ISSN: 0976-4607
Research Article

International Journal of Innovative Pharmaceutical Research

Journal homepage: www.ijipr.com

Design and Evaluation of Valsartan Mouth Dissolving Tablets Using Solid Dispersion Technique

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ABSTRACT

This research work was designed to enrich the solubility of valsartan by solid dispersion technique and to develop the mouth dissolving tablets. Valsartan is an anti-hypertensive drug which belongs to BCS Class II having low solubility and therefore low oral bioavailability (25%). In the present study, SDs of valsartan with water insoluble carrier like guar gum were prepared by solvent evaporation method in the weight ratios of 1:1, 1:2, 1:3 and 1:4 and the optimized solid dispersion (SD) was used in the development of valsartan mouth dissolving tablets. SDs was evaluated for drug content and *in vitro* dissolution studies. The results revealed that the dissolution of valsartan SDs was improved greatly at 1:3 ratio when compared with that of remaining ratios which shows 94.84% of drug release within 60 minutes. The above optimized SD was formulated as mouth dissolving tablets by direct compression using superdisintegrants like croscarmellose sodium (CCS), (V1-V3), crospovidone (CP), (V4-V6), and sodium starch glycolate (SSG), (V7-V9). Valsartan mouth dissolving tablets were evaluated for pre-compression and post compression parameters. Amongst the formulations prepared (V1-V9), V9 was found to be effective formulation comprising of SSG which showed the drug release of 98.15% within 18min.

Keywords: Croscarmellose sodium, Crospovidone, Mouth dissolving tablets, Sodium starch glycolate, Solid dispersion, Valsartan.

INTRODUCTION

A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption (Dhirendra K *et al*). Oral bioavailability of a drug depends on its solubility and or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method. SD technology has been successfully been used for improving the solubility of the drugs and hence bioavailability (Ganesh Chaulang *et al*). The tablet is the most widely used dosage form now-a-days because of its convenience in terms of self-administration, compactness and ease in manufacturing. But, geriatric, paediatric and psychiatric patients experiences difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome these problems, researchers have developed advanced drug delivery system known as mouth dissolving tablets (A Gupta *et al*). *Valsartan* belongs to angiotensin II receptor blocker and is widely used for the treatment of hypertension. It is selected as a model drug in the present work because of its relatively poor aqueous solubility and bioavailability (25%) and extensive first pass metabolism. The *valsartan* requires the quick onset of action. This can be accomplished by improving the solubility of *valsartan* and formulating the same into mouth dissolving tablets. In order to overcome these shortcomings, the present study initially attempts to enhance the solubility of *valsartan* by solid dispersion technique using guar gum as carrier in different ratios. Using optimized SDs mouth dissolving tablets were formulated.

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MATERIALS AND METHODS

Materials

Valsartan (Strides Arcolab Ltd., Bangalore), CCS, Citric acid, (Sd fine chemicals Ltd., Mumbai), Crospovidone (Sri Krishna pharmaceuticals, Hyd.), SSG (HiMedia Pvt. Ltd., Mumbai), Mannitol, Potassium dihydrogen phosphate, di-sodium hydrogen phosphate, sodium chloride (Merck Pvt. Ltd., Mumbai.) and Magnesium stearate, Talc (Oxford Laboratory, Mumbai).

Preparation of valsartan solid dispersions

Solid dispersions of valsartan with a hydrophilic carrier (guar gum) were prepared in different ratios of drug–carrier. The solvent evaporation method was used for the preparation of SD in the present study. In this method, 0.5 g of valsartan was accurately weighed and dissolved in a minimum amount of methanol in which hydrophilic carrier was suspended. The solvent was evaporated using a water bath at 45^0C.The obtained solid was ground, sieved through a sieve no. 60 and store in air tight containers (Monica rao *et al*). Composition of different formulations of solid dispersions of valsartan was shown in Table.1.

