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SOLUBILITY ENHANCEMENT OF VALSARTAN TABLETS USING MIXTURE OF ALKALIZER AND SOLUBILIZING AGENT

*Amaresh Prusty[1]

[1]Department of Pharmaceutics, College of Pharmaceutical Sciences, Puri, Odisha, India

E-mail: amareshprusty@gmail.com

ABSTRACT

The present research work emphasis on developing an efficient oral dosage form of Valsartan tablets by enhancing the solubility and dissolution rate by addition of an alkalizer and solubilizing agents' enhancer respectively. The solubility of API can significantly affect the drug absorption and therefore its bioavailability. Out of various approaches used, modulation of the micro environmental pH could improve dissolution behavior of drugs with pH-dependent solubility for Solubilization of Valsartan leading to better oral absorption. Valsartan tablets are prepared by wet granulation method with alkalizer NaOH in tablet with increasing concentration which is used to maintain microenvironment pH and also by using of Meglumine (MEG) for enhancing dissolution allow Valsartan tablets for maximum drug release into the alkaline environment. The flow properties of the granules were studied and all formulation was found to have comparatively with good compressibility index and hausner ratio. It is an easiest process for improving the solubility. Formulation F10 Valsartan tablets show the best result on the drug release and stability study was carried out at accelerated conditions of 40° C and 75% RH indicates tablets remain stable in accelerated stability study. Valsartan Tablets was prepared using different excipients enhancing the solubility and dissolution rate by addition of an alkalizer and dissolution enhancer respectively.

***KEYWORDS*:** Valsartan, pH-modifier, Meglumine, Dissolution Rate, Stability.

INTRODUCTION

Out of different types of dosage forms solid dosage forms like tablet and capsule are most popularly and preferred drug delivery system because the solid dosages form having more patient compliance easy to administration, availability, without any dose dumping, good physical and stability than the other dosage form **(Sameer G *et al.*, 2005; Cheiny W, 1992; lachman L *et al.*, 1987).** Oral drug delivery products has been known for decades as the most widely utilized route of administration among all the routes that have been explored the more therapeutic activity in systemic route. Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. Valsartan used to treat high blood pressure, heart failure and diabetic kidney disease. Valsartan is an angiotensin-II receptor blocker that shows high affinity for the angiotensin-II receptor type-1 (AT1). It is believed that Valsartan is a dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD) **(Flesch G *et al.*, 1997; Supriya A *et al.*, 2018)**. The stability issue of Valsartan has been arisen by formulation with the pH considering the change in physio-chemical properties. Due to high lipophilicity & high- volume distribution, Valsartan has good tissue permeation. However, Valsartan is a biopharmaceutical classification system (BCS) class II drug that has extremely low water solubility but is freely soluble in highly alkalized solutions, so the solubility of Valsartan is dependent on the pH of solution. The solubility of API can significantly affect the drug absorption and therefore its bioavailability. So various approaches are used for solubilisation of Valsartan by preparing formulation in microenvironment pH. It will take less time & efficacy will be long term period. The modulation of pH in dosage forms is a promising way to modify the release rate of several pH-dependent and ionizable drugs **(Govada KB *et al.*, 2016; Siepe S *et al.*, 2006).** Incorporation of weak acids as pH modifiers enhances release rate of weakly basic drugs by reducing the micro environmental pH, which can be defined as the pH of the saturated solution in the immediate vicinity of the drug particles and has been used to modify the dissolution of ionizable drugs from pharmaceutical formulations in a predictable manner. So pH factor plays great role in the increasing of solubility drug **(Riis T *et al.*, 2007; Nam HA *et al.*, 2011**). Adding MEG in the formulation was proved to be an effective method to achieve the desired release behavior and it could be advantageous for increased bioavailability of Valsartan (Young HC et al., 2016). This research work emphasis on the designing of an efficient oral dosage form of Valsartan by enhancing the solubility and dissolution rate by addition of an alkalizer and dissolution enhancer respectively. MEG is a pH-adjusting agent. It is also used as a solubilizing agent.

