



FORMULATION AND EVALUATION OF SUSTAIN RELEASE MATRIX TABLETS OF VALSATRAN

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ABSTRACT

The aim of present is to develop & evaluate extended release matrix tablet of Valsartan. Valsartan is an Hypotensive agents. But owing to its shorter half life it needs frequent administration. In present study, an attempt has been made to develop extended release matrix tablet of Valsartan there by reducing its frequency of administration & other dose related side effects. Different types of Eudragit S 100, Sodium CMC and HPMC K4M were used as polymers. Total 12 formulations were prepared in trial batches. The formulation was evaluated for various pre compression & post compression parameters. All the formulations showed compliance with the pharmacopoeial standards. On the basis of evaluated parameters formulation V8 was considered to be the best one. Formulation V8 containing polymer Sodium CMC showed 98.53 % invitro drug release profile. The release data for formulation V8 was fitted to various mathematical models like zero order, first order, Krosmeayer Peppas & Higuchi model. It was observed that drug follows Peppas release mechanism.

KEYWORDS: Valsartan, Extended release system.

INTRODUCTION

Valsartan is an angiotensin II receptor antagonist that is used for the treatment of hypertension. It treat the hypertension by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II selectively by blocking the binding of angiotensin II and angiotensin I receptor in many tissues. The most preferred route for this drug is oral delivery in form of tablets. Valsartan have poor water solubility, low bioavaibility (approximately 20-25%), and shorter half-life (nearly 6 h) (Abdelbary et al 2004). Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily (Bandelin, 2008). The low bioavailability and short half-life of valsartan make the development of sustained-release forms desirable.

Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system (Armstrong and James, 1996). These systems sustain the release of drug and maintain the plasma drug concentration in therapeutic window except any fluctuation and increase the therapeutic efficacy of drug. They show their action by avoiding peak and trough in dosing and show constant plasma drug concentration in therapeutic window. Sustained release system have benefits like patient compliance and avoidance of multiple dosing, increased plasma drug concentration, avoidance of side effects and overcoming the problems associated with conventional system (Hingmire et al 2008). Among various approaches used for novel drug delivery systems (Dahiya and Gupta, 2011; Tripathi et al 2011; Khan et al 2012; Mishra et al 2013; Verma et al 2014), matrix tablet is one of the most widely used and popular method. The goal of designing sustained or controlled release drug delivery systems of Valsartan matrix tablets is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing dose required, or providing controlled drug delivery

EXPERIMENTAL

Materials Valsartan (Val) was obtained as a gift sample from Torrent pharmaceuticals Private Limited, Ahmedabad. HPMC K15M was purchased from S. Kant. Healthcare Limited, Vapi, Gujarat. Lactose was obtained from Qualigens Fine Chemicals, Mumbai. Magnesium stearate was procured from S. D.Fine Chemicals Limited,



Mumbai and Talc was obtained from Nice Chemicals Pvt. Limited, Cochin. Other chemicals used were of analytical reagent grade.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The solid powder sample directly placed on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 400 cm^{-1} .

Methods Drug excipients interaction (Rowe et al 2006) Compatibility of the drug with excipients was determined by differential scanning calorimeter (Perkin Elmer, USA). This study was carried out to detect any change on chemical constitution of the drug after combination with the excipients. The samples taken for DSC study were physical mixtures of Val : HPMC K15M (1 : 1).

Analytical method development

Determination of Wavelength:

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - $1000\text{ }\mu\text{g/ml}$). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – $100\text{ }\mu\text{g/ml}$). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution

- $10\text{ }\mu\text{g/ml}$). The working solution was taken for determining the wavelength.

Determination of Calibration Curve

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - $1000\text{ }\mu\text{g/ml}$). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – $100\text{ }\mu\text{g/ml}$). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan \theta = h / r$$

Tan θ = Angle of repose h = Height of the cone ,

r = Radius of the cone base

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3 . The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, V_0 , was read.