Evaluation of valsartan solid dispersions

Percentage yield

Percentage yield was calculated to know about efficiency of any method and thus its help in selection of appropriate method of production. The final weights of the prepared solid dispersions were taken and percentage yield was calculated by using the given formula (Lakshmi K *et al*). The results were shown in Table No. 7.

$$\%\text{yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug content

Equivalent weight of prepared solid dispersions containing 100 mg drug were taken and transferred into 100 ml Standard flask Then take 1 ml from above solution and diluted up to 100 ml simulated salivary fluid p^H 6.8 and repeat the same again by take 1 ml from above solution and diluted up to 100 ml simulated salivary fluid p^H 6.8. The resulting solutions were filtered through a 0.45µ membrane filter and diluted accordingly. The absorbance of the solutions was measured at 217 nm. Percentage of drug content was calculated by using the given formula (Lakshmi K *et al*). The results were shown in Table No. 8.

$$\%\ \text{Drug content} = \frac{\text{Observed value}}{\text{Actual value}} \times 100$$

In vitro dissolution studies

In vitro dissolution studies of pure valsartan and solid dispersions were conducted with the USP type II apparatus (paddle type). The dissolution studies were performed using 900 ml simulated salivary fluid of p^H 6.8 as dissolution medium at 37±0.5°C with 50 rpm speed. Samples of each preparation equivalent to 10 mg of drug were added into the dissolution medium. The sample of 5 ml aliquots were withdrawn periodically (15, 30, 45 and 60 min) and filtered through 0.45µ membrane filter. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted suitably and the samples were analyzed for their drug content by using UV spectrophotometer at wavelength of 217 nm. Percentage of drug dissolved at various time intervals was calculated by plotting time on X- axis against percent cumulative drug release on Y-axis (Shingala ketan *et al*). The results were shown in Table No. 9 and Figure.1.

Preparation of valsartan mouth dissolving tablets

Valsartan mouth dissolving tablets were prepared by direct compression method using valsartan optimized SD prepared by solvent evaporation technique. The amount of complex equivalent to 40 mg of drug per tablet were taken and mixed with directly compressible diluents and superdisintegrants in a mortar with the help of pestle. The blend was then compressed using 8 mm round faced punch by using tablet punching machine (Metkari VB *et al*). The total weight of tablet was 220 mg. The formula which included variable amounts of all excipients was shown in the Table.2.

Table.1 Composition of different formulations of solid dispersions

S. No.	Ingredients	Formulation code			
		F1	F2	F3	F4
1	Valsartan	1	1	1	1
2	Guar gum	1	2	3	4
3	Solvent (methanol) (ml)	10	10	10	10

Table.2 Preparation of valsartan mouth dissolving tablets (*40 mg of valsartan (VAL) ≈ 156.16 mg of SD complex)

Ingredients (mg)	V1	V2	V3	V4	V5	V6	V7	V8	V9
SD complex	Equivalent to 40 mg of VAL	Equivalent to 40 mg of VAL	Equivalent to 40 mg of VAL	Equivalent to 40 mg of VAL	Equivalent to 40 mg of VAL	Equivalent to 40 mg of VAL	Equivalent to 40 mg of VAL	Equivalent to 40 mg of VAL	Equivalent to 40 mg of VAL
CCS	3	6	12	-	-	-	-	-	-
Crospovidone	-	-	-	3	6	12	-	-	-
SSG	-	-	-	-	-	-	3	6	12
Mannitol	51.84	48.84	42.84	51.84	48.84	42.84	51.84	48.84	42.84
Citric acid	4	4	4	4	4	4	4	4	4
Mg. Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	220	220	220	220	220	220	220	220	220

Table.3 Effect of angle of repose on flow property of powders

Angle of repose	Type of flow of powder
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Table.4 Effect of carr's index on flow property of powders

Carr's index	Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
> 40	Very very poor

Table.5 Effect of hausner's ratio on flow property of powders

Hausner's ratio	Flow property
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
> 1.60	Very very poor

Table.6 Weight variation tolerances for uncoated tablets

Average weight of tablets (mg)	Max. percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

Pre compression studies (CVS Subrahmanyam *et al*)

The powder blend was subjected for the following studies.

Angle of repose

The angle of repose of powders was determined by the funnel method. Accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula. The effect of angle of repose on flow property of powders was listed in Table No. 3 and the results were tabulated in Table.10.

$$\tan\theta = \frac{h}{r}$$

Where,

h = height of the powder cone

r = radius of the powder cone

Bulk density and tapped density

A quantity of 5.5 gms of powder from each formula was introduced into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed. Then bulk density (BD) and tapped density (TD) were calculated by using the given formula and the results were tabulated in Table.10.

$$BD = \frac{\text{Weight of the powder}}{\text{Initial volume}}$$

$$TD = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Carr's index

The Compressibility of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it is packed. The effect of carr's index on flow property of powders was listed in Table.4. The formula for carr's Index is given below and the results were tabulated in Table.10.

$$\text{Carr's index } (\%) = \frac{TD - BD}{TD} \times 100$$

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is

calculated by using the given formula and the effect of hausner's ratio on flow property of powders was listed in Table No. 5. The results were tabulated in Table.10.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

Post compression studies (Lachman L *et al*)

Thickness

Tablet thickness can be measured using digital vernier calipers. 3 tablets were taken and their thickness was measured and the average thickness for each tablet was calculated. The results were tabulated in Table.11.