MATERIALS AND METHODS

Materials

Valsartan was procured from Matrix Laboratories ltd, India. Microcrystalline cellulose and Mannitol used as major part

of diluents and Crospovidone is used as disintegrant procured from Merck Chemicals Ltd, India. Other ingredients like Magnesium stearate which is used as a lubricant due to less cost than other lubricant obtained from S.D. Fine chemicals, Mumbai, India and Sodium hydroxide used as an alkalizer which is increase the solubility of drug followed by increasing in dissolution rate and Meglumin used as a major dissolution enhancing agent both were also procured from S.D. Fine chemicals, Mumbai.

Methods

Preparation of Valsartan Tablets

Trial tablets are prepared by wet granulation method but without API (Dummy granulation). The API was mixed with the paste part with the sodium hydroxide by proper mixing. Based on the existing developed product of API, it was decided to carry out the trials initially by using aqueous granulation method with an average weight of around 280 mg for core tablets. For improvement of dissolution Meglumin is used for enhancing dissolution and also Crospovidone used as super disintegrating agents by maintaining controlled environmental conditions at a temperature of NMT 25°C and RH NMT 65% during entire processing and packing operations of the product. The tablets were prepared by compressing the thoroughly mixed materials using 6mm round, flat and plain punches on a 16 station tablet punching machine (Karnavati Tablet Punching Machine). The Formula for the preparation of Valsartan tablets shown in Table 1.

Table 1: Formulation for Compressed Tablets.

Quantity(mg/tablet)										
Formulation Code & Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Dry mixing										
MCC (Avicel PH 101)	125.00	125.00	125.00	125.00	125.00	125.00	125.00	125.00	125.00	125.00
Mannitol SD 200	44.00	40.00	43.00	41.00	39.00	39.00	37.00	35.50	36.00	35.00
Crospovidone XL-10	7.00	8.00	7.00	9.00	8.50	10.00	10.00	10.00	9.50	10.00
Drug Solution										
Valsartan	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00
Sodium Hydroxide	2.50	2.50	2.50	3.00	3.00	3.00	3.00	3.50	3.50	3.50
Meglumine	10.00	11.50	12.00	12.00	12.00	12.00	13.00	13.50	13.00	13.50
Purified Water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Lubrication										
Crospovidone XL-10	8.00	10.00	8.00	8.00	10.50	10.00	10.00	10.00	10.00	10.00
Magnesium Stearate	3.50	3.00	2.50	2.00	2.00	2.00	2.50	2.50	3.00	3.00

Characterization of tablets (Pre Compression Parameters)

Drug-Excipients Compatibility Study

The Drug substance and excipients were mixed and filled in glass vials. The vials were kept in both closed and opened condition under 40°C/75%RH, 30°C75%RH & 60°C and UV chamber. Exposed Samples were withdrawn from the different condition, with respective day's interval 7^{th}, 15^{th} and 30^{th} days and studied.

Bulk Density

The power sample under test was screened through sieve no.12 and the sample equivalent to 25 gm was weighed

and filled in a 100 ml graduated cylinder and the power was leveled and the unsettled volume, Vo was noted. The bulk density was calculated in g/cm^3 by the formula.

Bulk density = M/Vo

M = Powder mass. Vo = apparent unstirred volume

Tapped Density

The power sample under test was screened through sieve no.18 and the weight of sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder was carried out using tapped density tester at a nominal rate of 300 drops per minute for 500 times initially and the tapped volume Vo was noted. Tapping was proceeding further for an additional tapping 750 times and tapped volume, Vb was noted. The difference between two tapping volume was less the 2%, Vb was considered as a tapped volume Vf. The tapped density was calculated in g/cm^3 by the formula,

Tapped density=M/V_f

M =weight of sample power taken

V_f =tapped volume

Compressibility Index

The bulk density, tapped density was measured and compressibility index was calculated using formula,

C.I. = (Pt -Po)/(Pt)x 100

Pt=tapped density Po=bulk density

Hausner Ratio

Hausner ratio of the blend was calculated using the following formula,

Hausner ratio=Pt/Po

Pt=tapped density Po=bulk density

Relation between flow property with Hausner's ratio and C. I. Shown in Table 2.

