Pulverizing

the drug and releasing retardant before compression is another option [10].

The goal of this work was to create Valsartan sustain-release matrix tablets by mixing release retardant polymers with chitosan and sodium alginate cross-linking agents of various concentrations.

Valsartan stimulates aldosterone production and narrows blood capillaries to decrease blood pressure [11-14]. It treats congestive heart failure and lowers death rates in left ventricular dysfunction following a myocardial infarction. Due to its short half-life of 5-6.5 hours and frequent dosage, Valsartan was considered for sustained-release matrix tablets. Tabs are safe, cost-effective, and convenient, improving patient adherence15-18. This medication's shorter half-life makes it excellent for sustain-release tablets [19–20].

Materials and Methods

The pure Valsartan was obtained as a gift sample from Yarrow Chem Products, Mumbai.Carbapol 934P**,** Chitosan**,** Sodium alginate and polyvinylpyrrolidone K30 were obtained from S.D fine chem. limited, Mumbai.

Preparation of sustain release matrix tablets by direct compression method

The straight compression method was used to make the valsartan matrix pills. The right amounts of drug and excipients were weighed out and mixed together correctly. The matrix pills were then made by directly compressing them with a punched machine 21–23. Valsartan 80 mg is in each pill. All seven Formulations designs (F1–F7) are shown in Table 1.

Table 1: Formulation development of Valsartan by direct compression technique

Composition	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Valsartan	80	80	80	80	80	80	80
Carbopol	100	100	100	100	100	100	100
Chitosan	-	5	10	15	-	-	-
Sodium alginate	-	-	-	-	5	10	15
PVP-K30	5	5	5	5	5	5	5
Magnesium Stearate	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2
Microcrystalline Cellulose	QS	QS	QS	QS	QS	QS	QS
Total Weight (mg)	**250**	**250**	**250**	**250**	**250**	**250**	**250**

*QS-Quantity Sufficient; *Composition in milligrams*

Determination of λmax

To make the initial stock solution, 100 mg of valsartan was precisely weighed and diluted in 100 ml of 0.1 N NaOH. To make II stock solution, 10 ml of the aforesaid solution were obtained and diluted to 100 ml using the same solvent. The stock solution II aliquot quantity was further diluted with 0.1 N NaOH to provide the following drug concentrations per ml of the final solution: 5µg, 10µg, 15µg, 20µg, 25µg, and 30µg. The absorbance was then measured at 249 nm in a UV spectrophotometer using 0.1 N NaOH as a blank. The absorbance vs. concentration curve was drawn on lines 24–25.

Compatibility study using FT-IR

The careful selection of excipients that are included to aid administration and support the constant release and bioavailability of the medication while preventing degradation is essential for the successful formulation of a stable and effective solid dosage form. Using a Thermo Nicolet FTIR, infrared spectroscopy was performed, and the spectrum was obtained between 4000 and 400 cm-1. Through the observation of any change in the drug's peaks in the spectrum of the physical combination of drug, the interaction between the drug and the excipients was seen via IR-spectral investigations. 100mg of potassium bromide (dried at 40–50oC) was combined with 3 mg of the medication, which had been weighed. To create a clear pellet, the mixture was collected and crushed in a hydraulic press at a pressure of 10 tons. The IR spectrophotometer scanned the particle. The process is the same for all pertinent excipients used [26].

Pre-formulation parameters

Melting point

The capillary technique was used in triplicate to determine the drug's melting point [27].

Determination of angle of repose

Powder (mix blend) in measured amounts was poured onto the graph paper via the funnel at a predetermined height. The heap's height was measured. Pencil was used to outline the heap's circumference. The angle of repose was then computed using the parameter "r," which was determined from the area of the circle 28–30 and the area of the created circle was computed using the big and small squares that are present within the circle.

$Tan\ \theta = h/r$Equation 1

Where,θ=theangleofrepose,h=heightoftheheapofthepowder andr=radiusofthe heap of the powder.

Determination of Bulk Density and Tapped Density

A 100 ml measuring cylinder containing 20g of the blended mixture (W) was filled, and the starting volume was noted. At intervals of two seconds, the cylinder was permitted to drop from a height of 2.5 cm onto a hard surface under its own weight. The tapping was kept up till the loudness didn't change any more31–32. The following formulas were used to compute the bulk density and the tapped density.

$Bulk\ Density = W/Vo$Equation 2

$Tapped\ Density = W/Vf$Equation 3

W= Weightof thepowdermixture,

Vo= Initial volume ofthepowder mixture

Vf= Final volume of the powder mixture.

Carr's compressibility Index (CI)

One significant metric that may be derived from the bulk and tapped densities is the compressibility index. Theoretically, a material has greater flow ability the less

compressible it is. A material with excellent flow property33–35 has values less than 20%.

$$CI = \frac{TD-BD}{TD} \times 100 \quad \text{Equation 4}$$

Hauser's Ratio

It is determined by the ratio of the tapped density to the bulk density and shows the granules' flow characteristics 36

$$Hausner's\ Ratio = Tapped\ density/Bulk\ density \quad \text{Equation 5}$$

Post-Compression Evaluation Parameters

The drug content uniformity, weight fluctuation, tablet hardness, friability, thickness, and in-vitro drug release using diverse media were among the assessment criteria that were applied to the tablets.

