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FORMULATION AND EVALUATION OF SUSTAINED RELEASE VALSARTAN MATRIX TABLET BY USING NATURAL GUMS.

Prasad S. Bhamare*, Mitesh P. Sonawane, Rajendra K. Surawase.
Department of Pharmaceutics, Loknete Dr. J. D. Pawar College of Pharmacy, Manur, Tal- Kalwan, Dist- Nashik (423501), Maharashtra, India.

Abstract:
Valsartan is Angiotensin-II receptor antagonist used in anti-hypertensive drug. The present study is deals with formulation, optimization, evaluation of Sustained release Valsartan matrix tablet. The SR tablets were Prepared by direct compression method and formulated using different natural gums.ratios, formulation such as F1-F9. Gums like Xanthan gum and guar gum were used. Compatibility of drug with various excipients was studies. The compressed tablet were evaluated and showed compliance with Pharmacopoeial limits. The concentration of Xanthan gum and Guar gum were different in all formulations (F1-F9). All the formulations were evaluated for pre-compression parameters and weight variation, Hardness,friability, drug content, in-vitro dissolution studies. The formulation 'F9' was found to be optimized formulation. It shows results for all evaluation parameters such as weight variation 320.14±0.42%, Friability 0.30%, Swelling index 85%, drug content 98.91±0.32%, and in-vitro dissolution study 99.91±2.1% at the end of 15 hrs.

keywords: *Valsartan, Guar Gum, Xanthan Gum, Sustained Release Matrix Tablets, etc.*

Corresponding author:
Prasad Shivaji Bhamare,
Department of Pharmaceutics,
Loknete Dr. J. D. Pawar College of Pharmacy,
Manur, Tal- Kalwan, Dist- Nashik (423501),
Maharashtra, India.
Email id.: prasadbhamare71@gmail.com,
MO. No. 9763557657/8421779701

QR code

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INTRODUCTION:

The oral route is most popular route for the administration of various drugs. The ease of administration leads to high levels of patient compliance. 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)[4].

The present investigation is aimed to formulate the matrix tablet of Valsartan with guar gum,and xanthan gum[5]. The sustained release systems for oral use are mostly solid and based on dissolution, diffusion or a combination of both mechanisms in the control of release of drugs[12]. Sustained release system have benefits like patient compliance, avoid multiple dosing, increase the plasma drug concentration, avoid side effects and overcome the problems associated with conventional system [7].

Criteria To Be Met By Drug Proposed To Be Formulated In Sustained Release Dosage Forms[7,13]

Some physicochemical parameters for selecting of drug to be formulated in a sustained release dosage form which mainly include the knowledge on the absorption mechanism of the drug from the gastro intestinal (GI.) tract.

Physicochemical parameters for drug selection

- Molecular size- < 1000 Daltons
- Aqueous solubility- More than 0.1 mg/ml for pH 1 to pH 7.8
- Apparent partition coefficient- High
- Absorption mechanism- Diffusion
- General absorptivity from all GI segment- Release should not be influenced by pH and enzymes

Pharmacokinetics parameters for drug selection

- Elimination half life- Between 2 to 4 hrs
- Absolute bioavailability- Should 75 % or more
- Absorption rate constant (Ka)- Must be higher than release rate
- Apparent volume of distribution- Larger Vd and MEC
- A total clearance- Not depend on dose
- Elimination rate constant- Required for design
- Therapeutic concentration- The lower Css and smaller Vd
- Toxic concentration- Apart the value of MTC and MEC safer the dosage form

MATERIALS AND METHODS:

Material:

Valsartan was received as a gift sample from IPCA Laboratories Pvt. Ltd. Mumbai , Guar gum, xanthan gum was obtained from Research-Lab Fine Chem. Industries, Mumbai, all other chemicals used were obtained from commercial sources and were of analytical grade.

Method:

Weigh the all ingredient in required quantity. Transfer all ingredients into a mortar triturate for 10 minutes until, to get fine powder and sieve the material. (#60) .Then transfer the material into blender for proper distribution of drug in blend for 10 minutes.Then addition of lubricant and mix well. Perform the micromeritic properties (Pre-compression studies). Compression: After the lubrication granules were compressed using 8 station rotary tabletting machine, equipped with flat-faced, round punches of 10-mm diameter [2,5,11,13].