The bulk density was calculated using the formula: Bulk Density = M / V_0

Where, M = weight of sample



V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100 \text{ Where, } b = \text{Bulk Density}$$

Tap = Tapped D

Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3. The tablets were prepared as per the procedure given below and aim is to prolong the release of Valsartan. Total weight of the tablet was considered as 200mg.

Procedure:

- 1) Valsartan and all other ingredients were individually passed through sieve no \neq 60.
- 2) All the ingredients were mixed thoroughly by triturating up to 15 min.
- 3) The powder mixture was lubricated with talc.
- 4) The tablets were prepared by using direct compression method

Table 1 : Formulation composition for tablets

INGREDIENTS (MG)	FORMULATIONS											
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Valsartan	40	40	40	40	40	40	40	40	40	40	40	40
Eudragit S 100	15	30	45	60	-	-	-	-	-	-	-	-
Sodium CMC	-	-	-	-	15	30	45	60	-	-	-	-
HPMC K4M	-	-	-	-	-	-	-	-	15	30	45	60
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4	4	4	4
Lactose	136	121	106	91	136	121	106	91	136	121	106	91
Total Weight	200	200	200	200	200	200	200	200	200	200	200	200

All the quantities were in mg.

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.



Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W_1 - W_2) / W_1] \times 100 \text{ Where, } W_1 = \text{Initial weight of three tablets}$$

$W_2 = \text{Weight of the three tablets after testing}$

Determination of drug content

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In vitro drug release studies Procedure

900ml of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of $37^\circ\text{C} \pm 0.5^\circ\text{C}$. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl were removed and pH 6.8 phosphate buffer was added process was continued up to 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at required wavelength using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero-order release kinetics the release rate data are fitted to the following equation.

$$F = K_0 t$$

Where, 'F' is the drug release at time 't', and 'K₀' is the zero order release rate constant. The plot of % drug release versus time is linear.



First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log (100-F)} = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k t^{1/2}$$

Where, 'k' is the Higuchi constant.

In Higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas Release Model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = K t^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I transport), n=1; and for supercase II transport, n> 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.

Hixson-Crowell release model

$$(100-Q_t)^{1/3} = 100^{1/3} - K_{HC}t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

RESULTS & DISCUSSION

The present study was aimed at developing sustained release tablets of Valsartan using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Preformulation parameters of powder blend

Table 2 : Pre-formulation parameters of Core blend

Formulation code	Angle of repose (Θ)	Bulk density (gm/cm ³)	Tapped density(gm/cm ³)	Carr's index (%)	Hausner's ratio
V1	26.06	0.721	0.910	20.77	1.22
V2	31.09	0.701	0.905	22.54	1.21
V3	30.07	0.694	0.852	18.54	1.05
V4	27.08	0.664	0.823	19.32	1.07
V5	32.15	0.652	0.807	19.21	0.98
V6	37.39	0.662	0.901	26.53	0.95
V7	31.47	0.667	0.907	26.46	0.99
V8	31.09	0.624	0.801	22.10	1.10
V9	28.12	0.648	0.862	24.82	0.91
V10	26.89	0.681	0.887	23.22	0.98
V11	25.9	0.651	0.817	20.32	1.13
V12	24.70	0.672	0.826	18.64	1.18

All the values represent n=3



Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties. The tapped density of all the formulations powders has good flow properties. The compressibility index of all the formulations was found to be below 26.53 which show that the powder has good flow properties. All the formulations has shown the hausner ratio below 1.22 indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression tablet.