Weight variation

Every time a tablet was being manufactured, its weight was measured to make sure the right quantity of medication was inside. To perform the USP weight variation test, each of the twenty tablets is weighed separately. The average weight is then determined and the individual weights are compared to the average. The tablets satisfied the USP requirement that no tablet vary by more than twice the percentage restriction and that no more than two tablets be outside the percentage limits [37–38]. Table 1 displays the official percentage departure of tablets from USP limits.

Table1: Weight Variation Limit

Average weight of tablet (mg)	% Difference Accepted
<130	±10
130-324	±7.5
>324	±5

Tablet hardness

The hardness of a tablet determines how resistant it is to breaking or shipment during handling, storage, and transit prior to use. The Monsanto hardness tester was used to measure the hardness of each batch of tablets. The kg/cm2 unit of measurement for hardness was used. Five pills were selected at random and their hardness evaluated. A total of five determinations average hardness was [39].

Friability

In general, friability refers to the weight of the tablets in the containers decreasing as a result of the particles being removed from the tablet surface. Poor tablet ingredient cohesiveness is often reflected in friability. Twenty tablets were weighed, and their initial weight was noted. The pills were then put in a Roche friabilator and spun for 100 revolutions at a speed of 25 rpm. The tablets were then taken out of the friabilator, the particles were brushed off, and the weight was once again recorded.40The following formula was used to determine the percentage friability:

$$\%\ Friability = \frac{Initial\ weight\ of\ tablet - Final\ Weight\ of\ the\ tablet}{Initial\ weight\ of\ the\ tablet} \times 100 \quad \text{Equation 6}$$

Tablet thickness

Tablet thickness plays a key role in maintaining tablet size consistency. Vernier callipers were used to measure thickness. Ten tablets from each formulation batch 40 were checked for thickness in order to make this determination [40].

Drugcontent uniformity

From each batch, ten tablets were weighed, and the average weight was determined. All of the pills were broken up, and 80 mg of medication powder was dissolved in pH 6.8 phosphate buffer to create a volume of 100 ml. A 10 ml volumetric flask containing 1 ml of the stock solution was filled with pH 6.8 phosphate buffers. After filtering the solution, absorbance was measured spectrophotometric at 249 nm using phosphate buffer with a pH of 6.8 as a blank. The amount of medication in a single pill was determined [41].

In-vitro dissolution studies

Dissolution tests were done in-vitro utilizing the USP-II (Paddle) dissolution equipment at 50 rpm. The dissolution medium consisted of 0.1N HCl for 2 hours and phosphate buffer pH 6.8 for the remaining hours, at a temperature of 37±0.50 at regular intervals, 5 ml was removed and replaced with new medium. The removed samples were diluted with pH 6.8, filtered, and UV spectrophotometer-analysed at 249 nm using pH 6.8 as a blank42. Calculated cumulative drug release percentage.

Mathematical modelling of drug release profile

By examining the release data using zero order, first order kinetics, and the Higuchi equation, the drug release from the Valsartan sustain release matrix tablets was investigated. Korsmeyer Peppas model was used to fit the data in order to understand the release process [40–42].

Zero order kinetics: If the cumulative percentage of drug release is plotted against time and the plot is linear, the data follows zero-order release kinetics and has a slope of K0. The following equation would predict a zero order release:

$$At = A0 - K0t \quad \text{Equation 7}$$

At= Drug release at time t

A0=Initial drug concentration.

K0=Zero-order rate constant (hr-1)

First order Kinetics

A straight line is produced when the data is shown as log cumulative percent of medication remaining vs time, suggesting that first order kinetics govern the release. You may get the constant "K" by multiplying the slope values by 2.303. The following equation might be used to forecast first order release.

$$LogC = logC0 - Kt/2.303 \quad \text{Equation 8}$$

C=Amountofdrugremainedat time t

C0 = Initial concentration of drug.

K=First-orderrate constant (hr-1).

Higuchi'smodel

A straight line results from plotting the data as cumulative drug release vs. square root of time, suggesting that the medication was released by a diffusion process. The slope (Higuchi's 1963) equals K. Higuchi's classical diffusion equation has been used to explain drug release from the formulation by diffusion.

Q= [Dε/ ε(2A-εCS)CSt]1/2 Equation 9

Q=Amount of drugreleased at time t

D=Diffusion co-efficient of the drug in the matrix. A =Total amount of drug in unit volume of matrix. CS= Solubility of the drug in the matrix.

ε=Porosity of the matrix.

t = Tortuosity.

Korsmeyer-Peppa's model

When the data is plotted as log of drug released versus time, yields a straight line with a slopequal to "n and the K"can be obtained from y-intercept. To study the mechanism of drug release, the release data were also fitted to the well-known exponential equation (Korsmeyer-Peppa's law equation), which is often used to describe the drug release behaviour from polymeric systems.

