Original Research

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF VALSARTAN

S. Dasthagiri*[1], P. Jagadeesh[2], K. Sayad Basha, S. Sheema Nafees

CH. Sri Vidhya Vardhani G. NethraVani

JNTUA-Oil Technological and Pharmaceutical Research Institute, Ananthapuramu, Andhra Pradesh-515001

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ABSTRACT

In the present investigation an attempt was made to prepare fast dissolving tablets of valsartan by using β-cyclodextrin as complexing agent to increase the bioavalability of formulation and polacrillin potassium and Ac-Di- Sol by direct compression of different ratios. Drug -excipient compatibility studies were proved by using FTIR. The tablets were evaluated for precompression parameters and post compression parameters persentase drug content and in-vitro drug release studies. Based on the results, formulation containing 1:1.25 ratio of valsartan: complexing agent and increased concentration of polacrillin potassium Ac-Di-Sol, (F-10) was identified as better formulation among all formulations developed for valsartan tablets. In-Vitro release of optimized formulation of valsartan fast dissolving tablets of F-10 was found to be 99.4% drug release within 45 mins and concluded that they are effective in patient compliance.

KEY WORDS: Fast dissolving tablets, Valsartan, β-Cyclodextrin, Polacrillin potassium.

Corresponding author: S. Dasthagiri,
Tel: +91-9490981469
E-mail: giri143sree@gmail.com

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INTRODUCTION:

Oral drug delivery systems

Oral drug delivery has been known for decades as the most commonly utilized administered route among all the routes that have been in use for dosage forms. The reasons that the oral route achieved such recognition may be in part qualified to its ease of administration. All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid) must be developed within the natural characteristics of GI Physiology, Pharmacokinetics, Pharmacodynamic and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

Tablet

A tablet is a pharmaceutical prescribed amount form. It comprises a mixture of active substance and excipients usually in a powder form, pressed or compacted into a solid dose.

Fast dissolving tablets properties

Tablets can be made in practically any shape. Diameter and shape are determined by the machine tooling. The thickness is determined by the amount of tablets material and the position of the punch in relation to each other during compression. Tablets require having sufficient strength that they do not break up in the bottle during handling and transport. Standards for tablet properties are published in the various in pharmacopoeia (USE, EP, etc.)[10] Solid dosage forms like tablets, capsules are the most popular form among all other dosage forms existing today because of its convenience of compression easy manufacturing and self-administration [1].It is difficult to swallow tablets as well as hard gelatin capsules and also when water is not available in the case of motion sickness, allergic attacks of coughing during the common cold and bronchitis. For these reasons tablets which rapidly dissolve or disintegrate in the oral cavity play important role and are called fast dissolving tablets.

Ideal properties of fast dissolving tablets

Not require water to consume and should dissolve in the mouth within few seconds. Allow high drug loading. Be compatible with taste masking and other excipients. Have a pleasing mouth feel. Leave residue in the mouth after oral administration. Have enough strength to withstand the rigors of the manufacturing process and post manufacturing handling. Exhibit low sensitivity to environmental conditions such as humidity and temperature. Be adjustable and amenable to existing processing and packaging machinery. Allow the manufacturing of tablets using conventional processing and packaging. Equipment low sensitivity to environmental condition. Require no water for oral administration. Have a pleasing mouth feel and taste masking. Manufacturing using conventional manufacturing method.

Techniques for preparing fast dissolving tablets

Many techniques have been reported for the formulation of fast dissolving tablets.