Table 3 : *In vitro* quality control parameters for tablets

Formulation codes	Average Weight (mg)	Hardness(kg/cm ²)	Friability (%loss)	Thickness (mm)	Drug content (%)
V1	198.56	4.1	0.48	4.25	98.65
V2	196.30	4.8	0.39	4.36	95.89
V3	198.32	4.9	0.50	4.12	96.33
V4	198.49	5.3	0.20	4.85	98.24
V5	197.69	4.0	0.42	4.20	96.39
V6	195.86	4.6	0.65	4.59	98.60
V7	200.05	5.4	0.51	4.75	97.41
V8	197.41	5.1	0.30	4.60	98.00
V9	196.74	4.2	0.24	4.39	97.15
V10	198.10	4.9	0.16	4.82	98.90
V11	198.40	5.0	0.52	4.47	97.19
V12	196.59	5.5	0.47	4.59	96.31

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 195.86 to 200.05 mg, so the permissible limit is $\pm 7.5\%$ (>200 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 4.0 to 5.5 kg/cm², which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 4.12 to 4.85 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 95.89 -98.90 %. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

*In Vitro* Drug release studies

Table 4: Dissolution data of Valsartan tablets

TIME (HRS)	% DRUG RELEASE											
	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	15.85	12.67	11.37	08.90	12.86	10.72	11.57	09.67	9.12	14.61	13.72	11.71
1	20.34	17.50	15.23	12.34	15.21	17.97	13.20	17.29	15.26	21.16	19.93	17.24
2	24.61	27.92	24.69	18.46	25.62	21.35	23.76	23.72	28.10	29.47	26.40	30.63
3	29.72	36.11	30.74	23.20	30.16	26.07	31.83	30.48	39.28	34.15	31.96	36.42
4	36.51	40.76	36.15	29.86	34.86	30.26	36.65	36.89	45.19	42.74	39.12	45.90
5	42.30	47.35	43.72	38.10	46.39	37.21	43.43	54.31	58.93	49.81	43.80	48.74
6	47.80	51.89	48.23	43.86	50.12	42.63	50.78	60.14	62.16	58.27	47.10	55.45
7	56.10	56.34	54.17	48.54	53.76	50.47	56.68	66.72	72.10	69.10	50.62	60.27
8	63.71	67.21	60.78	53.65	57.35	55.52	60.10	72.43	87.93	76.43	56.34	67.10
9	70.49	72.24	65.12	59.83	65.18	61.11	68.82	78.92	96.99	82.91	60.15	75.72
10	78.35	76.97	71.59	67.31	70.56	67.23	70.19	81.21		89.19	73.27	83.16
11	83.26	81.70	75.10	72.79	77.80	73.10	86.09	85.78		95.87	83.92	89.47
12	97.42	88.14	80.91	78.19	82.17	89.40	93.14	98.53			90.20	94.18

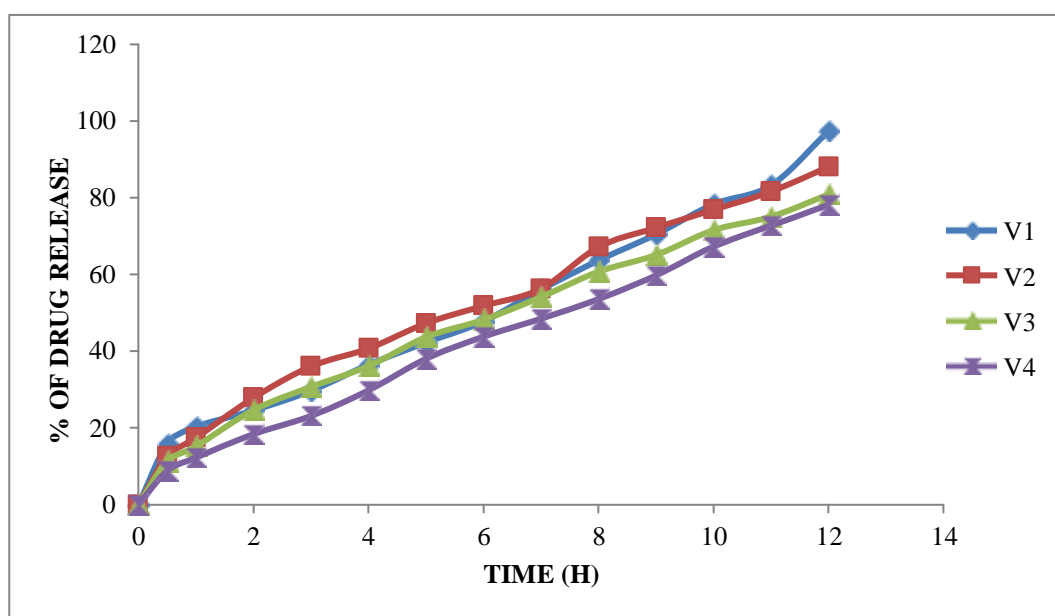


Fig 1 : Dissolution profile of Valsartan(V1, V2, V3, V4 formulations)