Mt/ Ma= Ktn Equation 10

Mt/Ma= fractionof drug released at time t

K=Constantincorporatingthestructuralandgeometricalcharacteristicsofthe drug/polymer.

n=Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying logon both sides,

Log Mt/ Ma= Log K+ n log t Equation 11

Table 2: Mechanism of Drug Release

S. No	n	Drug release mechanism	Rate as a function of time
1.	0.45	Fickian release	$t^{-0.5}$
2.	0.45<n =0.89	Non-Fickian transport	t^{n-1}
3.	0.89	Class II transport	Zero order release
4.	Higherthan0.89	Supercase II transport	t^{n-1}

Stability studies

In accordance with ICH requirements, a three-month stability study was conducted on the chosen formulations. The chosen formulas were put into glass bottles with a large opening, sealed securely with aluminium foil, and sealed. Stability tests for the chosen formulations were conducted in the current research for a specified duration of three months at 25ºC/60% and 40ºC/75% RH42–43.

Results and Discussion

Determination of λ max of Valsartan: The λ max of the Valsartan was found to be249nm in 0.1 N NaOH.

Calibration curve

In a UV spectrophotometer, the absorbance of valsartan was measured at 249 nm using 0.1 N NaOH as a blank. Plotting absorbance vs. concentration produced the graph (figure 1).

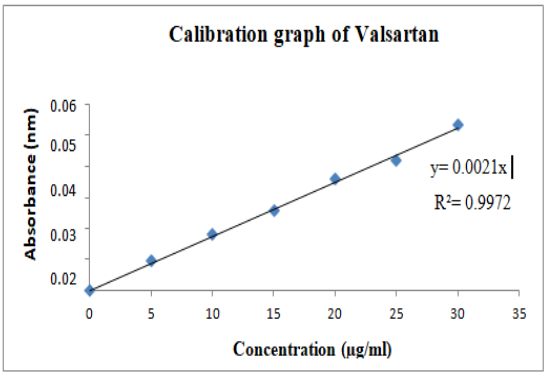

Figure 1: Calibration Curve of Valsartan in 0.1N NaOH

Compatibility studies using FT-IR

The drug and polymer combination spectra showed all of the distinctive peaks of valsartan, showing compatibility between the two substances. Based on the findings, it was determined that the functional group was not interfering, as the main peaks of valsartan were shown to remain unchanged in the drug-polymer physical combinations, suggesting their chemical compatibility. The drug's chemical integrity has not changed much, according to the spectrum. Values for interpretation as well as every spectrum shown in figures 2–5 and Table 3.

Table 3: Interpretations of FTIR-spectrum

Composition	Functional groups with wave number (cm^{-1})				
	N-H(s)	N-O(b)	C-H(b)	C-O(s)	O-H(b)
Valsartan	1652.13	1559.62	1428.42	1282.82	845.82
Valsartan-Chitosan	-	1551.92	1389.82	1274.16	896.12
Valsartan-Sodium alginate	1644.21	1551.62	1397.42	1274.16	857.32
Valsartan-Carbopol	-	1551.12	1397.21	1274.16	857.12
Valsartan-Physicalmixture	1706	1551.12	1388.72	1274.16	865.12