1. Direct compression
2. Freeze drying /Lyophilization
3. Tablet moulding
4. Spary drying
5. Sublimation
6. Mass extrus

MATERIALS AND EQUIPMENT

Table no 1: List of equipments `

S.no	Name of the equipments	Manufacturers name
1	Dissolution test apparatus eight stage	Labindia disso 2000
2	Dissolution test apparatus IP/BP/USP-14 stage	Labindia disso 2000

3	Tablet compression machine	Cadmach-multipunch Tablet machine
4	Hot air oven	Kadavil equipments
5	P^H meter	Elicoli 120
6	Roche friabilator	Labindia
7	Disintegration apparatus	Labindia
8	Monsanto hardness tester	Shreeji chemicals
9	UV-Visible spectrophotometer 2201	Labindia with UV analist software

Table no 2: List of materials

S.no	Materials used	Raw materials supplied by
1	Valsartan	Aurobindo pharmaceuticals Ltd.
2	β-Cyclodextrin	Aurobindo pharmaceuticals Ltd.
3	Polacrillin potassium	Anushul agencies, Mumbai.
4	Ac-Di-Sol	Analytical grade
5	Micro crystalline cellulose	Analytical grade
6	Sodium saccharin	Signet chemical corporation, Mumbai.
7	Talc	Signet chemical corporation, Mumbai.
8	Magnesium Stearate	Analytical grade

PREFORMULATION STUDIES

A preformulation study involves the application of biopharmaceutical principles to the physicochemical parameters of a drug with the goal of designing an optimum drug delivery system. Preformulation testing is defined as investigation of physical and chemical properties of drug substances alone and when combined with excipients. Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use.

Preparation of stock Solution

Take 100 mg of Valsartan and add 80 ml of P^H 6.8 phosphate buffer shake it for 10 minutes and makeup the volume up to 100 ml with of P^H 6.8 phosphate buffer. From this prepare various solutions in the range of 200-800 µg/ml and take the absorbance at 227 nm.

FORMULATION DEVELOPMEN:-

Formulation of compressed tablets of valsartan

Valsartan tablet can be prepared using by direct compression method.

Direct compression method

Valsartan immediate release tablets were prepared by direct compression method according to formulae given in the table. Blend can be prepared by passing the ingredients through 60-mesh sieve separately and collected. The drug and β-Cyclodextrin were mixed in small portion to increase the bioavailability of formulation. Then this mixture was combined with other recipient i.e. Polacrilline potassium as disintegrant, Ac-Di-Sol as super disintegrant and microcrystalline cellulose, lactose were mixed in small portion of both at each time and blended to get a uniform mixture and kept aside. Then the other ingredients were weighed and mixed in geometrical order and the tablets were compressed using flat face 8mm size punch to get a tablets to 300mg weight using tablet compression machine.

Table no 3: Formulation development of Valsartan table

S.no	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Valsartan	80	80	80	80	80	80	80	80	80	80	80	80
2	β-Cyclodextrin	40	40	40	60	60	60	80	80	80	100	100	100
3	Polacrilline potassium	10	10	---	11	12	---	12	13	---	14	12	---
4	Ac-Di-Sol	8	---	10	10	----	10	11	---	11	12	---	12
5	Micro crystalline cellulose	154	162	162	131	140	142	109	119	121	86	100	100
6	Sodium saccharine	3	3	3	3	3	3	3	3	3	3	3	3
7	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8	Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
9	Total weight of tablet	300	300	300	300	300	300	300	300	300	300	300	300

Precompression parameters

Angle of Repose

The angle of repose can be measured by the friction forces in a loose powder it is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. The weighted amount was taken in funnel just touches the apex of the heap of blend 'The blend was now allowed to flow through the funnel freely on the surface. The diameter of the powder cone was determined and angle of repose is determined by the following formula.

$$\mathbf{Tan(\theta)= h/r}$$

Where, Θ=angle of repose, H=height of the heap, R=radius of the heap

Bulk Densirty (D_b)

Bulk density (D_b) Is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density is then is then obtained by dividing the weight of sample in gms by final volume in cm^3.

$$\mathbf{D_b=M/V_b}$$

Where, M=mass of powder V_b=Bulk volume of the powder

Tapped Density (D_t)