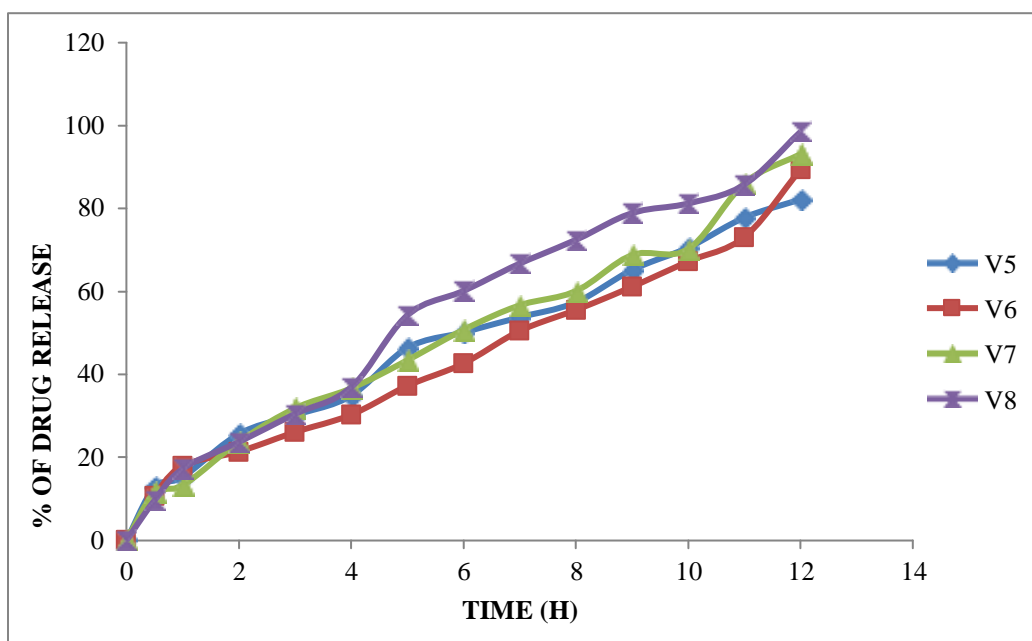


Fig 2 : Dissolution profile of Valsartan (V5, V6, V7, V8 formulations)