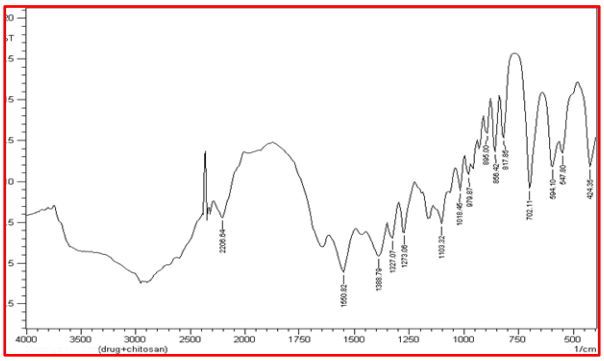

Figure 2: FTIR Spectrum of Valsartan

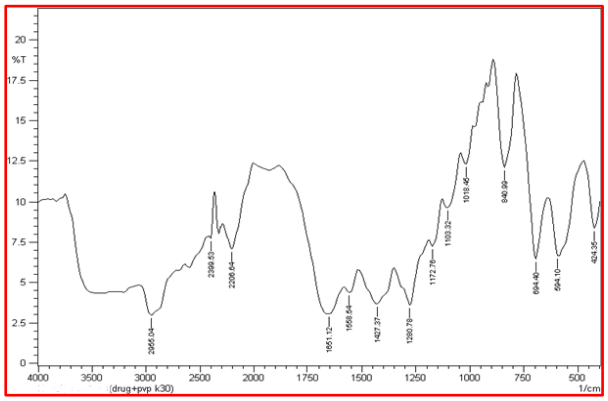

Figure 3: FTIR Spectrum of Valsartan-Carbopol

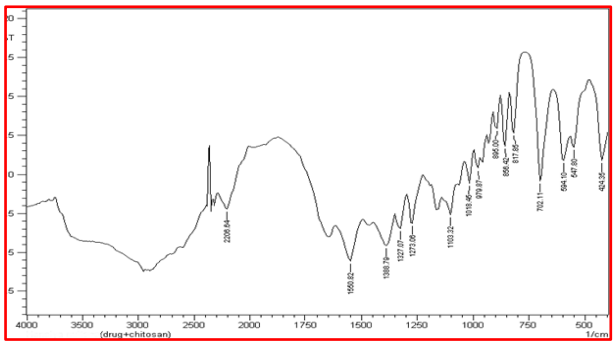

Figure 4: IR Spectrum of Valsartan-Chitosan

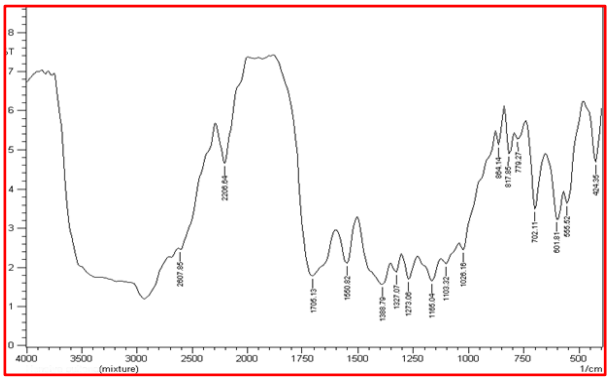

Figure5: IR Spectrum of Drug-Physical mixture

Evaluation of powder blended characteristics

Foreachtypeofformulation,blendsofValsartanandotherexcipientswerepreparedand evaluated for various parameters such as bulk density, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose. Bulk density was found in the range of 0.355- 0.3850g/cm^3 and the tapped density between 0.4101-0.4880g/cm^3 indicating both parameters were found to

be within the limits. Using the above two density data, Carr's compressibility index were calculated. The compressibility index and Hausner's ratio was found in the range of 7.27-18.42% and 1.053-1.24 respectively indicating that all powder blends showed excellent to acceptable flow properties. The flow property of all powder blends was better explained from angle of repose. The angle of repose was found in the range of 25.33-31.43°. The results of angle of repose showed all powder blends exhibited good to acceptable flow property. The results of pre-compression parameters are shown in table 4.

Table 4: Evaluation parameters of pre-formulation characteristics of powder blend

Formulations Number	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.3716±0.0011	0.4101±0.0025	7.27±0.659	1.177±0.0076	29.7 ± 30.41
F2	0.3803±0.0005	0.4120±0.0026	7.58±0.514	1.053± 0.0060	25.3 ± 30.63
F3	0.3843±0.0015	0.4120±0.005	7.43±0.760	1.059±0.0088	28.4 ± 40.35
F4	0.376±0.0020	0.4270±0.0037	13.78±0.386	1.073±0.0053	27.4 ± 80.52
F5	0.355±0.0017	0.4600±0.0024	17.31±0.794	1.224±0.011	31.3 ± 40.13
F6	0.3810±0.0045	0.4880±0.0065	18.42±0.120	1.24±0.0020	28.2 ± 60.43
F7	0.3850±0.0081	0.4384±0.133	10.88±0.030	1.123±0.0021	27.27 ± 0.42

Physical evaluation of tablets

After compression various quality control tests were carried out, which demonstrated following organoleptic properties *viz*. colour, odour and shape. All formulations **(F1 to F7)** were found to be white in colour, odourless and concave round flat with break-line on one side.

Table 5: Post-compressionparametersresults

Formulation	Diameter (mm)±SD	Thickness (mm)±SD	Weightvariation (mg)	Hardness (kg/cm²)	Friability (%)	Drugcontent (%)
F1	7.82±0.012	3.9±0.09	250.89±0.12	7.3±0.04	0.61±0.007	98.25±0.044
F2	7.80±0.002	4.0±0.02	253.88±0.60	7.8±0.03	0.52±0.005	100.31±0.037
F3	7.85±0.007	4.2±0.01	251.12±0.52	8.0±0.07	0.58±0.031	98.54±0.07
F4	7.84±0.022	3.9±0.07	249.81±0.13	6.5±0.04	0.72±0.016	99.67±0.087
F5	8.0±0.015	4.0±0.04	250.80±0.32	6.8±0.08	0.665±0.09	99.37±0.058
F6	7.94±0.010	3.8±0.09	248.92±0.44	7.1±0.03	0.714±0.01	98.97±0.073
F7	7.97±0.016	4.1±0.01	252.61±0.60	6.0±0.05	0.447±0.00	101.61±0.08

Discussion about the physical parameters

Thickness of tablets

All the formulations were evaluated for their thickness using "Vernier calipers" as per procedure in methodology section 4 and the results are shown in table 5. The average thickness for all the formulations was found in the range of 3.8-4.2 mm which is within the allowed limit of deviation i.e. 5% of the standard value. Also the crown diameter of all the tablet formulation was in the range of 8.0-7.8 mm.

Hardness

Tablet hardness is one of the critical parameter to evaluate the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before its administration. All the controlled release matrix tablet formulations of Valsartan were evaluated for their hardness as per procedure in methodology section 4 and the results were

dissipated in table 5.Hardnesstestwasperformed by Monsanto hardness tester. All the formulations have an average hardness in between 6.0 to 8.0 kg/cm2. This ensures good handling characteristics of all formulation batches.

Friability

Friability is determined to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. Friability of prepared tablets was determined by using "Roche friabilator". The entire controlled release matrix tablet formulations were evaluated for their percentage friability and the results are shown in table 5. The average percentage friability for all the formulations was found in between 0.447% to 0.72%, which is found within the pharmacopoeial limit (i.e. less than 1%). So the maximum friability was 0.72% observed for F4 and the minimum friability 0.447% observed for F7.

