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Preparation And Characterization Of Immediate Releasefilm Coated Tablets Of Valsartan -Hydrochlorothiazide (160/12.5mg)

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ABSTRACT

Objective:The motive of the currentworkwas to Preparation and Characterization of Immediate Release film coated tablets Valsartan -Hydrochlorothiazide (160/12.5mg) to reduce the multiple dosing and to achieve more effective reduction of hypertension.

Background:

The oral route is the very effective and favoured method for the introduction of medications to systemic circulation because of ease of diagnosis, patient compliance and flexibility.
Materials and Methods: Valsartan - Hydrochlorothiazide tablet tends to film coated to prevent the drug from degradation. Preliminary studies were performed out with the excipients and the drug and their physical & chemical compatibilities were checked and the drugs and they found compatible.The method of preparation was the wet granulation method.
Results:A maximum of nine formulation batches (f1-f9) have been prepared.Prepared formulations have also been tested for weight variance, friability, disintegration, analysis, in vitro drug release profile.The criteria tested are contained within the guidelines.The parameters tested were found within the limits. Among all formulations, the product of batch f9 has acceptable friability, assay and dissolution profile. It was further e xposed to an advanced stability test at 40±2^{0}C/75±5 per cent RH.

Keywords – Valsartan –Hydrochlorothiazide; Hypertension; Immediaterelease;Film coated Tablets

1. INTRODUCTION

1.1 Hypertension

Hypertension, sometimes referred to as venous hypertension, is an incessant condition in whi ch the venous beat is increased. Blood pressure is shortened by two estimates, systolic and di astolic, depending on either the heart muscle is contracted (systole) or free between pounds (d iastole). This reciprocals the most outrageous and least weight, independently. Commonplace

heartbeat still is inside the extent of 100–140mmHg systolic (top examining) and 60–90mmHg diastolic (base scrutinizing). Hypertension is said to be accessible if it is routinely at or more than 140/90 mmHg(Tripathi et al;2009).Hypertension is assigned either basic (fundamental) hypertension or discretionary hypertension; around 90–95% of cases are requested as "basic hypertension" which infers hypertension with no obvious central therapeutic explanation. The remaining 5–10% of cases (assistant hypertension) are realized by various conditions that impact the kidneys, halls, heart or endocrine system(Fisher et al;2005).

1 .1.1 Antihypertensive medicine

Antihypertensive medications are the types of drugs used to cure hypertension(Magidet al;2011)Studies shows that decrease in the blood pressure in 5 mmHg can reduces the chances of cardiac failure by 34% and ischemic cardiac disease by 21%.(Law et al ;2003).Beginning at 2009, the thiazide becomes the first choice for the treatment of hypertension in most of the prescriptions(Nelsion et al ;2010). While clinical evidence shows that calcium channel blockers and thiazide type diuretics are first line drugs for a large no. Of people ,an ACE inhibitor in United Kingdom for below 55 years of age(Nelson et al;2001).
1.2 Tablet Coating-Tablet covering is the procedure to cover the tablets. All medications have their own trademark, similar to certain medications are severe in taste,some are touchy to light or oxides or has an undesirable smell, some are hygroscopic in nature. It is performed to various reasons.(Palma et al;2002).

1.2.1Coating is performed for the accompanying reasons:
1. Giving controlled, persistent discharge or decrease the recurrence of medication dosing.
2. Keeping up physical or concoction medicate honesty.
3. Upgrading item acknowledgment and appearance.
4. Maintains state of the tablets(Hosny et al;1998).
5.The center contains a substance that is inconsistent with seeing light and subject to climate oxidation, for example by adding a cover to improve trustworthiness(Doorman et al;1980)
.
6. Covering can change the medicine release profile, e.g., enteric covering, osmotic siphon, pulsatile conveyance (Rowe et al;1978).

Drug Profile

VALSARTAN

Structure

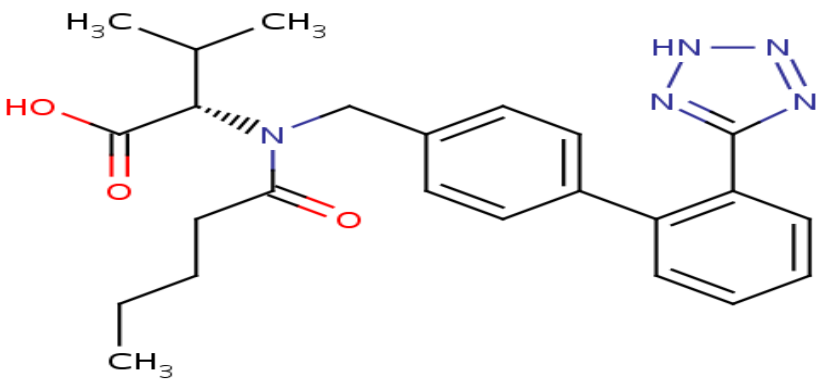

Figure 1 Structure of Valsartan.[http://en.wikipedia.org/wiki/valsartan]