Tapped density is the ratio of total mass of the tapped volume of the powder. It was determined by placing a graduated cylinder containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping was continued until the difference between successive volumes is less than 2%.It is expressed

$$\mathbf{D_t=M/ v_t}$$

Where, M= mass of powder v_t = volume of the tapped packing

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow and is given by

$$\mathbf{Hausner's\ Ratio=D_t /D_b}$$

Where, D_t =Tapped density, D_b= Bulk density

Porosity

The porosity € of powder is defined as the ratio of void volume to the bulk volume of the packaging. The porosity of the powder is given by

$$€=V_b-V_p/V_p=1-V_p/V_b$$

Porosity is frequently expressed in percentase and is given as

$$\% \quad €=(1-V_p/V_b)x100$$

Carr's index (or) %compressibility

It is expressed in percentage and indicates powder flow properties and is given by

$$I=D_t-D_b/D_tx100$$

Where, D_t =Tapped density of the powder D_b=Bulk density of the powder

Table no 4: Flow properties

Compressibility index	Flow character	Hausner's ratio
5-10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.45
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
More than 40	Very Very poor	More than 1.60

Data for Bulk density, Tapped density, Compressibility index and Hausner's ratio of all formulation.

Formulation	Bulk density (gm/ml) Avg±SD	Tapped density (gm/ml) Avg±SD	Hausner's Ratio (%) Avg±SD	Carr's index Avg±SD
F1	0.375±0.005	0.523±0.015	1.20±0.10	20.7±0.1
F2	0.417±0.011	0.543±0.011	1.13±0.01	19.3±0.1
F3	0.424±0.020	0.530±0.011	1.2±0.10	20.06±0.01

F4	0.311±0.02	0.428±0.011	1.13±0.01	21.36±0.11
F5	0.438±0.015	0.530±0.011	1.11±0.01	18.36±0.15
F6	0.425±0.035	0.535±0.011	1.18±0.01	20.73±0.02
F7	0.386±0.020	0.480±0.079	1.15±0.01	19.6±0.1
F8	0.326±0.020	0.371±0.011	1.15±0.03	15.36±0.30
F9	0.422±0.01	0.476±0.015	1.16±0.15	16.2±0.1
F10	0.351±0.01	0.423±0.015	1.11±0.005	14.06±0.15
F11	0.456±0.032	0.420±0.011	1.05±0.036	9.66±0.32
F12	0.413±0.026	0.406±0.0152	1.10±0.01	10.06±0.15

Post compression studies of prepared formulation

Weight variation

Twenty tablets were collected and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The weight variation limits as per USP are as follows.

Weight variation tolerances for tablets

Average weight of tablet(mg)	Percentage difference
130 or less	10 % w/w
130 to 324	7.5% w/w

Hardness

Hardness or tablet crushing strength, the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in Kg/cm^2.

Friability (F)

Friability is the tablet determined using Roche friabilator. This device subjects the tablet to the joint effect of abrasion and shock in a plastic chamber spinning at 25 rpm and dropping a tablet at I height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100revolutions.Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

% Friability=Loss in weight/Initial weight x100

Thickness

Twenty tablets were collected and each tablets thickness was measured by using Vernier caliper. The allowable limit was ± 0.35 % w/w. The resistance of the tablet to chipping. Abrasion or breakage under condition of storage.

Disintegration test

Disintegration was defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, was a soft mass having no palpably firm core. Place I dosage unit in each of the six tubes of the basket. Operate the apparatus, Using water or the specified medium as the immersion fluid, maintained at 37± 2°c.At the end of the time limit specified in the monograph, list the basket from the fluid and observe the tablets. All of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement was met if not less than 16 of the total of 18 tablets tested were disintegrated.

Percentage drug content

Preparation of Buffers and Reagents

Sodium hydroxide solution (0.2M)

Eight grams of sodium hydroxide was taken in 1000 ml volumetric flask containing about 700 ml distilled water and volume was made up to the mark with distilled water.

Potassium di hydrogen phosphate solution (0.2M)

27.218 gm of potassium di hydrogen phosphate was added in 1000ml volumetric flask containing about 700ml distilled water and volume was made up to the mark with distilled water .

Procedure of determining drug content

Three uncoated tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of tablet powder was taken from the crushed blend. Then the samples were transferred to100 ml volumetric flasks and were diluted up to the mark with P^H 6.8 Phosphate buffer solution. The contents were shaken periodically and kept for 24 hours for salvation of drug completely. The mixture was filtered, appropriately diluted and absorbences were measured at λ_{max} 227 nm against blank reference. The drug content in each tablet was calculated using the standard calibration curve of Valsartan in P^H6.8 Phosphate buffer solution.