Evaluation Parameters Of Sustained Release Valsartan Matrix Tablet :

Preparation of calibration curve of Valasartan :

The calibration curve of Valsartan was performed in methanol. The calibration curve was found to be linear in the concentration range of 2-10 µg/ml having a coefficient of regression value $R^2 = 0.999$ and line equation, $y = 0.056x + 0.005$.

I) Pre-compression parameters:

Angle of repose (θ):

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by the angle of repose.

Bulk density:

Bulk density is defined as the mass of a powder, divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

Tapped density:

The measuring cylinder containing a known mass of the blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured.

Hausner's ratio:

Hausner ratio is an indirect index of ease of power flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = \frac{\rho_t}{\rho_d}$$

Carr's compressibility index:

The compressibility index of the granules was determined by the Carr's compressibility index. (%) Carr's Index can be calculated by using the following formula

$$\textbf{Carr's Index (\%)} = \frac{TBD - LBD}{TBD} \textbf{ x 100}$$

II) Post-compression parameters:

Hardness test:

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling during manufacture, packaging and shipping. The hardness of the tablets was determined using Digital Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition.

The friability of tablets was determined by using Electro lab, USP EF 2 friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 RPM for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

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

% Friability of tablets less than 1% is considered acceptable

Weight variation test:

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Uniformity of thickness:

The crown thickness of individual tablet may be measured with a digital vernier calliper, which permits accurate measurements and provides information on the variation between tablets.

Drug content:

For the determination of drug content in each tablets twenty tablets were taken and crushed to fine powder with pastel and mortal. The 1.15 gram of powder were taken and diluted with methanol up to 100 ml in the volumetric flask. The solution were subjected to sonification for fifteen minutes. Then these sonicated solutions were filtered through 0.20 micron filter paper. Then the solution were assayed for drug content at 249 nm using high performance liquid chromatography finally calculated drug content of Valsartan .

Determination of swelling index:

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulation was determined by various techniques. The water uptake study of the tablet was done using USP dissolution apparatus II. The medium used was distilled water, 900 ml rotated at 50 rpm. The medium was maintained at 37±0.5 ◦C throughout the study. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed. Swelling characteristics of the tablets were expressed in terms of water uptake by using following formula

$$\text{Swelling index} = \frac{Wt - Wo}{Wo} \times 100$$

Where, Wo= weight of tablet before immersion.
Wt= weight of tablet at time t.

***In vitro* dissolution studies:**

The drug release studies were performed by USP Type II dissolution test apparatus pH 6.8 phosphate buffer solution was used as dissolution medium. The temperature and speed of the apparatus were maintained at 37±0.5ºC and 50 rpm respectively. The samples were withdrawn at predetermined time interval and analyzed for drug concentration at 249 nm by UV-visible spectrophotometer (LABINDIA 3000+) after filtration.

Stability Studies:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The ability of a pharmaceutical product to retain its chemical, physical, microbiological and biopharmaceutical properties within specified limits throughout its shelf life and recommended storage conditions.

RESULT AND DISCUSSION:

In the present study an attempt was made to design the sustained release matrix tablet formulation of Valsartan. Valsartan is a anti-

hypertensive drug it has plasma half life about 4-6 hrs. with systemic bioavailability of about 26 ± 2%. So this was chosen as the model drug candidate.

Formulation and manufacture of SR matrix tablets is a least complicated approach widely in industry for obtaining oral controlled release. Matrix tablet formulation needs an efficient release retarding material which plays a critical role in regulating drug release from matrix tablets. The objective of the study is to design Valsartan SR tablets employing a combination of xanthan gum and guar gum for better sustained release . Valsartan SR tablet formulation was optimized by 3^2 – factorial design. Optimization of pharmaceutical formulations involves choosing and combining ingredients that will result in a formulation whose attributes confirm with certain prerequisite requirements. The choice of the nature and qualities of additives (excipients) to be used in a new formulation shall be on a rational basis. The application of formulation optimization techniques is preparing a series of formulations, varying the concentration of the formulation ingredients in some systematic manner. These formulation are then evaluated according to one or more attributes, such as hardness, dissolution, appearance, swelling index and stability. Based on the results of these tests, a particular formulation (or series of formulation) may be predicated to be optimal.