Weight variation test

As the powder material was free-flowing, tablets obtained were uniform in weight due to uniform die fill with acceptable variation as per IP standards. The weight variation for all formulations was found in the range of 249.92 to 253.88 mg and results were dissipated in table 5. All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits (<5%). The weights of all the tablets were found to be uniform with low standard deviation values.

Drug content

The percentage of the drug content for formulation F1 to F7 was found to be between 98.25%w/w and 101.61%w/w. It complies with official specifications. The results were shown in table 5.

***In-vitro* drug release study**

In this study carbopol was chosen as polymer and it was combined with chitosan and sodium alginate to explore their sustain release capability. The *in-vitro* release data for chitosan-carbopol and sodiumalginate-carbopol based Valsartan sustain released matrix tablets are represented in **table 6** and illustrated in **figure 7.** The *in-vitro* release of Valsartan, from prepared matrix tablets formulations was mainly affected by dissolution medium, concentration of chitosan, concentration of sodium alginate and concentration of polymers. *The in-vitro* release of Valsartan form prepared matrix tablets also depends on swelling behavior of the tablets, higher the tablet swells comparative the lesser amount of drug release. The *in-vitro* release study was performed in 0.1 N HCl for initial first 2 hrs, and then the medium was replaced by phosphate buffer pH 6.8) and study was continued for 24 hour. The *in-vitro* release of Valsartan was higher in first 6-7 hours in all formulations. After 1 hour, approximately10.29%- 18.34% of Valsartan from chitosan-carbapol tablets, 16.90%- 21.91% from sodium alginate-carbapol, 25.12% from tablets containing only release retardant polymer has been released. Initially amount of drug release was higher but after 6-7 hrs drug release was retarded. Formulation F_1 do not contains any crosslinking agent, so almost all drugs was released at the end of 12 hrs. Formulation F_2, F_3, F_5,and F_7 containing lower concentration of chitosan and sodium alginate showed almostalldrugreleasewithin16 hrs, 20 hrs, 16 hrs and 18 hrs respectively. Thus these formulations were not considered as good formulation as the maximum amount of drug was released before desire period of timei.e.24 hrs. The ionic interaction between crosslinking agents and negatively charged polymers was greatly reduced at this pH 6.8 and forms a loose network with increase porous surface which allows great part of dissolution media. Formulation F_4 and F_7 containing highest concentration of chitosan and sodium alginate respectively along with carbopol gum respectively prolong the release of Valsartan to 24 hrs which might be due to the fact that the self-assembled poly electrolyte complexes film was formed on the surface of cross linking agent-polymer based system. Swelling study also showed that formulation which contains higher concentration of cross linking agent showed higher swelling capacity and prolonged the drug release to 24 hrs.

Table 6: In-vitro drug release profile of Valsartan sustain release matrix tablets

Time(Hrs)	Cumulative Percentage Drug Release						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
0	0	0	0	0	0	0	0
1	25.12±0.09	18.34±0.43	15.386±0.33	10.29±0.55	21.91±0.54	18.25±0.32	16.90±0.85
2	40.02±0.12	29.24±0.21	26.905±0.45	25.64±0.62	30.92±0.43	29.25±0.22	25.99±0.42
4	58.82±0.14	35.45±0.33	31.465±0.21	30.94±0.53	39.33±0.54	35.20±0.64	33.71±0.79
6	72.41±0.14	48.71±0.2	46.137±0.13	41.54±0.45	51.64±0.51	48.82±0.73	41.55±0.54
8	80.03±0.28	59.99±0.54	52.186±0.43	48.96±0.38	63.93±0.65	61.73±0.85	54.08±0.64
10	91.61±0.34	68.41±0.55	63.97±0.42	59.68±0.42	72.96±0.72	69.40±0.88	61.27±0.53
12	99.07±0.12	77.09±0.22	71.33±0.54	63.38±0.38	81.23±0.42	77.73±0.95	75.14±0.43
14	--	85.86±0.26	76.50±0.65	74.11±0.43	89.37±0.45	86.24±0.76	82.67±0.48
16	--	92.15±0.33	85.96±0.66	83.39±0.14	95.39±0.62	92.28±0.87	88.75±0.48
18	--	99.71±0.42	90.88±0.59	85.21±0.11	99.77±0.11	95.62±0.73	92.23±0.48
20	--	--	98.54±0.43	93.39±0.14	--	99.99±0.61	94.54±0.48
24	--	--	--	99.54±0.11	--	--	98.78±0.48