Table 2: Relation between flow property with Hausner's ratio and C. I.

Compressibility index	Flow property	Hausner's ratio
≤10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very very poor	>1.60

Characterization of Post Compression Parameters of Tablets

Thickness, Length and Width

Thickness, length and width of prepared Valsaratn tablets are measured individually by Vernier calliper.

Hardness and Friability Test

The crushing strength (Kg/cm²) of tablets was determined by using Electronic Hardness tester. The friability of the tablets was determined in Roche Friabilator and expressed in %. 10 tablets from each batch were weighed accurately and placed in the tumbling chamber and rotated at 25 rpm for a period of 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability (PF) was calculated using formula

PF = (Weight original – Weight final) / Weight original X 100.

Weight Variation Test

Twenty tablets were selected randomly and weighed individually. Average

weight and Standard deviation was calculated.

Disintegration Time:

6 tablets are taken and disintegration time was measured by disintegration apparatus. It is phenomenon of tablet breakdown mechanism in which the tablet breakdown into smaller granules is known as disintegration. The time required to disintegrate the tablets is known as disintegration time.

***In vitro* dissolution studies**

Dissolution medium was prepared by dissolving 13.61gm of phosphate dihydrogen phosphate in 800ml water, then adjust with 2M sodium hydroxide to a pH of 7.5 and dissolution is performed using USP type –II apparatus (Disso 2000, Lab India) and details of dissolution is given in **Table 3**. In each dissolution vessel one tablet was dissolved and dissolution is performed as per above parameter of dissolution apparatus. At the end of dissolution time, 20 ml of samples was withdraw sample from the middle portion between the surface and dissolution medium and top of the paddle which NLT 1cm from the vessel wall. Then it was Filtered by 0.45µm membrane filter and diluted with 5ml of standard solution. The samples were analyzed at wavelength of 220 nm using double beam UV-Visible spectrophotometer (Genesis-2,USA). The content of drug was calculated using the equation generated from standard curve. The %cumulative drug release was calculated.

Table 3: Details of Dissolution Instrument

Dissolution Medium	**900 ml of Phosphate buffer pH7.4**
Apparatus	Paddle (USP-II)
Speed	75 RPM
Temperature	37°C ∓ 0.5°C
Time	30 minutes
Withdraw volume	20ml

Assay

During assay first standard stock solution was prepared by accurately weighing of 80.00mg of Valsartan taken in a 100ml volumetric flask and then by adding 60ml of solvent mixture. From standard stock solution 5ml taken and diluted with solvent mixture to make 50ml volume. Filter the solution through 0.45µm-membrane filter and inject it to the chromatogram. Took 20 prepared tablets, weigh it individually and then crossing by mortar and pestle to make into a powder form. Transfer the powder sample containing 40mg of Valsartan into a 100ml volumetric flask, by adding 60ml of solvent mixture and sonicated it for about 45minutes. Dilute solution from 5ml to 50ml with the solvent mixture and filter. Finally the resulting solution filter through a 0.45µm membrane pore size. Then assay can be performed using Chromatographic Technique as per details mentioned in **Table 4**. The test is not valid unless the theoretical plates is not less than 3000, the tailing factor is not more than 2.0 and relative standard deviation for replicate injection is not more than 2.0%. Inject test solution into the chromatogram and record the

chromatogram and measure the response for major peak and the result was calculated.

Table 4: Details of Chromatographic Technique

Column Details	150 mm x 4.0 mm, 5 µm, packed with octadecylsilanae bonded to porous silica [inertsil ODS-3 is suitable]
Detector	UV 298nm
Injection volume	20 µl
Flow rate	1.0ml/min
Buffer preparation	A-Dilute 5.0ml of Trimethylamine to 2000ml with water.
	B-Dissolve 2.72g of potassium dihydrogen phosphate in 1000ml of water, add 2.0ml of trimethylamine and adjust the pH to 2.4±0.05 with ortho-phosphoric acid.
Solvent mixture	A mixture of 80 volumes of buffer preparation A and 20 volumes of methanol.
Mobile phase	A mixture of buffer preparation B and acetonitrile (60:40).