For optimizing Valsartan SR tablet formulation employing guar gum and xanthan gum , a 3^2 – factorial design was used. In the 3^2 – factorial design the two levels of xanthan gum upto 08% and guar gum upto 10%.valsartan SR tablets were formulated employing the selected combination of xanthan gum and guar gum as per 3^2 – factorial study. The SR tablets were prepared by direct compression method as per the formulate and were evaluated for in-vitro drug release kinetics, swelling index.

The results for evaluation of prepared SR. matrix tablets viz. hardness, weight variation, friability, drug content uniformity were found range of 5.5± 0.03 to 5.6± 0.08, 320.10± 0.62 to 320.14± 0.42, 61.33± 0.17 to 99.91± 0.42 respectively for all formulation and showed all values within the limit. The friability of the tablets was found to be less than 1% which was considered within the limit. The drug content of the all formulation was found to be within the limits.

In above all formulation in which the F9 formulation having good drug release study up to 15 hrs. (99.91%). As per USP limit not less than 75% drug release up to 15 hrs. So the F9 formulation follows the USP limit. The result of kinetic models viz. zero order, higuchi, first order, Peppas model of all formulation (F1-F9). The optimize batch F9 showed r^2 value 0.9991 , 0.9991 , 0.1978 , 0.205 .respectively. (Table 9.5). the formulation prepared were found to release the drug by diffusion mechanism. The F9 formulation follows the zero order drug release which shows the highest r^2 value 0.9991. [table no.9]

All the for formulation shows a good stability, all tablet formulation are kept in environment test chamber for 45 days at 40 °c and room temperature. The F9 formulation is stable according to ICH guidelines and therefore it shows that the F9 formulation is an optimized formulation than all other formulation.

CONCLUSION:

All the prepared tablets was evaluated for different parameters and the formulations were shows satisfactory results. The formulation 'F9' shows comparatively good results for all evaluation parameters. Hence we conclude that the formulation 'F9' is optimized formulation.

ACKNOWLEDGEMENT:

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FIGURES:

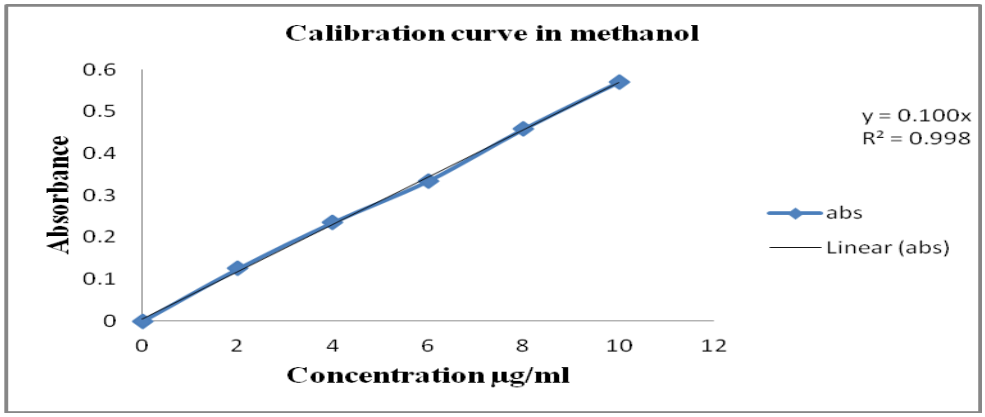


Fig 1: Standard calibration curve of Valsartan.

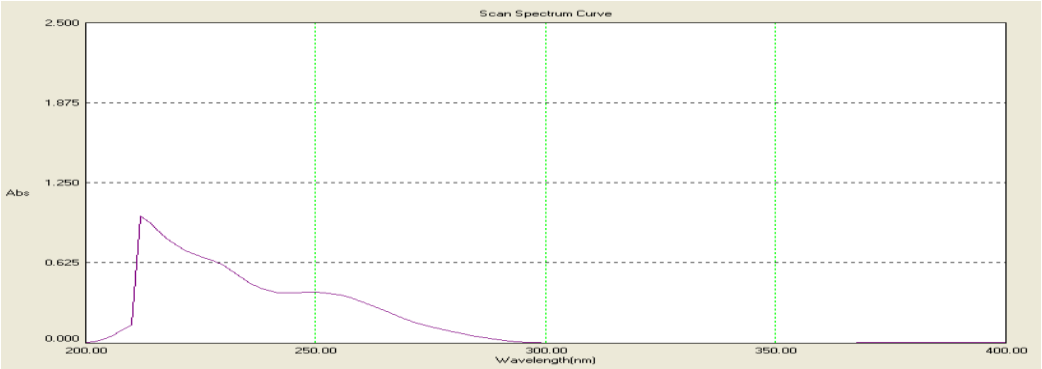


Fig 2: UV spectrum of Valsartan.