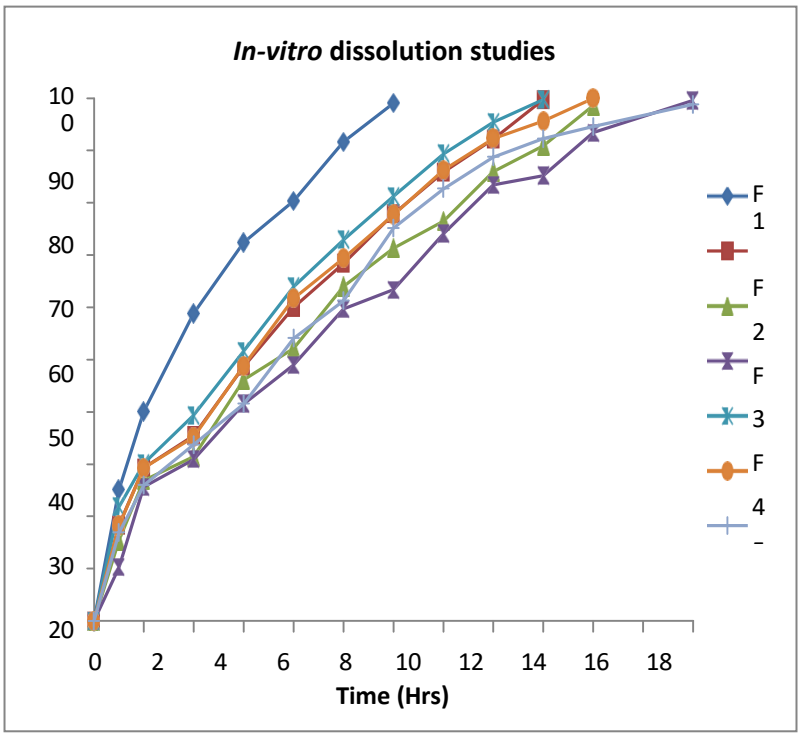

Figure 7: Comparative dissolution profile of the formulations F_1 toF_7

Release kinetic studies

The *in-vitro* drug release data of all formulations were analysed for determining kinetics of drug release. The obtained data were fitted to zero order kinetics, first order kinetics and Higuchi model. The highest correlation coefficient (r^2) obtained from these method gives an idea about model best fitted to the release data. From the results of kinetic studies, the examination of correlation coefficient r indicated that the drug release followed first order release kinetics. It was found that the value of "r" for first order ranged from 0.981-0.992, which is near to 1 when compared to Higuchi square root ranged from 0.892-0.958 and zero order ranged from 0.895-0.969. So, it was understood to be following first order release pattern followed by all formulations. Further, to understand the drug release mechanism, the data were fitted into Korsmeyer Peppas exponential model M_t / M_a = Kt^n. Where M_t / $M_a$is the fraction of drug released after time 't'and 'k' is kinetic constant and 'n'release exponent which characterizes the drug transport mechanism. The release exponent (n) ranges in between0.483-0.7911. For all the formulations F_1 to F_9 the values for 'n' ranged above 0.89 which indicates that all the formulations followed non-fickian release mechanism represented in table 7 and figure 8-11. The relative complexity of the prepared formulations may indicate that the drug release mechanism was possibly controlled by the combination of diffusion and erosion.

Table 7: Release exponent values and release rate constant values for different formulations

Batch	Zero order	First order	Higuchi's plots	Korsmeyer-Peppasplots		Best fit Model	Drug release mechanism
	R^2	R^2	R^2	R^2	N		
F_1	0.9293	0.982	0.9116	0.912	0.597	First order	Non-Fickian
F_2	0.969	0.974	0.8944	0.915	0.594	First order	Non-Fickian
F_3	0.916	0.984	0.9217	0.899	0.6077	First order	Non-Fickian
F_4	0.946	0.978	0.8926	0.892	0.577	First order	Non-Fickian
F_5	0.944	0.992	0.9581	0.902	0.488	First order	Non-Fickian
F_6	0.895	0.958	0.9022	0.929	0.7911	Firstorder	Non-Fickian
F_7	0.896	0.981	0.9258	0.938	0.4838	First order	Non-Fickian