Quality Target Product Profile (QTPP)

It is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. QTPP of Valsartan Tablets shown in **Table 5**.

Table 5: QTPP Elements

QTTPP Elements		**Target**	
Dosage form		Solid	
Dosage design		Tablet	
Route of administration		Oral	
Dosage strength		280mg	
Drug product quality attributes	Physical attributes	White to off white, circular shaped, flat beveled edges uncoated tablet having a break line on one side other side plain.	
	Identification by HPLC	The retention time of major in the chromatogram of the assay preparation correspond to that in the chromatogram of the standard preparation, as obtained in assay.	
	Assay	Valsartan 80mg	95.0% to 105.0% (78.00mg to 82.00mg)
	Average weight	280.0mg ±3% (Limits: 288.40mg to 272mg)	
	Dissolution	Valsartan 80mg	NTL 75% (Q) in 30minutes

Stability Studies

Stability study was carried out to assess the stability of the compression tablet of Valsartan. Stability studies were carried out at accelerated conditions of 40° C and 75% RH. Ten tablets were individually wrapped using aluminum foil and packed in ambered color screw cap bottle and

put at above specified condition in incubator for 3 month. After each month tablet sample was analyzed for the in vitro drug release study. Samples were evaluated for different parameters such as physical appearance, hardness, weight variation, drug content and dissolution.

RESULT:

Drug-Excipients Compatibility Study:

From compatibility study the physical changes as well as the chemical test observed in the formulation of trials and results are shown in **Table 6.**

Table 6: Results of Drug Excipients Compatibility Study

Sl. No.	Ingredients	Appearance of mixture		Result
		Initial day	After 30days	
1	Valsartan	White to off white granular powder	White to off white granular powder	Compatible
2	Microcrystalline cellulose PH 101	White free flowing powder	White free flowing powder	Compatible
3	Mannitol SD 200	White free flowing powder	White free flowing powder	Compatible
4	Crospovidone XL-10	White free flowing powder	White free flowing powder	Compatible
6	Sodium hydroxide	White free flowing powder	White free flowing powder	Compatible
7	Meglumine	White free flowing powder	White free flowing powder	Compatible
8	Magnesium stearate	White free flowing powder	White free flowing powder	Compatible
9	Valsaratn + Microcrystalline cellulose PH 101	White to off white granular free flowing powder	White to off white granular free flowing powder	Compatible
10	Valsaratn + Mannitol SD 200	hite to off white granular free flowing powder	White to off white granular free flowing powder	Compatible
11	Valsaratn + Crospovidone XL-10	hite to off white granular free flowing powder	White to off white granular free flowing powder	Compatible
13	Valsartan + Sodium hydroxide	hite to off white granular free flowing powder	White to off white granular free flowing powder	Compatible
14	Valsartan + Meglumine	hite to off white granular free flowing powder	White to off white granular free flowing powder	Compatible
15	Valsartan + Magnesium stearate	hite to off white granular free flowing powder	White to off white granular free flowing powder	Compatible
16	Placebo	White to off white granular free flowing powder	White to off white granular free flowing powder	Compatible
17	lsartan + Placebo	hite to off white granular free flowing powder	White to off white granular free flowing powder	Compatible

The flow properties of the granules were studied and results is shown in **Table 7**.