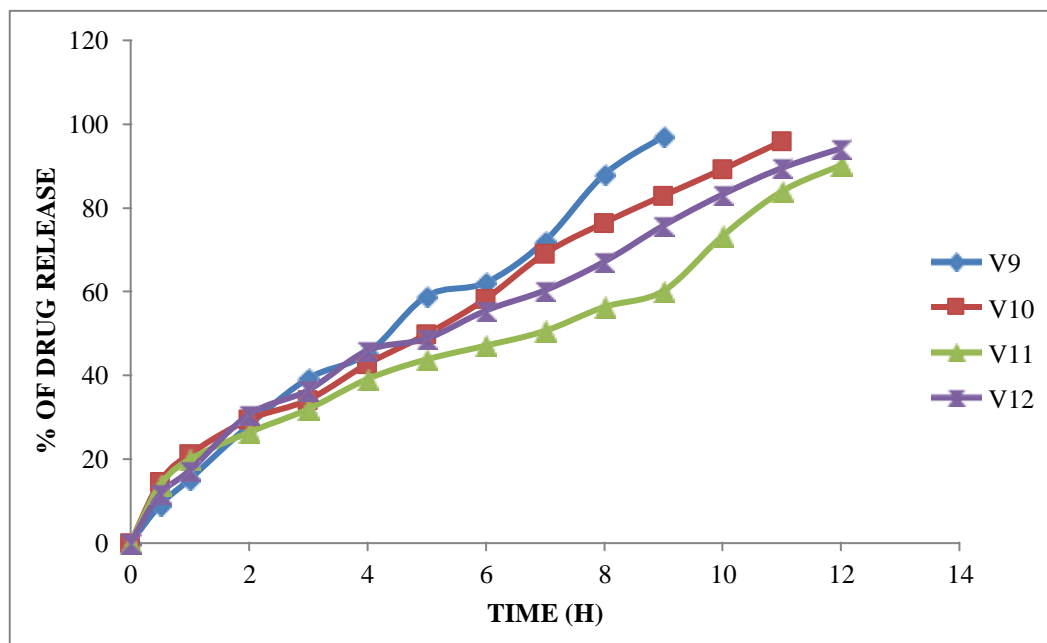


Fig 3 : Dissolution profile of Valsartan (V9, V10, V11, V12 formulations)

From the dissolution data it was evident that the formulations prepared with Eudragit S 100 as polymer were retard the good drug release up to desired time period i.e., 12 hours.

Formulations prepared with Sodium CMC retarded the drug release in the concentration of 60 mg (V8 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.53% in 12 hours with good retardation.

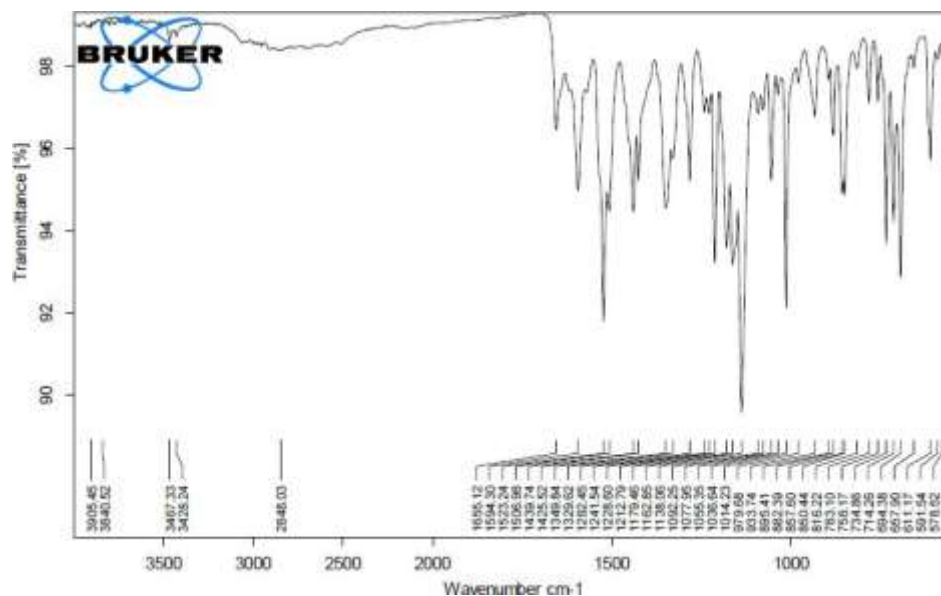
Formulations prepared with HPMC K4M retarded the drug release in the concentration of 60 mg (V12 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of



94.18 % in 12 hours with good retardation. Finally Concluded that V8 formulation was considered as optimized formulation.