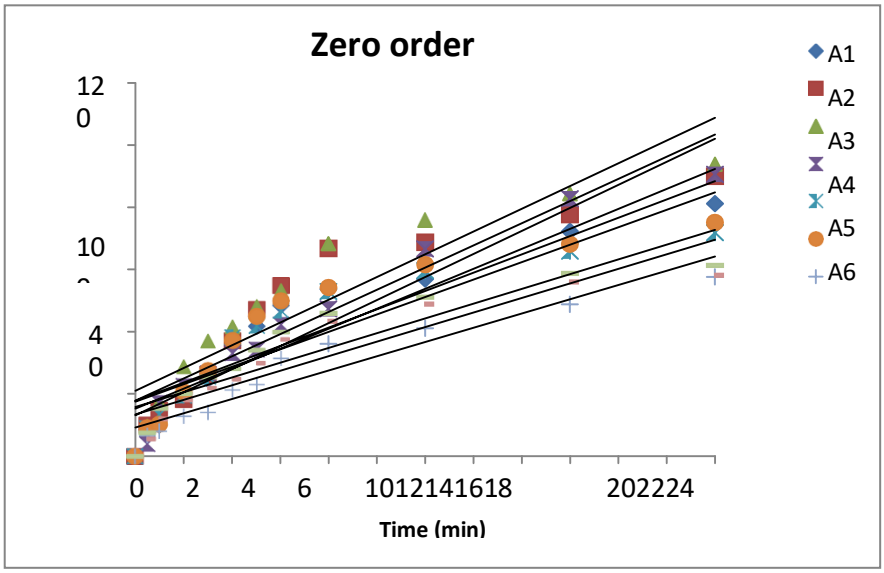

Figure 8: Comparative Zero Order release profile of formulationsF_1toF_7

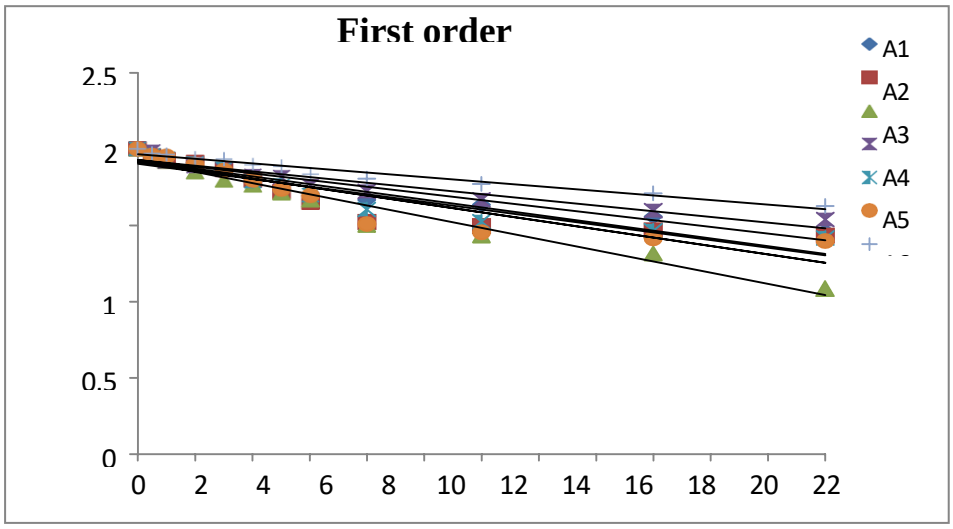

Figure 9: Comparative First Order release profile of formulationsF_1 toF_7

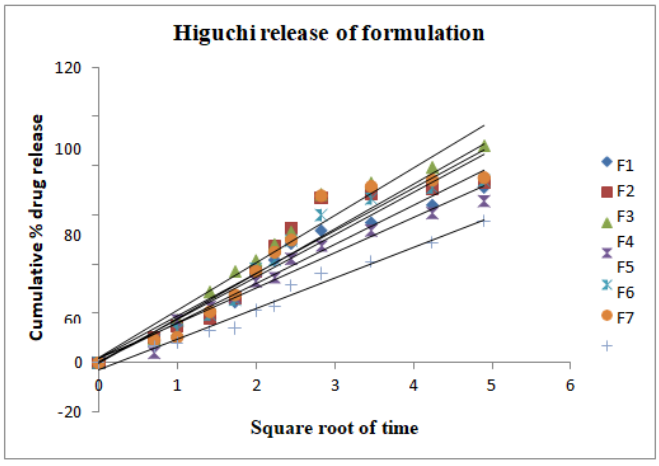

Figure 10: Comparative Higuchi release profile of formulationsF_1 toF_7

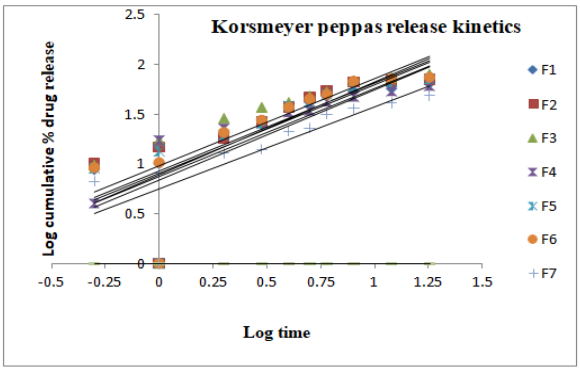

Figure 11: Comparative Korsmeyer peppas release profile of formulations F_1 to F_7

Stability studies

Two best formulations, F4 and F7, were chosen for three-month stability investigations at 25ºC/60% RH and 45ºC/75% RH based on in-vitro drug release data The stability investigations followed section four's procedure. The chosen formulations were assessed for appearance, hardness, friability, drug content, and in-vitro drug release. The investigation found no significant changes in physical appearance, hardness, friability, drug content, or drug release profile. Drug degradation was negligible after three months of stability trials. Thus, compositions were chemically and physically stable. **Table 8-9 and Figure 12-13** show stability study results.

Table 8:ResultsofstabilitystudiesforformulationF_4storedat25ºC/60%RH and 45ºC/75% RH

Storage period	Storedat25ºC/60%RH				Storedat40ºC/75%RH			
	FormulationF4				FormulationF4			
	Hardness Kg/cm²	% friability	%Drug content	%CDR	Hardness Kg/cm²	% friability	%Drug content	%CDR
Initial	8.1±0.07	0.57±0.1	99.76±0.3	99.4±0.4	8.1±0.07	0.62±0.2	99.8±0.3	99.7±0.2
1 month	7.89±0.12	0.61±0.3	98.92±0.1	99.7±0.4	7.8±0.098	0.60±0.1	98.6±0.2	99.1±0.3
2month	7.89±0.46	0.66±0.2	98.17±0.2	98.8±0.4	7.4±0.07	0.65±0.3	97.6±0.3	98.4±0.2
3 month	7.57±0.13	0.63±0.1	98.82±0.3	98.2±0.4	7.5±0.07	0.67±0.1	97.2±0.3	97.6±0.2

Table9: Results of stability studies for formulation F_7 stored at 25ºC/60%RH and 45ºC/75% RH