Data for Weight variation, Hardness, Friability, Thickness, Disintegration time, Percentase drug content of all formulations.

Formulation	Wt. variation Avg±SD	Hardness (Kg/cm^2) Avg±SD (n=3)	Friability(%) Avg±SD (n=3)	Thickness (mm) Avg±SD (n=3)	Disintegration time(mins) Avg±SD (n=3)	% Drug content Avg±SD (n=2)
F1	249.35±3.422	2.4±0.05	0.52±0.18	4071±0.040	5.45±0.189	103.65±0.41
F2	251.00±2.772	2.4±0.1	0.60±0.14	4.55±0.039	5.51±0.177	99.25±0.52
F3	259.35±1.631	3.2±0.36	0.52±0.19	4.56±0.055	5.23±0.102	103.05±0.45
F4	260.90±1.744	3±0.28	0.58±0.11	4087±0.045	4.11±0.103	97.65±0.42

F5	258.40±1.313	2.5±0.28	0.59±0.16	5.01±0.049	3.42±0.104	94±0.41
F6	260.70±1.080	2.6±0.28	0.49±0.14	4.83±0.042	2.46±0.059	98.15±0.38
F7	260.20±1.005	3.5±0.5	0.54±0.10	4.87±0.052	2.53±0.069	100.16±0.3897
F8	256.35±1.531	3±0.86	0.61±0.20	4.53±0.050	4.33±0.112	100.65±0.46
F9	250.90±1.734	3±0.86	0.60±0.18	4.44±0.044	4.01±0.107	103.58±0.41
F10	259.40±1.412	2.8±0.28	0.67±0.24	4.87±0.042	2.12±0.114	99.83±0.41
F11	262.60±1.180	3.3±0.28	0.55±0.15	4.60±0.041	2.56±0.059	98.81±0.43
F12	251.20±1.105	2.5±0.28	0.53±0.13	4.59±0.055	2.53±0.069	98.53±0.86