Hardness

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using monsanto hardness tester. An average of three observations is reported. The results were tabulated in Table.11.

Friability test

Friability of the tablets was determined using Roche friability. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Conventional tablets that lose less than 1% of their weight are acceptable. The results were tabulated in Table.11.

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight variation

The weight variation test is done by weighing 10 tablets individually, calculating average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The results were tabulated in Table.11.

$$\%\text{ Weight variation} = \frac{\text{Average weight} - \text{Initial weight}}{\text{Average weight}} \times 100$$

Evaluation of Valsartan mouth dissolving tablets

Disintegration test

It is time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes with the bottom containing a 10 mesh sieve. The basket is set a frequency of 28-32 cycles per minute in a medium of 900 ml which is maintained at 37 ± 2° C. The tablets were placed in the tubes and the time required per complete passage of tablet particles through 10 mesh sieve was considered as disintegration time of tablet (Mothilal M *et al*). The results were tabulated in Table.12.

***In-vitro* dispersion time test**

To determine dispersion time 10 ml measuring cylinder was taken in which 6 ml of simulated salivary fluid of p^H 6.8 was added and tablet was dropped in it. Time required for complete dispersion was noted. Three tablets from each formulation were selected randomly and the average dispersion time was determined (Ravi kumar *et al*). The results were tabulated in Table.12.

Wetting time

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten ml of simulated salivary fluid of p^H 6.8 containing a water-soluble dye is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time (Ravi kumar *et al*). The results were tabulated in Table.12.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of simulated salivary fluid of p^H 6.8. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R), was determined using following equation,

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where,

$\mathbf{W_b}$ is weight of tablet before water absorption

$\mathbf{W_a}$ is weight of tablet after water absorption.

Three tablets from each formulation were selected randomly and the average water absorption ratio was determined (Ravi kumar *et al*). The results were tabulated in Table No. 12.

Drug content

Five tablets were taken and powdered; the powder equivalent to 8 mg of valsartan was dissolved in 100 ml of simulated salivary fluid of p^H 6.8, filtered, diluted suitably to 10 mcg/ml concentration and analyzed at 217 nm using UV-Visible spectrophotometer (Ravi kumar *et al*).. The results were tabulated in Table No. 12.

***In vitro* dissolution studies**

In vitro dissolution studies of valsartan mouth dissolving tablets were conducted with the USP type II apparatus. The dissolution studies were performed using 900 ml simulated salivary fluid of p^H 6.8 as dissolution medium at 37±0.5°C with 50 rpm speed. A tablet of each formulation containing 8 mg of drug was added into the dissolution medium. The sample of 5 ml aliquots were withdrawn periodically (3, 6, 9, 12, 15 and 18 min) and

filtered. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted and analyzed for their drug release by using UV spectrophotometer at wavelength of 217 nm. % of drug dissolved was calculated by plotting time on X- axis against % cumulative drug release on Y-axis (Rohan D. Deshpande *et al*). The results were tabulated in Table No. 13 and Figure No.2.

RESULTS AND DISCUSSION -CONCLUSION

Percentage yield of Valsartan SDs containing guar gum as carrier was in the range of 92.50-96.20 as shown in Table No. 7. The yield was low for F1 and high for F4. From the results, it was observed that there was no significant loss of drug during the preparation of solid dispersion by Solvent evaporation method. The percentage drug content of Valsartan SDs containing guar gum as carrier was in the range of 89.20-98.09 as shown in Table No.8. It was low for F1 and high for F3.The results revealed that the ratios and carriers used to prepare solid dispersions have shown no effect on the drug content. *In-vitro* dissolution studies revealed that F3 formulation containing valsartan: Guar gum in 1:3 ratio showed highest drug release of 94.84% in 60 min as shown in Table No.9 and Figure No.1. The bulk density of all formulations, powder blend containing excipients was found to be in the range of 0.30 to 0.55 gm/ml, whereas the tapped density was observed between 0.34 to 0.60 gm/ml. From the results of bulk density and tapped density the values for compressibility index and hausner's ratio were calculated. The values for compressibility index were found between 7.69 to 14.28 %. The values for hausner's ratio were found in between 1.07 to 1.17. All these values are within the specified limit which indicates good flow properties. Angle of repose was found to be less than 30 which indicate good flow of powder.