Table 7: Characterization of precompression parameters of tablet

Bulk density(gm/ml)	0.1250
Tapped density(gm/ml)	0.222
Carr's index (%)	43.7500
Hausner's ratio	1.7777
LOD/Moisture content (%)	0.24
Granules: Fines Ratio (%)	1: 99

The compressed tablets were subjected to physicochemical characterization and all the ten Formulation batches are evaluated for their thickness, diameter, hardness, weight variation, friability and drug content. The results of physicochemical evaluations of the tablets are shown in the **Table 8.**

Table 8: Physical parameter of compressed tablet

Formulations	**Physical parameter**				
	Average weight (mg)	**rdness (kg/cm^2)**	**Thickness (mm)**	**bility (%)**	**DT (Min: Sec)**
F1	280.0 ±0.12	4.9±0.04	3.80±0.03	0.42±0.042	08:00
F2	279.0±0.72	4.9±0.04	3.72±0.46	0.34±0.036	07:50
F3	282.0±1.12	5.0±0.03	3.50±0.42	0.42±0.42	07:00
F4	281.0±1.12	4.9±0.02	3.47±0.02	0.34±0.036	06:50
F5	280.0±1.12	4.7±0.06	3.79±0.02	0.25±0.021	07:10
F6	280.0±1.93	4.9±0.04	3.77±0.02	0.17±0.020	06:10
F7	280.0± 0.012	4.9±0.04	3.49±0.02	0.49±0.052	06:20
F8	279.0± 0.012	5.0±0.03	3.45±0.02	0.42±0.042	06:00
F9	280.0± 0.012	4.9±0.02	3.48±0.02	0.34±0.036	05:50
F10	281.0± 0.012	5.0±0.03	3.46±0.02	0.42±0.042	05:20

Mean ± SD, n=3

Disintegration Time (DT) of Formulations

All prepared Valsartan formulation batch tablets DT studied by disintegration apparatus and results are shown in fig. 1.

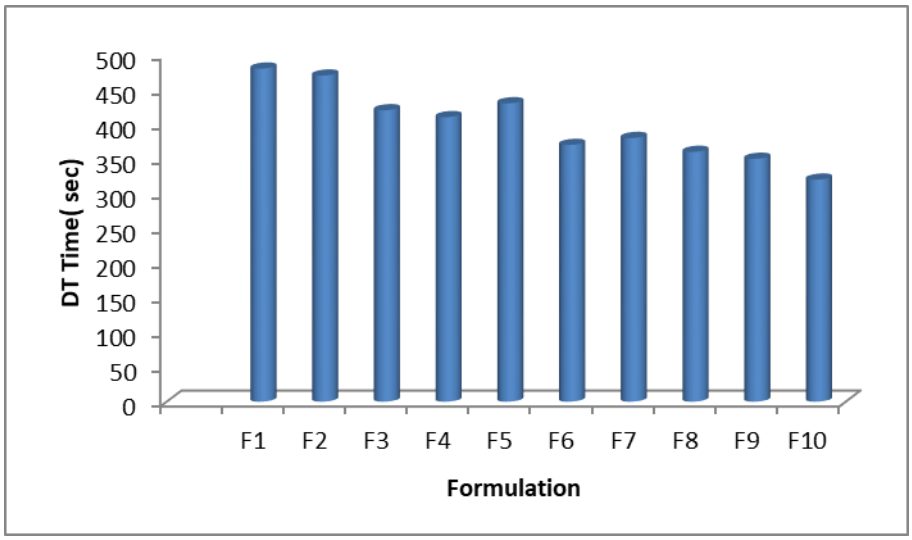

Fig. 1: Details study between Disintegration Time Vs Formulations

Dissolution

In all batches i.e. F1 to F10 alkalizer sodium hydroxide was used in increasing concentration along with meglumine. The incorporation of pH modifiers was attempted due to the fact that the chemical structure of drug Valsartan is pH-dependent so pH modifiers can be used along with Meglumine to increase its solubility leading to an increase in the dissolution rate. The cumulative % drug release of all prepared batches is shown **Table 9** and in **Figure 2**.