In-Vitro drug release

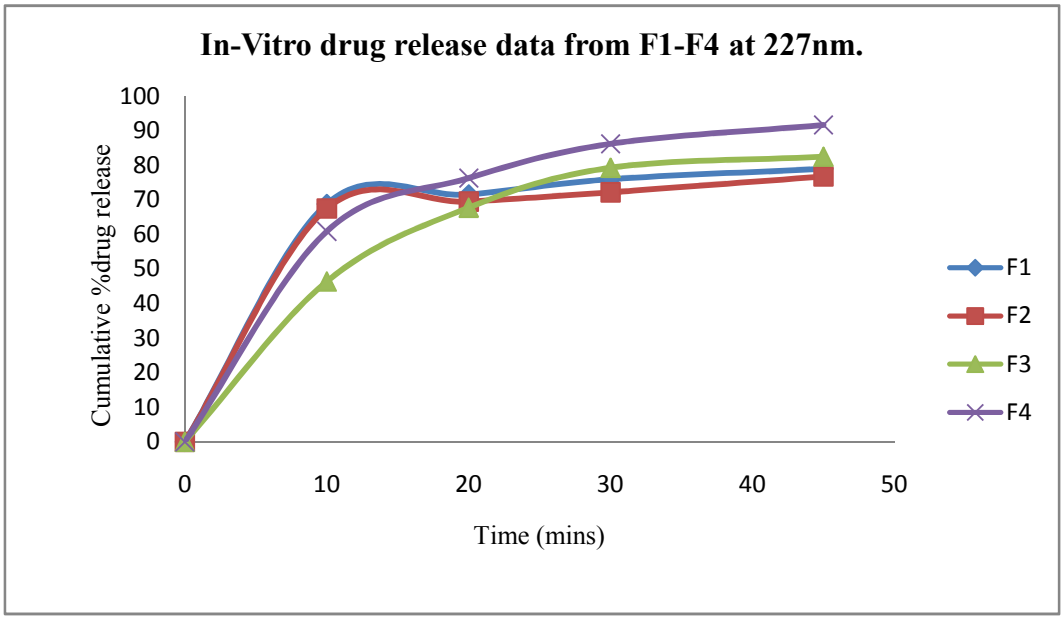
Preparation of stock solution

Take 100 mg of Valsartan and add 80 ml of phosphate buffer P^H 6.8. Shake it for 10mins and make up the volume upto 100 ml with phosphate buffer P^H 6.8.From this prepare various solution in the range of 200-800 µg/ml and take the absorbance at 227nm.

In-Vitro drug release data from F1-F4 at 227nm.

S.no	**Sampling time**	**Cumulative %drug release Avg±SD (n=6)**			
		F1	**F2**	**F3**	**F4**
1	0	0	0	0	0
2	10	68.5±0.25	67.2±0.25	45.8±0.56	60.4±0.45
3	20	71.2±0.27	69.1±0.36	66.9±0.79	75.4±0.85
4	30	75.6±0.29	71.6±0.54	78.4±0.81	85.4±0.76
5	45	78.3±0.61	76.0±0.71	81.5±0.92	91.4±0.21

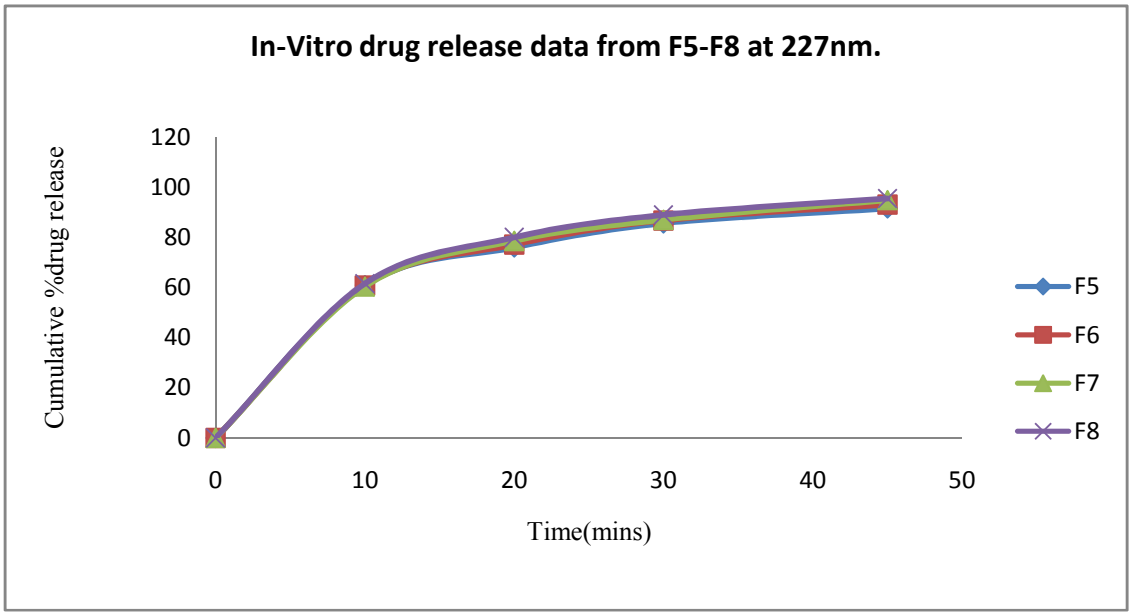
In-Vitro drug release data from F1-F4 at 227nm.



In-Vitro drug release data from F5-F8 at227nm.