Table1 Physicochemical properties of Valsartan

Thearpeutic category	Antihypertensive
Molecular formula	$C_{24}H_{29}N_5O_3$
Mol. weight	435.519 g/mol
IUPAC name	(S)-3-methyl-2-[N-({4-[2-(2H-1,2,3,4-tetrazol-5yl)phenyl] phenyl}methyl) pentanamido] butanoic acid
Appearance	White to off-white
Solubility	Valsartan is soluble in organic solvents like chloroform ethanol methanol acetone hexane
Melting point (°C)	116-117°C
BCS	Class II drug

Therapeutic Category

Antihypertensive

Pharmacodynamic

It is an angiotensin receptor antagonist which is used in patients suffering from hypertension. Not in any way like the angiotensin receptor rival losartan, Valsartan doesn't have a working metabolite or have uricosuric effects.

Mechanism of Action

Angiotensin II is the prevalent pressor administrator of the renin-angiotensin structure, with impacts including vasoconstriction, prompting of blend and nearness of aldosterone, heart incitation and renal reabsorption of sodium. Thusly, everything thought of it as obtains the beat to common level hypertensive patients.Valsartan, a particular angiotensin II rival, is utilized single or combination with other antihypertensive executives to curehigh blood pressure. Not at all like the angiotensin receptor rival losartan, Valsartan doesn't have a working metabolite or have uricosuric impacts.

Pharmacokinetics

Half-life	6hrs
Protein Binding	95%
Bioavailability	25-50%
Dose	80-320**.**

HYDROCHLOROTHIAZIDE

Structure

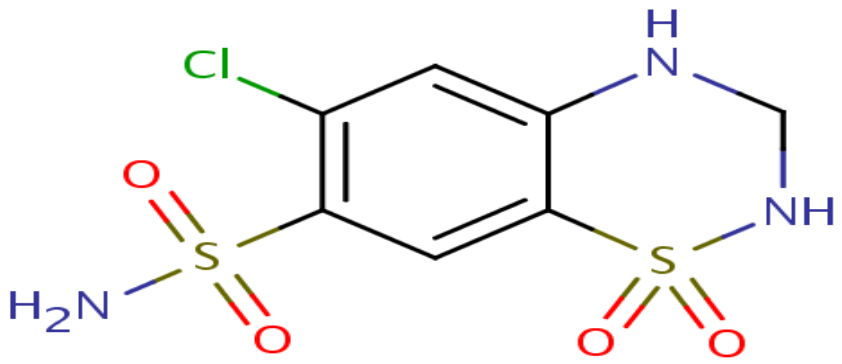

Figure 2 Structure of Hydrochlorothiazide

Table 2 Physicochemical Properties of Hydrochlorothiazide(vidhi et al;2014)

Thearpeutic category	Antihypertensive and thiazide Diuretics

Molecular formula	$C_7H_8ClN_3O_4S_2$
Molecular weight	297.739
IUPAC name	6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
Appearance	White to off white crystalline powder
Solubility	Soluble in organic solvents such as methanol hexane chloroform and also water soluble
Melting point (ºC)	266-269ºC
BCS	Class IV drug

Mechanism of action

The site of movement of thiazide diuretics is essentially in the renal distal tangled tubule. It has been shown that there is a high-prejudice receptor in the renal cortex as the fundamental confining site for the thiazide diuretic movement and restriction of NaCl transport in the distal tangled tubule. The strategy for action of thiazides is through limitation of the $Na+Cl^-$ symporter perhaps by pursuing the Cl^- site, therefore impacting electrolyte reabsorption mechanisms: directly growing sodium and chloride release to an around proportionate degree, and in an indirect route by this diuretic action lessening volume of plasma, with resulting augmentations in plasma rennin development, aldosterone outflow and urinary potassium incident, and a decrease in serum potassium. The renin-aldosterone interface is mediated by angiotensin II, so with co-association of valsartan the decline in serum potassium is less enunciated as observed under monotherapy with hydrochlorothiazide(Tripathi et al;2009).