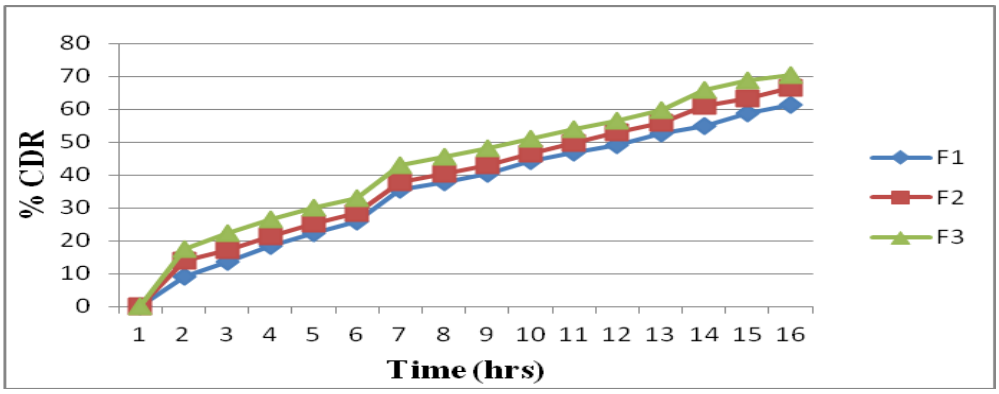


Fig 3: % Drug release of Valsartan formulation F1-F3

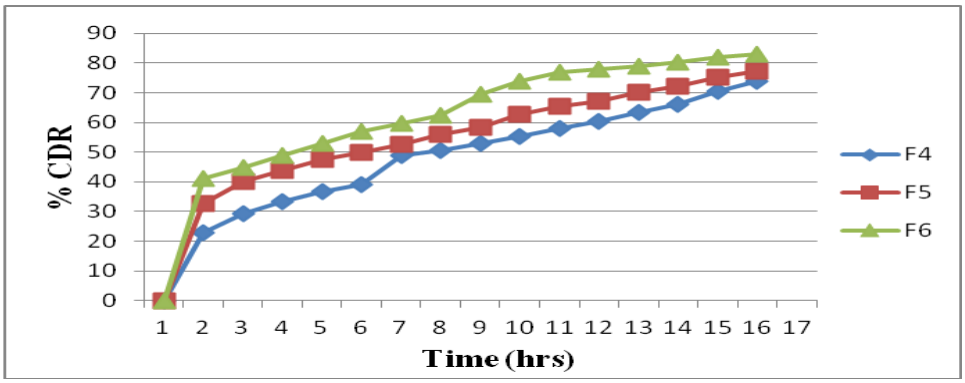


Fig 4: % Drug release of Valsartan formulation F4-F6