Table 9: Dissolution releasing rate of Formulation

Formulation code	**Valsartan releasing rate (%)**
F1	60.23±2.75
F2	67.89±1.96
F3	72.39±1.92
F4	78.54±2.36
F5	82.35±2.13
F6	86.65±2.35
F7	88.86±1.43
F8	92.30±2.13
F9	96.39±1.65
F10	98.89±1.65

Mean ± SD, n=3

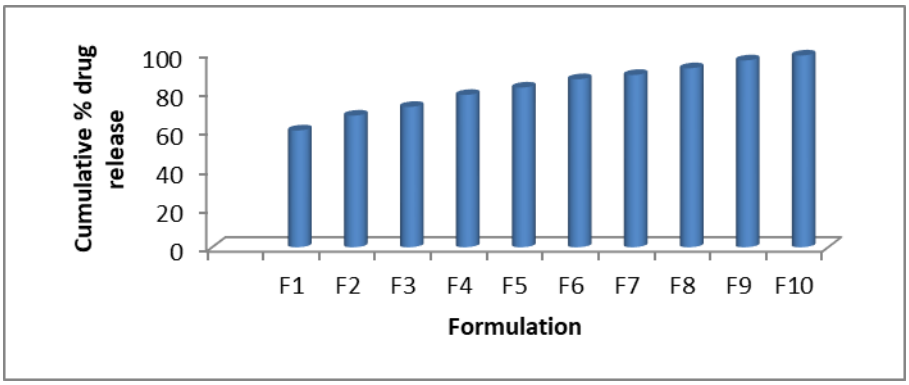

Fig. 2:. Details study between Cumulative % drug releases Vs Formulations

Table 10: Individual sample wave length by UV Spectroscopy

Sample ID	WL296.0
Standard	0.557
Disso_1	0.557
Disso_2	0.563
Disso_3	0.558
Disso_4	0.549
Disso _5	0.557
Disso_6	0.550

Table 11: Dissolution rate releasing of Tablets of F10 Formula by UV

Tablet No	Sample area	% Release
01	0.5570	99.12±1.99
02	0.5630	100.19±0.95
03	0.5580	99.30±1.75
04	0.5490	97.70±1.75
05	0.5570	99.12±0.95
06	0.5500	97.78±1.15

Mean ± SD, n=3

Assay

Percentage of assay of all batches is shown in **table 12** and in **Figure. 3**

Table 12: % of Assay of Valsartan in different formulation

Formulation	**% of Assay of Valsartan**
F1	96.08±1.65
F2	97.56±1.67
F3	98.54±1.19
F4	97.36±1.85
F5	99.89±1.67
F6	96.35±1.82
F7	98.45±1.67
F8	100.48±0.14
F9	99.36±0.14

F10	101.01±0.14

Mean ± SD, n=3

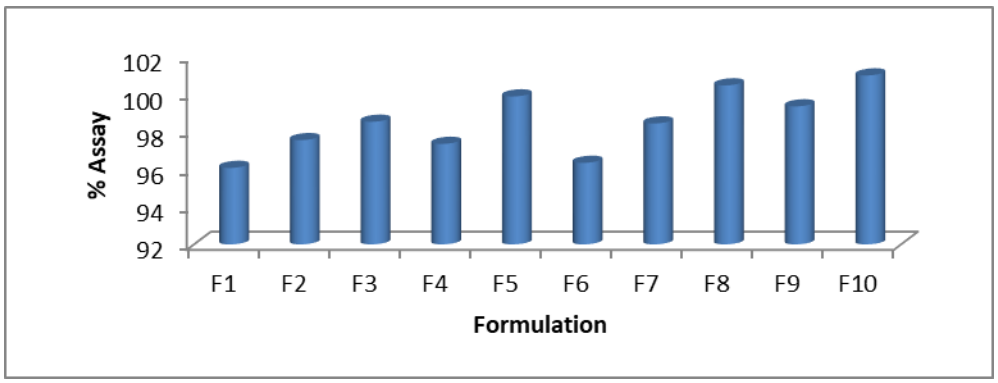

Fig. 3: Details study between percent of Assay value Vs Formulations

Stability studies of Selected Batch F10

A study was carried out to assess the stability of the formulation F10. All the parameters evaluated were within the range and the % cumulative drug release results are given in the **Table 13.**