Pharmacokinetics

Half-life	5.5to 12hrs
Protein Binding	69%
Bioavailability	50-60%
Dose	12.5mg**.**

3. EXPERIMENTAL WORK

2.1 Materials and Equipment

Table 3 Materials and Source

Sr.No	**Name of Material**	**Source**
1	Aerosil	Gujarat Alkalies and Chem Ltd., Gujarat
2	Colors	Morepenlab.Ltd, India
3	Crospovidone	Paracol Corporation

4	Hydrochlorothiazide	Jupiter pharma. Pvt. Ltd.
5	HydroxyPropylMethylCellulose	Loba ChemiePvt. Ltd., Mumbai
6	Isopropyl Alcohol (AR grade)	Loba ChemiePvt. Ltd., Mumbai
7	Lactose Monohydrate	Morepenlab.Ltd, India
8	Maize Starch	Morepenlab.Ltd, India
9	Methylene Dichloride	Morepenlab.Ltd, India
10	Magnesium Stearate	Morepenlab.Ltd, India
11	Microcrystalline Cellulose	Accent Microcell Industries (Ahmedabad)
12	Potassium Dihydrogen Phosphate (AR grade)	Loba ChemiePvt. Ltd., Mumbai
13	Polyethylene Glycol	Morepenlab.Ltd, India
14	Polyvinylpyrrolidone (PVP K30)	Loba ChemiePvt. Ltd., Mumbai
15	Sodium Hydroxide (AR grade)	Loba ChemiePvt. Ltd., Mumbai
16	Sodium Starch Glycolate	Morepenlab.Ltd, India
17	Sodium Lauryl Sulfate	Morepenlab.Ltd, India
18	Talc I. P.	Morepenlab.Ltd, India
19	Valsartan	Dr. Reddy Labs.Pvt. Ltd., Hyderabad

Table 4 Equipments

Sr. no.	**Equipment Name**	**Make**	**Model**
1	Bulk Density Apparatus	Electrolab, Mumbai	ETD 1020
2	Coating machine	Ideal Cures Mumbai	Delux
3	Disintegration Test Apparatus	Electrolab	ED-2AL

4	Electronic Balance	Mettler Toledo	PB 303-s
5	FTIR	Jasco, Japan	MV-4100
6	Hardness tester	Monsanto	HT 02
7	HPLC	Cyberlab, Mumbai	LC-100B
8	Moisture Appartus	Mettler Toledo	HB-43
9	Magnetic Stirrer	Remi , Mumbai	2 MLH
10	Melting Point apparatus	Veego, Mumbai	VMP I
11	pH Meter	Equiptronics	EQ-614
12	Roche Friabilator	Eletrolab, Mumbai	EF-2
13	Sonicator	Biomedica, Mumbai	BMI 599
14	Stability Chamber	Thermolab, Mumbai	TS 200 S
15	Tablet Compression Machine	Cadmach	CD3QR
16	USP Tablet Dissolution Apparatus	Electrolab, Mumbai	TDT 08 L
17	UV-Visible.D.B Spectrophotometer	Jasco, Japan	V-530
18	Vernier caliper	Mitutoyo	Digimatic

3.1 Preformulation Study

Preformulation represents the process of characterizing a drug substance, to learn about its properties and tendencies. Preformulation represents the stage where drug has been profiled to such a degree that we have all the information needed to complete the development process for dosage formulation. Data of information collected and evaluated during preformulationtesting has vital role in designing whole of the process of developing new rational dosage form. The study involves identification of the drug, establishment of analytical methodology and evaluation of physico-chemical properties of the drug (Raza *et al.,* 2015; Bhatia *et al.,* 2013; Sharma *et al.,* 2019). It mainly consists of preliminary preformulation in which molecular physical properties are evaluated and then development profile of API. Preformulation thinks about are pointed on distinguishing the physiochemical properties of medication substances and excipients that may impact the definition plan, technique for assembling and biopharmaceutical properties of the subsequent item. (Manavalan et al;2012)

3.2Characterization of Drug

1) *Organoleptic properties*

Valsartan & Hydrochlorothiazide specimens are tested for colour, smell and appearance

2) *Melting point* **:**The liquefying point gadget was utilized to ascertain the softening purpose of the two medications utilizing the capillary technique(Kadam et al;2007).

3) Quantization of drug

UV scan of Valsartan

UV scan of Valsartan was prepared to know the λ max .Ultraviolet (UV) spectrum of 10 µm/ml solution of the drug in phosphate buffer (pH 6.8) was recorded in the range of wavelength from 200-400 nm using UV spectrophotometer.

UV scan of Hydrochlorothiazide

UV scan of Hydrochlorothiazide was recorded to know the λ max. Ultraviolet (UV) spectrum of 10 µm/ml solution of the drug in phosphate buffer (pH 6.8) was recorded in the range of wavelength from 200-400 nm using UV spectrophotometer.

4) Compatibility study

To Check Drug excipients compatibility study two methods are employed

A) Physical Compatibility Test

The drug and other excipients (1:1) were filled in amber color vials sealed in box cartons, and were stored in different temperature conditions for 15 days, after 15 days samples were observed for physical changes.