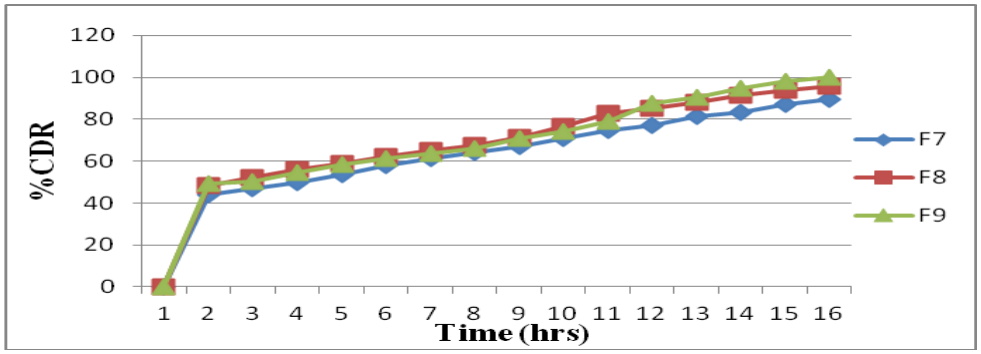


Fig 5: % Drug release of Valsartan formulation F7-F9

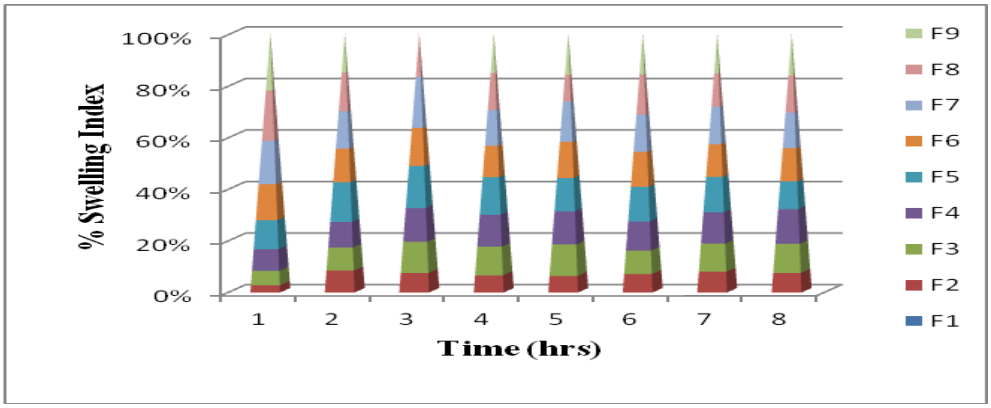
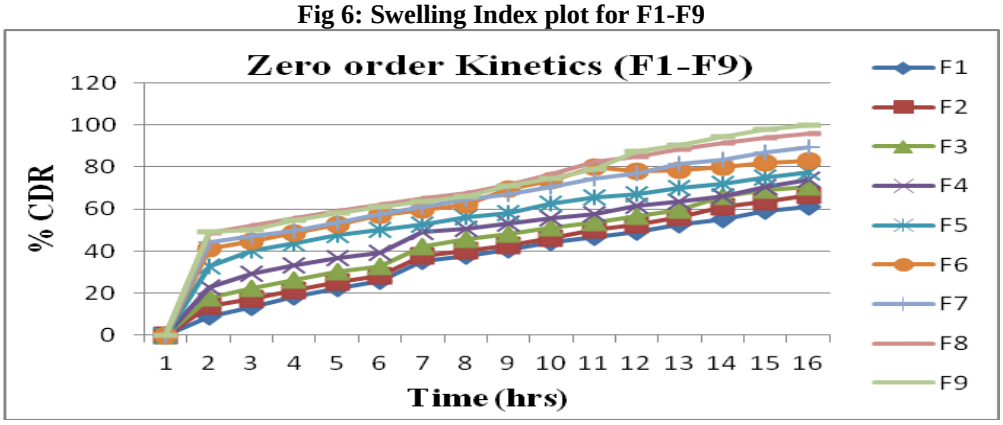