Table 5 : Release kinetics

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
9.67	0.5	0.707	0.985	-0.301	1.956	19.340	0.1034	-1.015	90.33	4.642	4.487	0.155
17.29	1	1.000	1.238	0.000	1.918	17.290	0.0578	-0.762	82.71	4.642	4.357	0.285
23.72	2	1.414	1.375	0.301	1.882	11.860	0.0422	-0.625	76.28	4.642	4.241	0.401
30.48	3	1.732	1.484	0.477	1.842	10.160	0.0328	-0.516	69.52	4.642	4.112	0.530
36.89	4	2.000	1.567	0.602	1.800	9.223	0.0271	-0.433	63.11	4.642	3.981	0.660
54.31	5	2.236	1.735	0.699	1.660	10.862	0.0184	-0.265	45.69	4.642	3.575	1.067
60.14	6	2.449	1.779	0.778	1.601	10.023	0.0166	-0.221	39.86	4.642	3.416	1.226
66.72	7	2.646	1.824	0.845	1.522	9.531	0.0150	-0.176	33.28	4.642	3.217	1.425
72.43	8	2.828	1.860	0.903	1.440	9.054	0.0138	-0.140	27.57	4.642	3.021	1.621
78.92	9	3.000	1.897	0.954	1.324	8.769	0.0127	-0.103	21.08	4.642	2.762	1.879
81.21	10	3.162	1.910	1.000	1.274	8.121	0.0123	-0.090	18.79	4.642	2.659	1.983
85.78	11	3.317	1.933	1.041	1.153	7.798	0.0117	-0.067	14.22	4.642	2.423	2.219
98.53	12	3.464	1.994	1.079	0.167	8.211	0.0101	-0.006	1.47	4.642	1.137	3.505

Drug – Excipient compatibility studies

Figure 8.10 : FT-TR Spectrum of Valsartan pure drug.

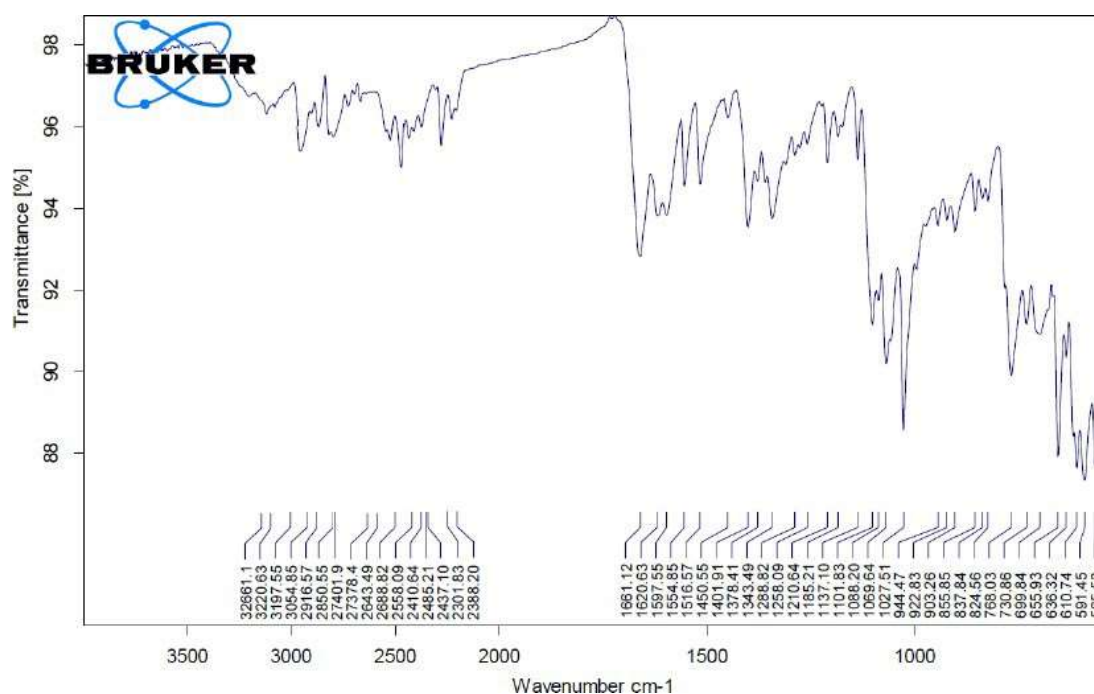


Figure 8.11 : FT-IR Spectrum of Optimised Formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Valsartan and excipients used in the preparation of different Valsartan Sustained release formulations. Therefore the drug and excipients are compatible to form stable formulations under study. The FTIR spectra of Valsartan and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