B*) Chemical Compatibility Test*

Fourier Transform Infra Red (FTIR) analysis

All prepared samples were subjected to FTIR spectroscopic studies to determine drug-carrier interaction. FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using Fourier Transform IR spectrophotometer. Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 2 cm^{-1}.

5) *Solubility*

For the assurance of dissolvability, excess measure of medication was included the dissolvable (water, 0.1 N HCl, 6.8 pH buffer) at room temperature and kept for 24 hrs with periodic shaking. The supernatant was taken and analysed by utilizing UV twofold shaft spectrophotometer(Mccrea et al;1995).

3.3 Development of UV Analytical Method

Standard Curve of Valsartan in pH 6.8 phosphate buffer

Valsartan (10 mg) was accurately weighed and transferred to 100 ml volumetric flask. It was then dissolved in 6.8 pH phosphate buffer. The volume was made up to 100 ml with 6.8 pH phosphate buffer. The resulting solution was considered as stock solution and further solutions of strengths 10, 20, 30, 40, 50µg/ml were made from the stock solution by appropriate dilution. The above solutions were filtered and analyzed by UV Spectro-photometer at λ_{max} 250 nm. All the dilutions were made using pH 6.8phosphate. Filtered buffer solution was used as a blank during spectrophotometric analysis.

Standard Curve of Hydrochlorothiazide in pH 6.8 phosphate buffer

Hydrochlorothiazide (10 mg) was accurately weighed and transferred to 100 ml volumetric flask. It was then dissolved in 6.8 pH phosphate buffer. The volume was made up to 100 ml with pH 6.8 phosphate buffer. The resulting solution was considered as stock solution and further solutions of strengths 5to25µg/ml were made from the stock solution by appropriate dilution. The above solutions were filtered and analyzed by UV Spectro- photometer at λ_{max} 270nm for hydrochlorothiazide. All the dilutions were made using pH 6.8 phosphate buffer solutions. Filtered buffer solution was used as a blank during spectrophotometric analysis.

Evaluation of granules

a) Bulk density

The term mass thickness (ρb) alludes to a measure used to depict a pressing of particles. The mass thickness of a powder relies on molecule size circulation, molecule shape and the inclination of the particles to cling to each other. It is (gm/ml) and was decide utilizing an equalization and estimating chamber. At first the heaviness of the estimating chamber was tarred. At that point, 4 gm pre sieved (40#) mass medication were filled the estimating chamber utilizing a pipe and gauged (M).

Bulk Density =Weight of powder

———————

Volume of powder

ρb= M

——

Vb

b) Tapped Density

Tapped thickness is the proportion of mass of powder to the tapped volume. The estimating chamber containing a known mass of mix was tapped for a fixed (500) number of taps. The base volume (Vt) involved in the chamber and the weight (M) of the mix was estimated. The tapped thickness (ρt) was determined utilizing following equation.

$$\text{Tapped thickness} = \frac{\text{Weight of powder}}{\text{Tapped Volume of powder}}$$

$$\rho t = \frac{M}{Vt}$$

c) Carr's Index (CI)

Tapped and mass thickness estimations can be utilized to appraise the carr's record of a material. Carr's list was dictated by,

$$CI = \frac{\text{Tapped thickness} - \text{mass thickness}}{\text{Tapped thickness}} \times 100$$

Compressibility record can be a proportion of the potential quality that a powder could develop in its curve in a container and furthermore the straightforwardness with which such a curve could be broken. It is in a roundabout way identified with the relative stream rate, cohesiveness and molecule size. It is basic, quick and well known strategy for anticipating stream qualities.

Table 5 Grading of the powders for their stream properties as indicated by Carr's Index.

Sr.No.	**Solidification Index (Carr %)**	**Stream**
i.	5-15	Brilliant
ii.	12-16	Great
iii.	18-21	Reasonable for Passable
iv.	23-35	Poor
v.	33-38	Poor
vi.	>40	Incredibly poor

d) Angle of repose

AR(α) was resolved using the technique of the channel. The solution was pumped through a pipe that could be lifted upward until the most intense cone stature (h) was achieved. The length of theα = tan -1 (h/r)

Tab. 6 Relationship between edges of rest and stream properties.

Sr.No.	Edge of rest (degrees)	Flow
I	< 25	Excellent
ii.	25-30	Good
iii.	30-40	Passable
iv.	>40	Very poor

The lower the edge of rest, better the stream property. Unpleasant and unpredictable surface of particles gives higher edge of rest.

e) Hausner ratio

Hausner's ratio is a record of simplicity of powder stream; it is determined by following equation.Hausner ratio = $\frac{\text{Tapped density}}{\text{Bulk density}} = \frac{\rho t}{\rho b}$

f)Moisturecontent

The dampness substance of the granules was resolved thermo gravimetrically. An example weighing roughly 5 g was spread onto an aluminum dish and was put in the analyzer. The example was warmed to 1000C and evaporative dampness misfortunes were recorded and naturally revealed as percent dampness content.(Palma et al;2002).