Fig 6: Swelling Index plot for F1-F9



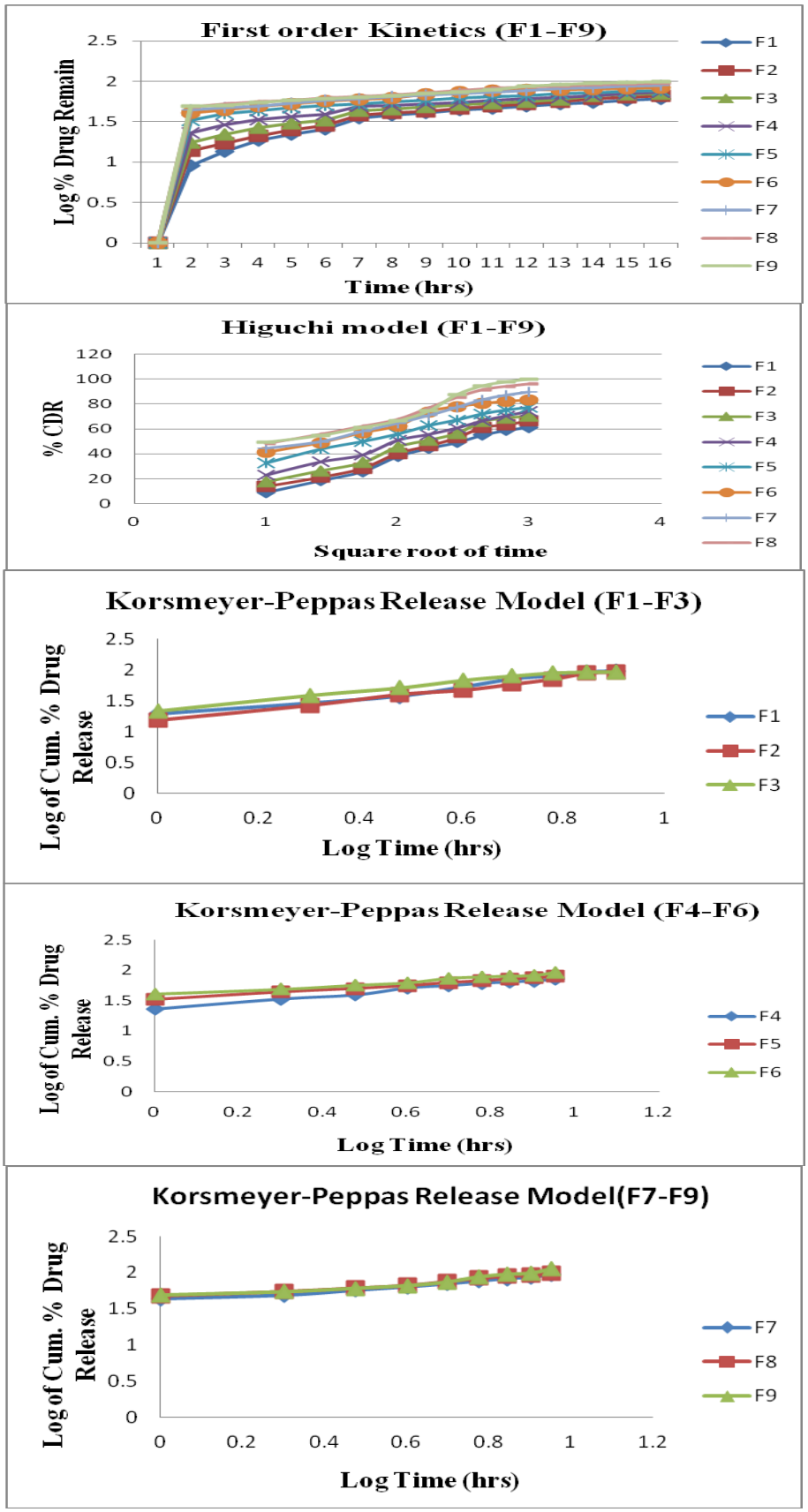


Fig 7: Drug release kinetics plot for F1-F9

TABLES:

Table 1 :Absorbance –concentration data for standard curve of Valsartan.

Sr. no.	Concentration(µg/ml)	Absorbance			
		I	II	III	Average
1.	0	0.000	0.000	0.000	0.000
2.	2	0.212	0.211	0.212	0.212
3.	4	0.405	0.406	0.406	0.406
4.	6	0.614	0.615	0.614	0.614
5.	8	0.805	0.805	0.804	0.805
6.	10	0.998	0.997	0.998	0.998

Table 2: Composition of Sustained release Valsartan matrix tablets

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Valsartan	81.5	81.5	81.5	81.5	81.5	81.5	81.5	81.5	81.5
Xanthan gum	2.592	2.304	2.016	1.728	1.440	1.152	0.864	0.576	0.288
Guar Gum	4.80	8.0	11.20	14.40	17.60	20.80	24.00	27.20	30.40
Magnesium stearate	22.4	22.4	22.4	22.4	22.4	22.4	22.4	22.4	22.4
Lactose	183	180	177	174	171	168	165	162	159
Talc	25.708	25.796	25.884	25.972	26.06	26.148	26.236	26.324	26.412

Table 3: Post-compression Parameter of Trail Batches (T1-T6)

Formulation Code	Thickness (mm)	Hardness (kg/cm^3)	Friability (%)	Content Uniformity (%)	Drug release (%) Up to 15 hrs.
T1	4.17± 0.01	5.6± 0.04	0.020	69.20± 0.11	69.08± 0.01
T2	4.12± 0.03	5.3± 0.04	0.030	75.00± 0.20	70.00± 0.01
T3	4.15± 0.04	5.5± 0.04	0.020	61.58± 0.21	62.00± 0.01
T4	4.14± 0.03	5.6± 0.04	0.030	58.60± 0.16	58.60± 0.01
T5	4.17± 0.02	5.5± 0.04	0.010	70.00± 0.15	70.50± 0.01
T6	4.15± 0.01	5.2± 0.04	0.020	98.10± 0.19	99.12± 0.01