Table 13: Stability studies of F10 batch Valsartan Tablets

Time (hr)	Days (0)	Days (30)	Days (60)	Days (90)
0.00	0.00	0.00	0.00	0.00
0.5	27.27±1.13	27.89±1.65	27.67±1.39	28.05±2.35
1.0	39.68±2.68	40.24±1.65	40.37±1.26	40.98±1.65
1.5	45.36±1.65	45.96±2.97	44.98±1.98	46.11±2.35
2.0	48.32±0.14	49.00±1.65	49.47±2.66	49.79±2.97
2.5	56.09±2.38	56.23±2.66	56.67±1.65	57.17±2.35
3.0	65.27±2.97	65.88±1.65	65.98±2.4	66.09±2.93
3.5	73.81±1.98	75.65±1.98	75.73±2.66	75.89±1.26
4.0	81.03±2.93	82.32±2.66	82.57±2.35	83.00±1.26
4.5	82.84±2.17	82.98±2.93	82.95±2.35	83.07±1.65
5.0	88.73±1.98	88.87±2.97	88.93±1.26	89.23±1.39
6.0	93.31±2.38	94.21±2.93	94.56±2.97	94.89±2.93
7.0	98.87±1.39	98.73±1.05	98.85±1.19	98.97±1.26

Mean ± SD, n=3

DISCUSSION:

From the Drug excipients compatibility study we observed that in between API and excipients there was not inter change physical changes as well as the chemical test observed in the formulation of trials.

From the flow property it was found all granules show excellent flow property which is helpful for tablet formulation.

All 10 batches of compressed tablets were subjected to physicochemical tests. The hardness was found to be from 4.7 to 5.0 kg/cm² and in all cases friability was less than 1%. Out of all formulations, F10 batch tablets have very less DT time indicating excellent release of drugs in the dissolution media.

The solubility of was dependent on pH and was high in strong acidic or basic

conditions but very low under neutral conditions. Interestingly, incorporating alkalizers from 2mg to 3.5 mg in Valsartan tablets greatly increased drug solubility compared to the addition of acidifiers. For this reason, alkalizers were chosen to be the pH modifiers to increase dissolution rate. The result herein seemed to be correlated with previous studies which show micro environmental pH has a significant impact on stability of compounds which demonstrate pH dependent stability in solution (**Zhao K *et al.*, 2016; Mehtap S *et al.*, 2018; Park JB *et al.*, 2018**). So from the above results we have found F10 is the most suitable batches and six tablets of this batch are randomly selected further to check % drug release and we have found drug release pattern almost equal in all tablets. Individual sample wave length by UV Spectroscopy and drug release pattern of tablets of F10 batch is mentioned in **Table 10** and **11**.

From the assay value it was confirmed all the formulation trials assay value found satisfactory results as per followed monograph.

From the stability study we have found dissolution results were obtained within the range. Hence it is stated that no degradation was observed for about one month after the formulation for selected batch F10.

CONCLUSION

In this research study Valsartan tablet are prepared. The selection and quantity of excipients was drawn up on the basis of the general recommendation for the concentrations of the various excipients from the literature. The drug excipients compatibility study was performed with 1:1 ratio and 10:1 ratio wherever required and the result of this study showed that all the ingredients viz; API and excipients, were compatible with each other. For enhancing the drug solubility, an Alkalizer was incorporated in the formulation. Due to the API's pluffy in nature, wet granulation method was chosen. From the Drug excipients compatibility study we observed that in between API and excipients there was not inter change physical changes as well as the chemical test observed in the formulation of trials. The flow properties of the granules were studied to check different precompression parameters. The physical parameters of different formulation batches shows F10 is the most suitable batch showing better disintegration time and found to have better drug release profile than other formulations. Here NaOH is strong base which can help to dissolve the drug as the drug is soluble in strong base. Meglumine is used as a basic agent who also helps for dissolving the drug so the desired solubility of the formulation can be achieved. Further the tablets were to be studied for stability at various time intervals and climate zone as per ICH guidelines. Valsartan Tablets was prepared using different excipients enhancing the solubility and dissolution rate by addition of an alkalizer and dissolution enhancer respectively.

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Conflict of interest

The authors declare that they have no conflict of interests.

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