S.no	Sampling time	Cumulative %drug release Avg±SD (n=6)			
		F5	F6	F7	F8
1	0	0	0	0	0
2	10	60.4±0.56	60.3±0.56	60.2±0.28	61.0±0.71
3	20	75.2±0.85	76.8±0.45	78.2±0.51	79.2±0.95
4	30	85.3±0.45	85.95±0.91	86.5±0.65	88.4±0.76
5	45	91.4±0.26	92.95±0.26	94.3±0.71	95.6±0.10

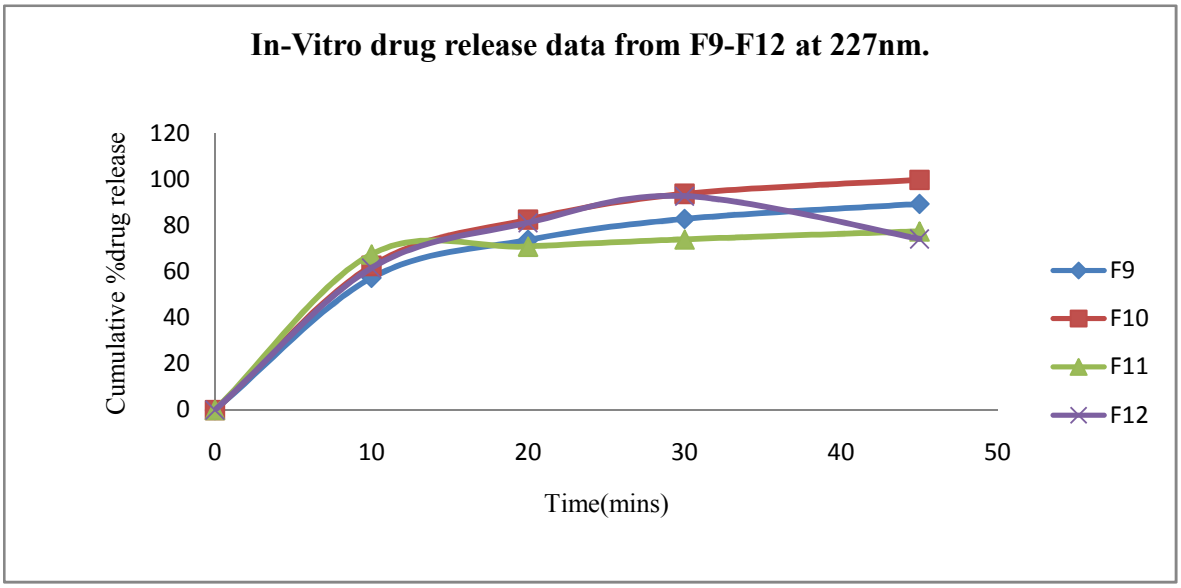
In-Vitro drug release data from F5-F8 at 227nm.



In-Vitro drug release data from F9-F12 at 227nm.

S.no	Sampling time	Cumulative %drug release Avg±SD (n=6)			
		F9	F10	F11	F12
1	0	0	0	0	0
2	10	56.7±0.56	61.9±0.56	66.85±0.59	61.5±0.01
3	20	73.2±0.52	81.7±0.78	70.15±0.65	81.1±0.05
4	30	82.4±0.42	93.1±0.52	73.67±0.25	92.6±0.06
5	45	88.9±0.41	99.4±0.24	77.15±0.24	73.9±0.25