(n=3, ±S.D.) (S. D. =standard deviation

Table 4: Pre-compression Evaluation Parameters (F1-F9)

Batch Code	Angle of repose	Bulk density (gm/cm$^{3)}$	Tapped density (gm/cm$^{3)}$	Compressibility index (%)	Hausner's Ratio
F1	22.25± 0.01	0.54± 0.06	0.629± 0.05	14.87± 0.64	1.1757± 0.07
F2	20.68± 0.03	0.53± 0.03	0.597± 0.03	16.38± 0.31	1.186± 0.03
F3	21.33± 0.02	0.50± 0.04	0.644± 0.04	14.76± 0.55	1.1730± 0.07
F4	22.97± 0.03	0.54± 0.05	0.634± 0.07	15.91± 0.22	1.1780± 0.06
F5	21.62± 0.02	0.54± 0.08	0.633± 0.04	14.51± 0.86	1.1697± 0.02
F6	20.58± 0.10	0.53± 0.06	0.626± 0.05	15.33± 0.25	1.1811± 0.07
F7	20.95± 0.01	0.53± 0.01	0.618± 0.01	14.43± 0.41	1.1687± 0.01
F8	21.83± 0.03	0.54± 0.13	0.628± 0.08	14.89± 0.55	1.1749± 0.03
F9	21.75± 0.04	0.52± 0.14	0.617± 0.09	14.45± 0.72	1.1655± 0.05

(n=3, ±S.D.) (S. D. =standard deviation

Table 5: Post-compression Evaluation Parameter (F1-F9)

Batch Code	Thickness (mm)	Hardness (kg/cm^3)	Friability (%)	Weight Variation (%)	Content Uniformity (%)
F1	4.12± 0.01	5.5± 0.03	0.20	320.10± 0.62	61.33± 0.17
F2	4.17± 0.05	5.5± 0.02	0.20	310.15± 1.20	66.58± 0.23
F3	4.15± 0.06	5.4± 0.04	0.30	320.09± 0.55	70.45± 0.10
F4	4.18± 0.01	5.2± 0.05	0.20	330.02± 0.85	73.83± 0.20
F5	4.15± 0.06	5.5± 0.07	0.20	310.20± 0.44	77.29± 0.44
F6	4.16± 0.07	5.5± 0.03	0.20	310.15± 0.25	83.00± 0.85
F7	4.21± 0.02	5.4± 0.05	0.30	310.20± 0.15	89.50± 0.55
F8	4.13± 0.03	5.5± 0.02	0.20	320.02± 0.54	95.79± 0.71
F9	4.18± 0.03	5.6± 0.08	0.30	320.14± 0.42	99.91±0.32

(n=3, ±S.D.) (S. D. =standard deviation)

Table 6:Cumulative % Drug Release (F1- F9)