Table.7 % practical yield of valsartan SDs containing Guar gum

S. No.	Formulation code	% yield
1	F1	92.50
2	F2	93.66
3	F3	93.75
4	F4	96.20

Table.8 % Drug content of valsartan SDs containing Guar gum

S. No.	Formulation code	% Drug content
1	F1	89.20
2	F2	94.60
3	F3	98.09
4	F4	95.87

Table.9 Dissolution data of Valsartan and valsartan SD containing Guar gum in different ratios

S. No.	Time (min)	% Cumulative drug release				
		Pure drug	F1	F2	F3	F4
1	15	4.05	29.54	31.74	38.61	37.32
2	30	14.75	45.88	51.22	68.11	54.94
3	45	26.03	60.97	65.68	81.08	68.80
4	60	35.14	75.74	83.20	**94.84**	85.14

Table.10 Physical parameters of powder blend

S.No	Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (^{0})
1	V1	0.34	0.39	12.80	1.15	25.87
2	V2	0.36	0.42	14.28	1.17	26.50
3	V3	0.36	0.39	7.69	1.08	23.38
4	V4	0.30	0.34	11.76	1.14	20.22
5	V5	0.42	0.45	6.66	1.07	22.61
6	V6	0.55	0.60	8.33	1.09	23.38
7	V7	0.36	0.42	14.20	1.17	24.77
8	V8	0.45	0.50	10.00	1.11	24.67
9	V9	0.40	0.45	11.10	1.14	27.82

Table.11 Physical parameters of valsartan mouth dissolving tablets

S.No	Formulation code	Hardness (Kg/cm^2)	Thickness (mm)	% Friability	% Weight variation
1	V1	4.2	3.6	0.462	1.888
2	V2	4.4	3.7	0.473	2.696
3	V3	4.7	3.9	0.460	2.199
4	V4	4.2	3.6	0.460	2.200
5	V5	4.1	3.7	0.460	2.490
6	V6	4.8	3.6	0.490	3.418
7	V7	4.3	3.9	0.490	3.636
8	V8	4.2	3.9	0.480	3.852
9	V9	4.8	4.1	0.480	4.370

Table.12 Evaluation tests of valsartan mouth dissolving tablets

S.No	Formulation code	Disintegration time (sec)	*In-vitro* dispersion time (sec)	Wetting time (sec)	Water absorption ratio (%)	% Drug content
1	V1	43	84	86	84.42	97.05
2	V2	37	69	60	85.76	95.05
3	V3	25	55	44	92.78	95.59
4	V4	55	92	98	86.03	94.99
5	V5	46	76	67	90.93	94.12
6	V6	30	68	53	97.88	93.45
7	V7	33	74	66	84.73	92.12
8	V8	27	49	40	89.07	94.38
9	V9	21	32	34	94.72	94.45

Table.13 Comparative dissolution data of valsartan mouth dissolving tablets

S. No.	Time (min)	% Cumulative drug release								
		Formulation containing crospovidone			Formulation containing CCS			Formulation containing SSG		
		V1	V2	V3	V4	V5	V6	V7	V8	V9
1	3	16.00	17.98	24.78	20.25	23.08	27.47	21.66	23.63	28.75
2	6	35.54	42.34	45.74	39.79	43.76	47.42	42.34	46.59	49.14
3	9	56.81	59.20	62.74	58.49	61.46	64.58	59.76	62.03	65.71
4	12	68.12	73.50	78.63	70.95	74.07	78.25	73.60	75.91	81.01
5	15	77.75	84.12	89.51	82.57	87.66	92.62	86.25	90.92	94.46
6	18	80.30	86.53	92.20	85.95	90.50	94.75	89.79	93.33	**98.15**

Figure.1 Dissolution profile of Valsartan and valsartan SD containing Guar gum in different ratios