3.4 Formulation of Film Coated Tablet:

To Formulate a quality Tablet in a validated and cGMP way. It is important that the selected process is capable of-

- Avoid capping and separation of tablet in two or more layers.

- Providing sufficient hardness.
- To produce high yield.
- To film coat the tablet to mask the bitter taste of tablet. .(Wilson et al;1997)

Manufacturing Process

Manufactured by using wet granulation method.

Procedure:

a) Sifting

Shift the Valsartan, microcrystalline cellulose lactose monohydrate and Crospovidone using 30# sieve.

b) Paste Preparation

Dissolve maize starch in 50 ml purified water. Boil water in paste kettle and dissolve the pvpk30 in boiling water. Then add solely the slurry of starch into boiling pvp-k30 solution.

c) Granulation

Dry mix the Valsartan , microcrystalline cellulose, lactose monohydrate and Crospovidone for 5 minutes. Add slowly the paste to dry mixed granules. Run the impeller for getting the proper granules .Add additional water if required. Check for the end point by checking the ampere load of granulator.

d) Drying

Firstly airdry the wet mass for 5 minutes, rack the material. Then dry the granules to get the LOD below 3%w/w.

e) Sizing

Sift the dried granules through 40# sieve and size the oversize granules using 2.0mm screen.

f) Blending and Lubrication

Load the sized granules into blender, add Hydrochlorothiazide, Dried maize starch,Sodium starch glycolate, Crospovidone , Aerosil, Talcum and MCC ph102.Then run the blender for 15 minutes at 11 rpm.Then add Magnesium stearate into blender and run the blender for 5 minutes.

g) Compression

After the lubrication was done we go for the compression of the tablets.The compression of the tablets were done by using tablet compression machine. (Tobiska et al;2003)

f) Coating

When the Tablets were prepared after that we prepared the coating solution according to the batch size and go for film coating.(Palma et al;2002).

Flow chart for Wet Granulation

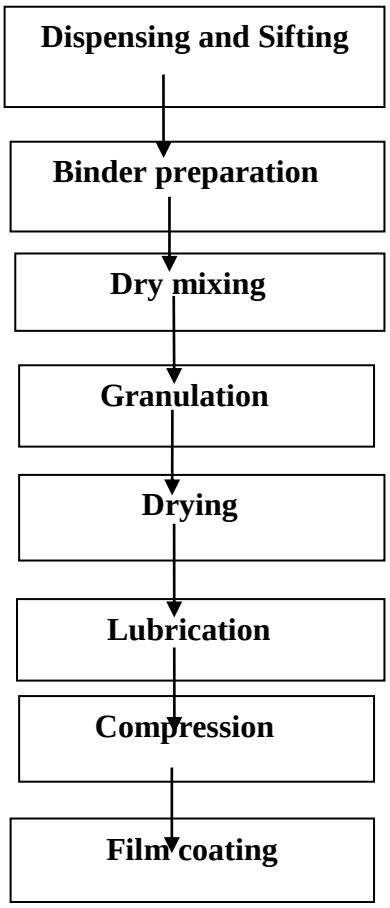

Figure 3 flow chart of wet granulation

Formulation

Table 7 List of formulation

Ingredients	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F -7**	**F-8**	**F-9**
Valsartan	160	160	160	160	160	160	160	160	160
Hydrochlorothiazide	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.75	12.75
MCC Plain	15	71.5	30	25	30	65	30	43	43
Lactose Monohydrate	45	_	30.5	40.5	45	_	35.5	18	18
CrosPovidone	15	40	15	15	15	15	15	26	26
SLS	3		5	5	5	3	5	4.5	4.5
PVP k 30	-	-	-	-	-	-	-	5	5

M. Strach(P)	_	_	_	_	_	7	-	4	4
P.Water	Q.s	-	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Aerosil	3	3	3	3	3	3	3	4	4
Dried M.Strach	15		15	14	10	20	10	12	12
SSG	13		13	13.7	13	_	13	10	10
Cross Povidone	10	_	10	10	10	20	10	15	15
Mg. Sterate	4	9	4	4	4	2.5	4	3	3
Talc	2	_	2	2	2	2	2	3	3

Table 8 Coating formula

Sr. No.	**Ingredients**	**Quantity(in gm)**
1	HPMC 5cps	3.0
2	PEG-400	0.8
3	Red oxide of iron	0.55
4	Iron oxide yellow	0.50
5	Titanium dioxide	0.95
6	Talc	0.70
7	I.P.A	100 ml
8	MDC	160 ml

4 RESULTS AND DISCUSSION

4.1 Preformulation study

1) Organoleptic properties

Table 9 Organoleptic properties of Valsartan Hydrochlorothiazide

Organoleptic Properties	**Valsartan**		**Hydrochlorothiazide**
	Observed	**Reported**	**Reported**
Color	White	White	White

Odour	Odourless	Odourless	Odourless
Description	Crystalline powder	Crystalline powder	Crystalline powder

The drugs obtained were checked for Organoleptic properties and it was found that the organoleptic properties of obtained Valsartan hydrochlorothiazide drug were same.