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F_7				Formulation F_7			
	Hardness Kg/cm²	% friability	%Drug content	%CDR	Hardness Kg/cm²	% friability	Drug content	%CDR
Initial	6.48±0.16	0.55±0.3	100.7±0.4	98.5±0.5	6.7±0.09	0.55±0.3	96.9±0.3	98.8±0.5
1 month	6.44±0.16	0.57±0.4	99.9±0.2	98.6±0.5	6.6±0.11	0.56±0.1	96.6±0.3	98.6±0.5
2 month	6.38±0.19	0.64±0.5	99.9±0.3	98.2±0.5	6.3±0.21	0.58±0.1	96.5±0.3	97.9±0.2
3 month	6.32±0.16	0.64±0.4	98.6±0.6	97.5±0.5	6.2±0.23	0.62±0.3	96.2±0.3	97.6±0.3

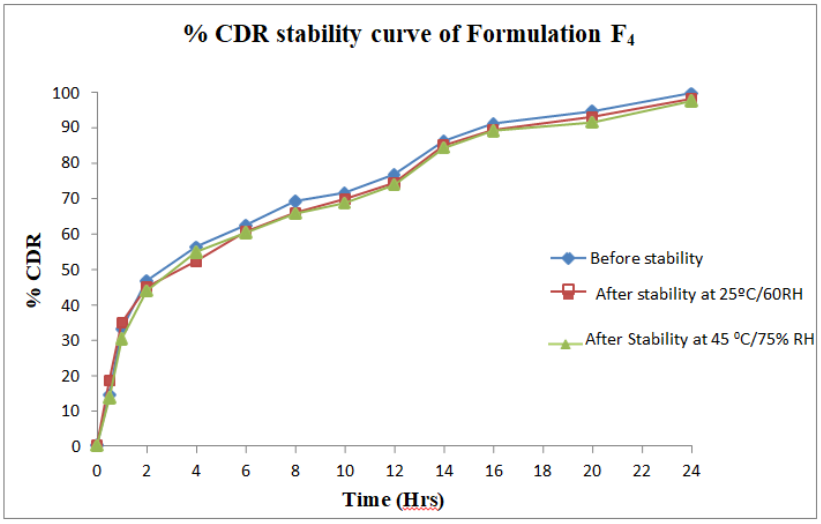

Figure 12:% CDR stability curve of formulationF_4 before and after stability

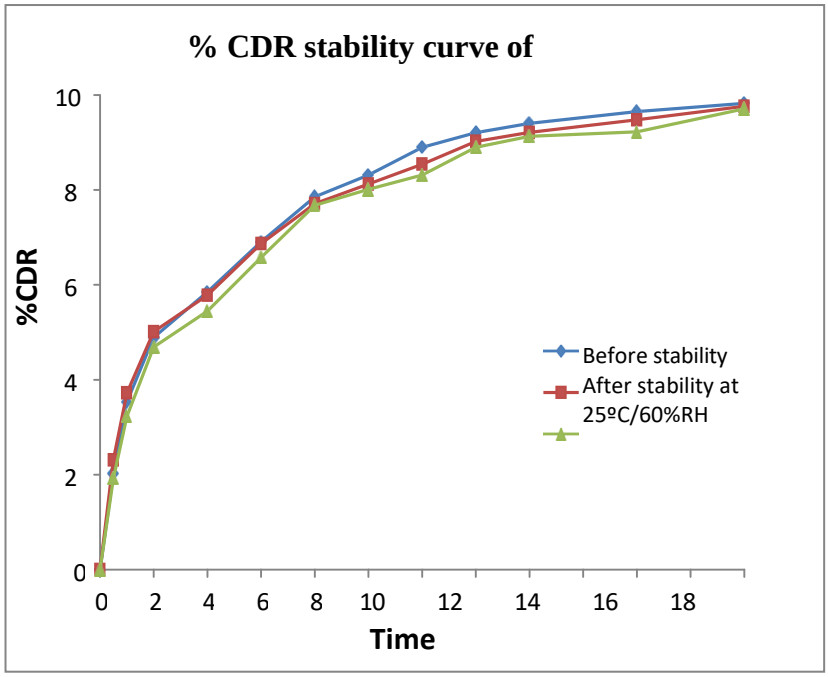

Figure 13:% CDR stability curve of formulation F_7 before and after stability

Conclusion

Angle of repose, bulk density, tapped density Hauser's ratio, and Carr's index of all formulations were within limits. No chemical interaction between medication and excipients was found in FTIR investigations. The powder mixes were crushed into tablets and tested for weight fluctuation, thickness, hardness, friability, and drug content. All formulation batches performed well. USP Type-II dissolving equipment was used to study medication release in simulated stomach and intestinal liquids for 24 hours. Drug release was maintained for 24 hours in formulations with increased chitosan (99.54%) and sodium alginate (98.78%) concentrations. In-vitro drug release follows first order and suggests non-fickian mechanism. Tablet formulations were stable throughout stability trials. Polymer and cross linking agents are crucial to Valsartan sustain release matrix tablet composition. Finally, the matrix tablet with increased cross linking agent concentration released drug less and polymers had comparable diffusion and erosion kinetics.

Funding

No Funding

Acknowledgement

The authors thankful to the management and Department of Pharmaceutics, Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati, Andhra Pradesh.

Conflict of Interest

Authors are declared that no conflict of interest.

Author Contribution

All author are contributed equally

Inform Consent and Ethical Considerations

Not Required

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