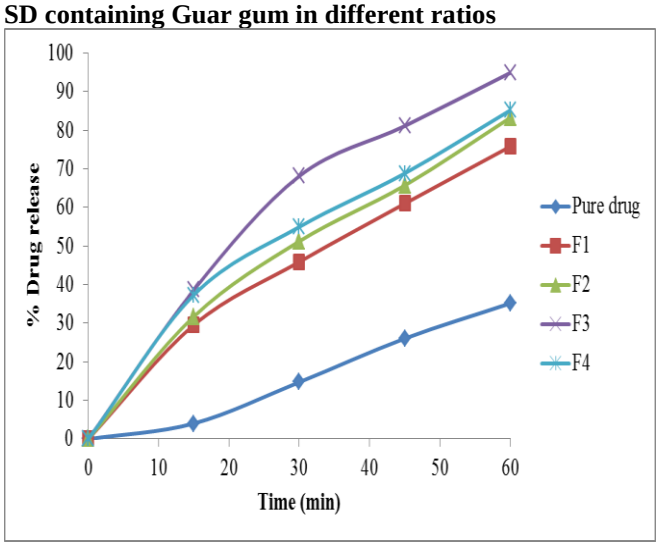
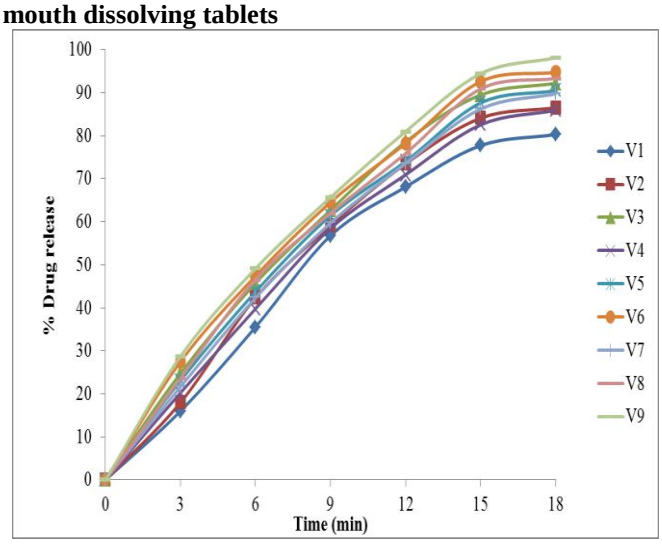


Figure.2 Comparative dissolution profile of valsartan mouth dissolving tablets



Overall these values indicate good flow properties of powder blend, uniform die fill and better compression ability (Table No.10). Hardness test for all formulations was carried out and observations obtained were in the range of 4.1 to 4.8 kg/cm^2. Hardness for all formulations was observed to be proper, which signify that crushing strength of all formulations was maintained after direct compression. The thickness of all formulations was found to be uniform as it was obtained in the range of 3.6 to 4.1 mm. Friability test was conducted for all formulations, all formulations indicated that % loss was less than 1%, which showed the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation. The % weight variation of all formulations was found to be in the range of less than ± 7.5, which complies with USP specification and signifies that there is uniformity in flow of powder blend which leads to uniform die fill (Table No.11). From the results it is observed that V9 formulation shows decrease in wetting time, disintegration time, *in vitro* dispersion time and more water absorption ratio. It indicates that high capillary action and high swelling action of sodium starch glycolate improves the wicking and swelling action tablets. Disintegration time for all formulations was found to be in the range of 21 to 55 sec. wetting time of tablets are found in the range of 34 to 98 sec and the water absorption ratio was found in the range of 84.42 to 97.88 %. As the porosity of formulation is increased by the superdisintegrating agents and water uptake is increased due to increased capillary action, the formulation is shows less wetting time. The less wetting time helps in the quick dispersion of the formulation when come in contact with the saliva. Disintegration study states that there was decrease in disintegration time with successive increase in concentration of superdisintegrants. *In vitro* dispersion time indicates complete dispersion of formulation in the saliva and it was found to be in the range of 32 to 92sec and it is due to more porosity of superdisintegrants. Quick dispersion of formulation favors fast disintegration of formulation. Drug content of all formulations was observed between 92.12 to 97.05%. Drug content for all formulations shown uniformity which indicating that there was uniform flow and uniform distribution of drug (Table No.12). The *in-vitro* dissolution study results revealed that valsartan mouth dissolving tablets prepared with SSG showed better drug release (98.15%) than when compared to CCS and crospovidone as shown in Table No.13 and Figure.2.

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