2) Melting Point

Table 10 M.P of Valsartan Hydrochlorothiazide

	Melting Point	
	Observed	**Reported**
Valsartan	116-117^{0}C	116-117^{0}C

Table 11M.P of Hydrochlorothiazide

	Melting Point	
	Observed	**Reported**
Hydrochlorothiazide	`269-271^{0}C	268-270^{0}C

The drugs were checked for its melting point and it was found that there were no significant difference in melting point of obtained Valsartan Hydrochlorothiazide drug and that of reported.

3) *Determination of* λ_{max}Valsartan standard solution was scanned (λmax) was found to be 250 nm in 6.8 pH phosphate buffer.

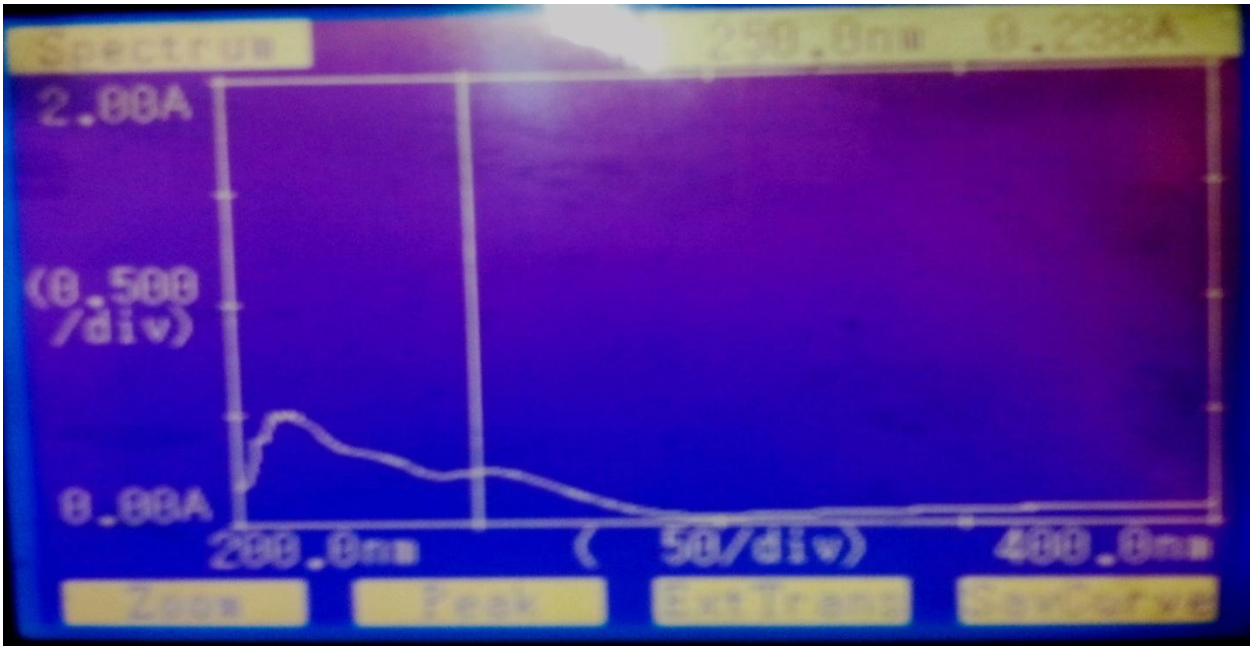

Figure 4 UV scan of Valsartan

λ_{max} of Hydrochlorothiazide

The standard solution of Hydrochlorothiazide was scanned **λ_{max}**. Maximum absorbance wavel ength was reported at 270 nm.