Time (hr)	% cumulative drug release (Mean± S.D.)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	9.04 ±1.4	13.91 ±2.4	17.62 ±2.1	22.95 ±2.6	32.66 ±2.3	41.00 ±1.0	44.25 ±1.6	48.41 ±1.3	49.20 ±1.2
2	13.5 ±2.1	17.12 ±1.6	22.33 ±1.2	29.25 ±2.4	40.12 ±1.4	44.70 ±1.6	47.00 ±1.0	52.29 ±1.1	50.33 ±2.3
3	18.5 ±2.3	21.25 ±2.1	26.45 ±2.6	33.45 ±2.5	43.75 ±1.6	48.87 ±2.2	49.54 ±1.6	55.83 ±2.4	54.62 ±2.5
4	22.24 ±1.6	25.33 ±2.3	30.16 ±1.3	36.54 ±1.2	47.45 ±2.1	52.79 ±1.8	53.41 ±2.1	58.95 ±2.4	58.25 ±2.1
5	25.79 ±1.5	28.33 ±2.4	32.95 ±1.2	38.95 ±1.8	49.91 ±1.3	56.87 ±2.1	57.83 ±2.1	62.16 ±1.1	61.04 ±1.6
6	35.41 ±2.6	37.87 ±2.7	43.08 ±2.3	49.03 ±1.5	52.54 ±2.4	59.83 ±2.2	61.04 ±1.9	65.29 ±2.4	63.75 ±1.6
7	37.91 ±1.7	40.37 ±1.3	45.70 ±1.8	50.70 ±2.4	55.87 ±1.5	62.24 ±1.6	64.37 ±1.3	67.62 ±2.1	66.29 ±2.2
8	40.54 ±1.9	42.87 ±1.3	48.16 ±1.5	52.95 ±1.2	58.20 ±1.3	69.50 ±2.1	67.20 ±2.1	71.45 ±2.3	70.81 ±2.5
9	44.41 ±2.1	46.41 ±2.3	51.08 ±1.6	55.41 ±1.6	62.62 ±1.2	73.70 ±1.3	70.66 ±1.6	76.66 ±2.4	74.29 ±2.3
10	46.75 ±1.3	49.87 ±1.5	53.83 ±2.8	57.83 ±2.4	65.41 ±2.1	76.79 ±2.4	74.54 ±2.1	82.70 ±2.7	79.08 ±2.1
11	49.08 ±1.8	52.83 ±2.4	56.45 ±1.1	60.45 ±1.3	67.12 ±2.4	77.83 ±1.3	77.08 ±1.4	85.12 ±2.3	87.41 ±2.3
12	52.65 ±2.4	55.92 ±2.6	59.75 ±2.6	63.54 ±1.7	70.20 ±1.4	78.75 ±1.1	81.25 ±2.3	88.29 ±2.2	90.33 ±2.5
13	55.04 ±1.5	61.20 ±1.3	65.91 ±2.3	66.25 ±2.1	72.12 ±1.7	80.20 ±2.1	83.25 ±2.2	91.20 ±1.2	94.58 ±2.4
14	58.95 ±2.1	63.33 ±2.6	68.91 ±1.5	70.37 ±2.4	75.25 ±2.6	82.04 ±1.6	87.04 ±2.1	93.95 ±1.7	97.91 ±2.3
15	61.33 ±1.2	66.58 ±2.2	70.45 ±2.6	73.83 ±1.7	77.29 ±2.2	83.00 ±1.1	89.50 ±2.5	95.79 ±1.6	99.91 ±2.1

Table 7: Characterization of Swelling index (F1-F9)

Time (hr)	Swelling Index (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	25.04	36.20	28.30	30.20	29.02	34.20	40.30	26.20	32.33
2	39.00	38.20	45.30	50.60	56.00	44.20	51.20	38.96	49.55
3	41.30	42.20	49.00	56.00	55.61	54.50	62.33	58.55	55.33
4	55.54	65.66	61.04	66.30	58.00	64.80	70.74	69.20	52.0
5	50.00	55.50	55.20	55.15	64.25	65.20	65.23	55.30	62.33
6	52.55	61.20	74.20	62.58	70.20	69.55	74.20	66.64	68.33
7	62.41	64.20	64.25	65.52	73.20	75.33	66.30	69.55	76.00
8	63.10	66.10	65.00	71.00	75.23	78.00	81.20	78.30	85.00

Table 8: Release of Drug Kinetics (F1-F9)

Sr. No.	Batch code	Zero Order Kinetics ($r^{2)}$	First Order Kinetics ($r^{2)}$	Higuchi ($r^{2)}$	Peppas (n)
1	F1	0.6133	0.1974	0.6133	0.1798
2	F2	0.6658	0.1967	0.6658	0.1825
3	F3	0.7045	0.1966	0.7045	0.1868
4	F4	0.7383	0.1970	0.7383	0.1847
5	F5	0.7724	0.1960	0.7724	0.1901
6	F6	0.8300	0.1918	0.8300	0.1964
7	F7	0.8950	0.1922	0.8950	0.1976
8	F8	0.9579	0.1903	0.9579	0.1998
9	F9	0.9991	0.1908	0.9991	0.2050

Table 9: Evaluation parameters of optimized Batch (F9)

Sr. No.	Evaluation parameters	Observation
1	Thickness (mm)	4.18± 0.03
2	Hardness (kg/cm^3)	5.6± 0.08
3	Friability (%)	0.30
4	Weight Variation (%)	320.14± 0.42
5	Content uniformity(%)	98.91±0.32
6	% CDR (up to 15 hrs.)	99.91±2.1