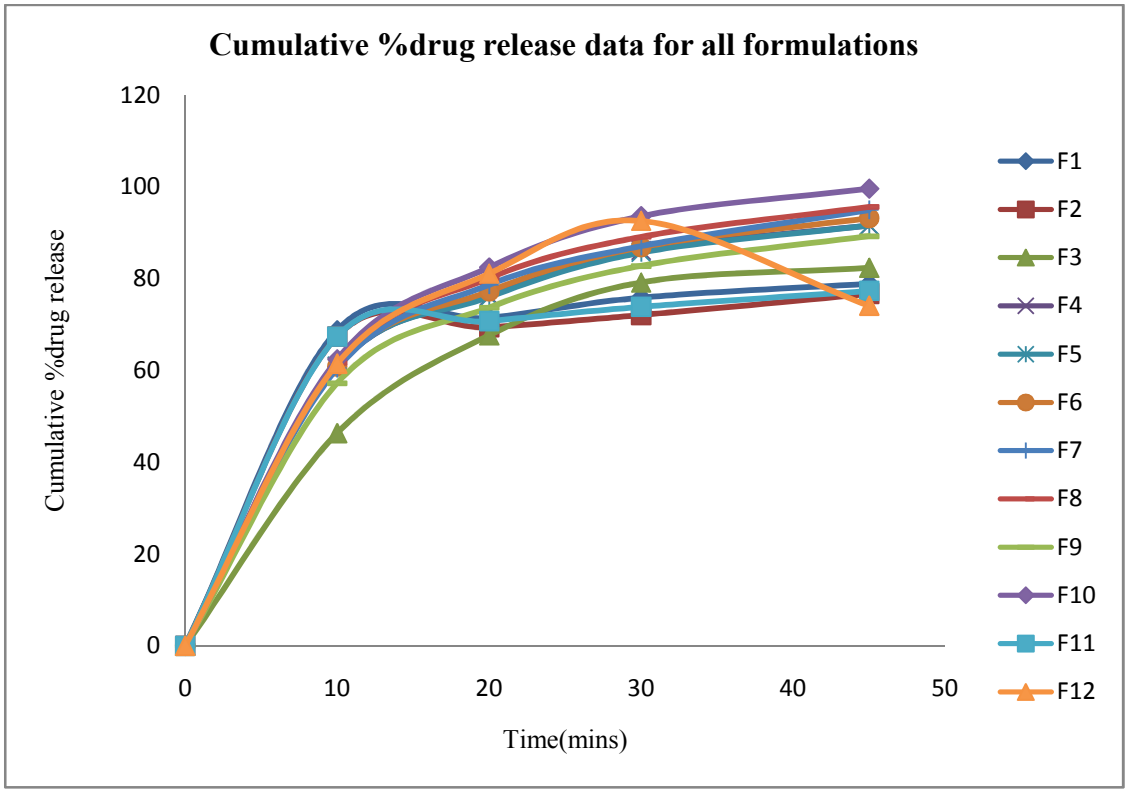
In-Vitro drug release data from F9-F12 at 227nm.



Cumulative %drug release data for all formulations

Formulation	Time(min)			
	10	**20**	**30**	**45**
F1	68.5±0.25	71.2±0.27	75.6±0.29	78.3±0.61
F2	67.2±0.25	69.1±0.36	71.6±0.54	76.0±0.71
F3	45.8±0.56	66.9±0.79	78.4±0.81	81.5±0.92
F4	604±0.45	75.4±0.85	85.4±0.76	91.4±0.21
F5	60.4±0.56	75.2±0.85	85.3±0.45	91.4±0.26
F6	60.3±0.56	76.0±0.45	85.9±0.91	92.9±0.26
F7	60.2±0.28	78.2±0.51	86.5±0.65	94.3±0.71
F8	61.0±0.71	79.2±0.95	88.4±0.76	95.6±0.10
F9	56.7±0.56	73.2±0.52	82.4±0.42	88.9±0.41
F10	61.9±0.56	81.7±0.78	93.1±0.52	99.4±0.24
F11	66.8±0.59	70.1±0.65	73.6±0.25	77.1±0.24
F12	61.5±0.01	81.1±0.05	92.6±0.06	73.9±0.25

Cumulative %drug release data for all formulations



Conclusion:-

In the present investigation an attempt was made to prepare fast dissolving tablets of valsartan by using β-cyclodextrin as complexing agent to increase the bioavalability of formulation and polacrillin potassium and Ac-Di- Sol by direct compression of different ratios. Drug -excipient compatibility studies were proved by using FTIR. The tablets were evaluated for pre compression parameters and post compression parameters persentase drug content and in-vitro drug release studies. Based on the results, formulation containing 1:1.25 ratio of valsartan: complexing agent and increased concentration of polacrillin potassium Ac-Di-Sol, (F-10) was identified as better formulation among all formulations developed for valsartan tablets. In-Vitro release of optimized formulation of valsartan fast dissolving tablets of F-10 was found to be 99.4% drug release within 45 mins and concluded that they are effective in patient compliance.

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