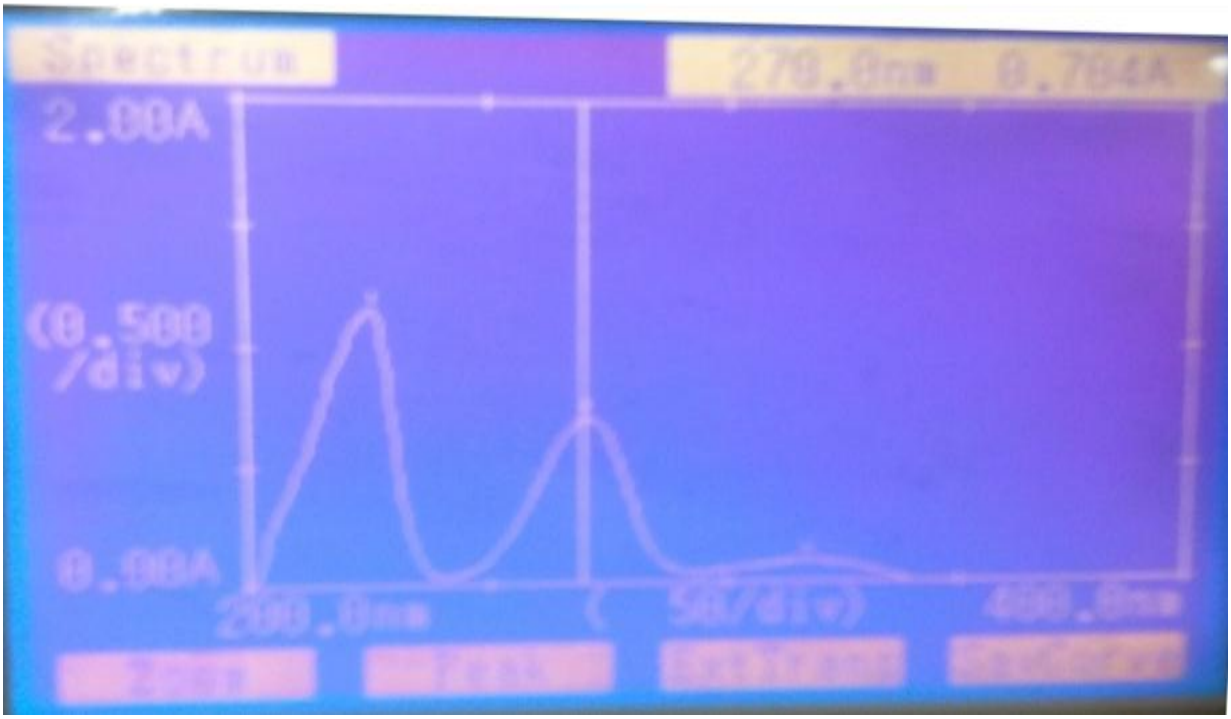

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Figure 5 UV scan of Hydrochlorothiazide

4. Compatibility study

a) Physical Compatibility

Following 15 days of processing at room temperature, no physical changes are found in the mixture of Valsartan Hydrochlorothiazide and excipients.

b)Chemical Compatibility

IR (FTIR) analysis

Drug-Excipients Compatibility tests The IR spectrum of different drug-excipient mixtures has shown that there is no drug-excipient interaction. There was therefore no contact between the medication and the excipients. So, the functionality of drug excipients was established.