CONCLUSION

Valsartan extended release matrix tablets were successfully prepared by using various polymers to retard the release and achieve the retard dissolution profile. Drug & polymer were found to be compatible as indicated by FTIR studies. From the observations it was concluded that polymers used in different concentrations differ in their ability to extend the drug release. Further it was concluded that polymer Sodium CMC showed better extended release property than Eudragit S 100 & HPMC K4M used in formulation of extended release matrix tablet. It was found that drug release from the matrix tablets was increased with increase in drug polymer ratio. It may be concluded from the present study that slow & controlled release of Valsartan over a period of 12hrs was obtained from formulation V8 using polymer Sodium CMC. The drug release kinetics revealed Peppas release model. Formulation & evaluation of extended release tablet of Valsartan was found to be satisfactory. On the basis of various evaluated parameters formulation V9 was considered to be the best one.

REFERENCES

1. Hirani JJ, Rathod D, Vadalía K. Orally Disintegrating Tablets: A Review. *Tropical Journal of Pharmaceutical Research*. 2009;8(2):161-72.
2. Dobbetti L. Fast-melting tablets: Developments and technologies. *Pharmaceutical Technology Europe*. 2000;12(9):32-42.
3. Chauhan V, Kumar. K, Teotia. D. Fast dissolving tablets: a promising approach for drug delivery *Universal Journal of Pharmaceutical Research*. 2017;2(4):51-7
4. Rahane R, Rachh P. A review on fast dissolving tablet *Journal of Drug Delivery & Therapeutics*. 2018;8(5):50-5.
5. Mehnaz Ali, Fabiha Faizah Ali, Rita NA, Bhuiyan MA. Comparative in vitro evaluation of some commercial brands of valsartan tablets marketed in Bangladesh. *The Pharma Innovation Journal*. 2018;7(4):1068-72.



6. Saydam M, Takka S. Bioavailability file: valsartan. *Fabad Journal of Pharmaceutical Sciences*. 2007;32(4):185-96.
7. Amidon G, Lennernäs H, Shah V, Crison J. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharmaceutical research*. 1995;12(3):413-20.
8. Wu C-Y, Benet L. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. *Pharmaceutical research*. 2005;22(1):11-23.
9. Addanki Gopikrishna, B. Ramu, G. Srikanth, Dr. Bigala Rajkamal (2016). Formulation of isoniazide sustained release formulation by using carbopol 934 P P. *Int J App Pharm Sci Res*. 1(2):60- 69. Doi: 10.21477/ijapsr.v1i2.10177.
10. B. Ramu, Kaushal K. Chandrul, P. Shanmuga Pandiyan. Using 24 Factorial Designs optimization of Repaglinide Gastroretentive Drug Delivery System. *Research J. Pharm. and Tech*. 2021; 14(2):725-729. doi: 10.5958/0974-360X.2021.00126.8
11. B Ramu, N. Ramakrishna, Meruva Sathish, D. Anoosha (2015). Formulation of tellmisartan Hcl Fast Disintegrating Tablets by Sublimation Technique. *International Journal of Pharm Tech Research*. 8(3), 330-339.
12. Mbah C. Solubilization of valsartan by aqueous glycerol, polyethylene glycol and micellar solutions. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*. 2006;61(4):322-4.
13. Ramu S, Kumar YA, Rao DS, Ramakrishna G. Formulation and Evaluation of Valsartan Oral Dispersible Tablets by Direct Compression Method. *American Journal of Advanced Drug Delivery*. 2014;2(6):719-33.
14. Corveleyn S, Remon J. Formulation and production of rapidly disintegrating tablets by lyophilisation using hydrochlorothiazide as a model drug. *International Journal of Pharmaceutics*. 1997;152(2):215-25.