FTIR spectroscopy of Valsartan

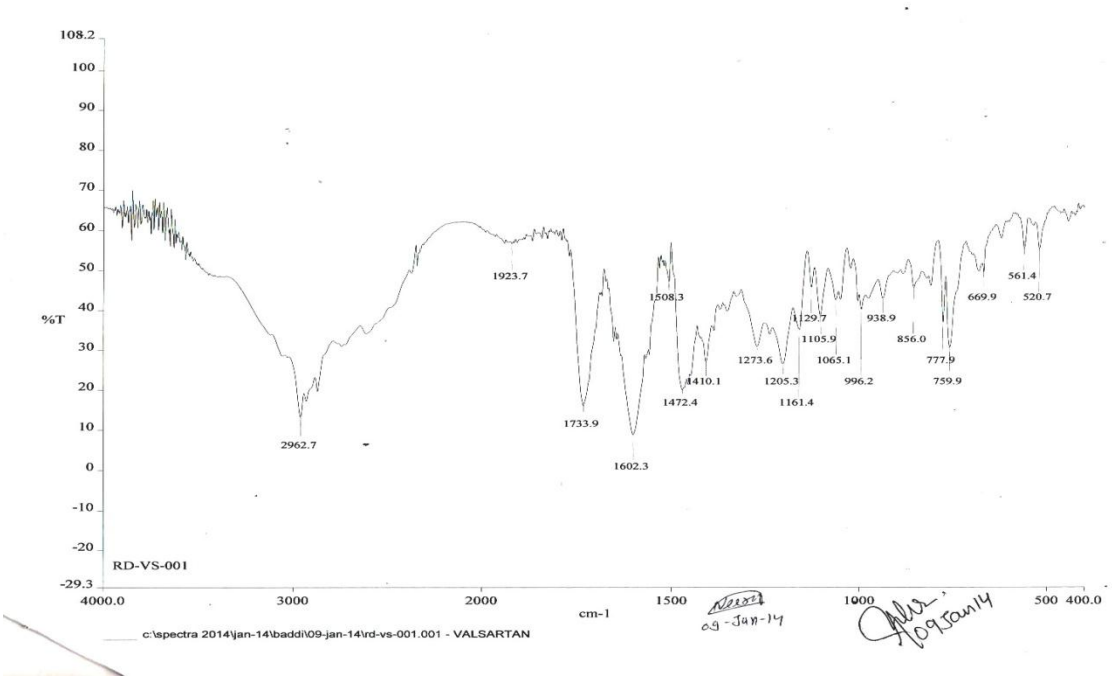


Figure 6 IR spectrum of Valsartan

Drug was characterized by FTIR spectroscopy. The spectrum was recorded using FTIR spectrophotometer (Jasco V530). The scanning range was 4000 to 400 cm $^{-1}$.

Table 12

Interpretation in FTIR spectrum of Valsartan

Remarks	**Peak (Wave number) cm^{-1} (Observed)**	**Peak (Wave number) cm^{-1} (Standard)**
Carboxyl carbonyl stretching	1710-1720	1700-1720
Amide carbonyl stretching	1600-1620	1600-1620
C-H bending	1460-1470	1460-1480

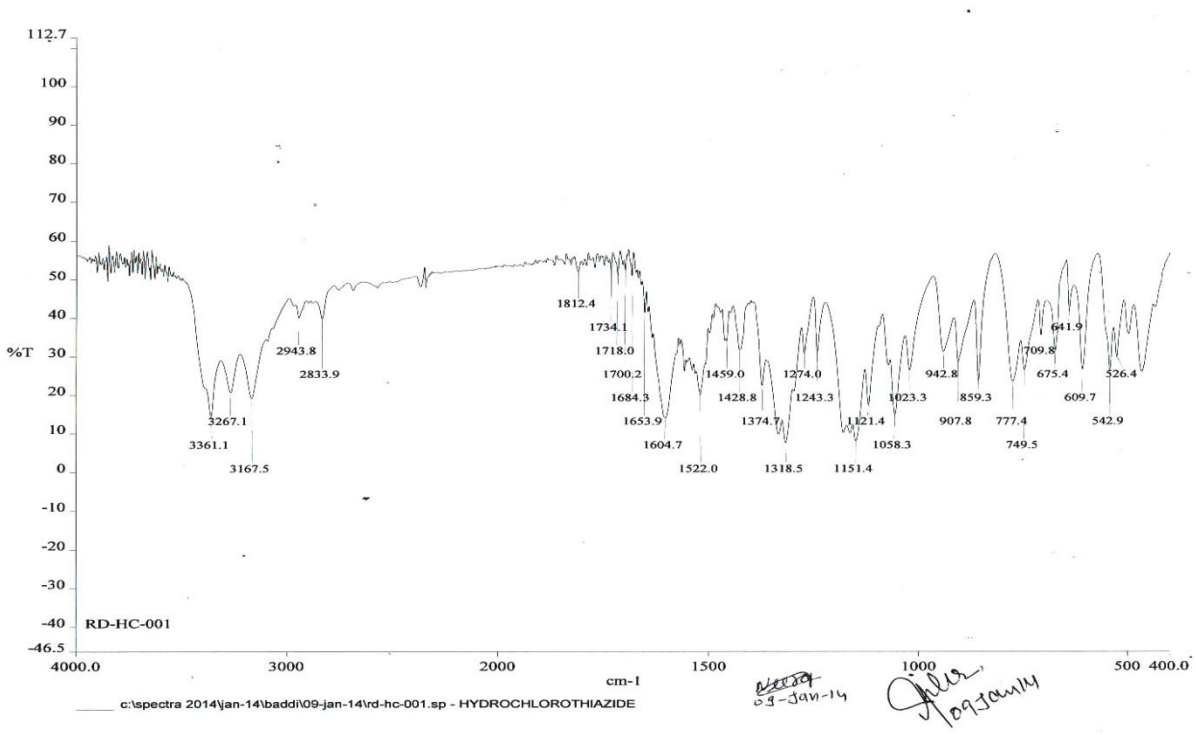


Figure 7 FTIR spectroscopy of Hydrochlorothiazide

Table 13

Interpretation in FTIR spectrum of Hydrochlorothiazide

Remarks	**Peak (Wave number) cm^{-1} (Observed)**	**Peak (Wave number) cm^{-1} (Standard)**
Carboxyl carbonyl stretching	1710-1720	1700-1720
Amide carbonyl stretching	1600-1620	1600-1620
C-H stretch	2833.5-2943.8	2700-3300
O-H bending	1243-1520	1200-1500

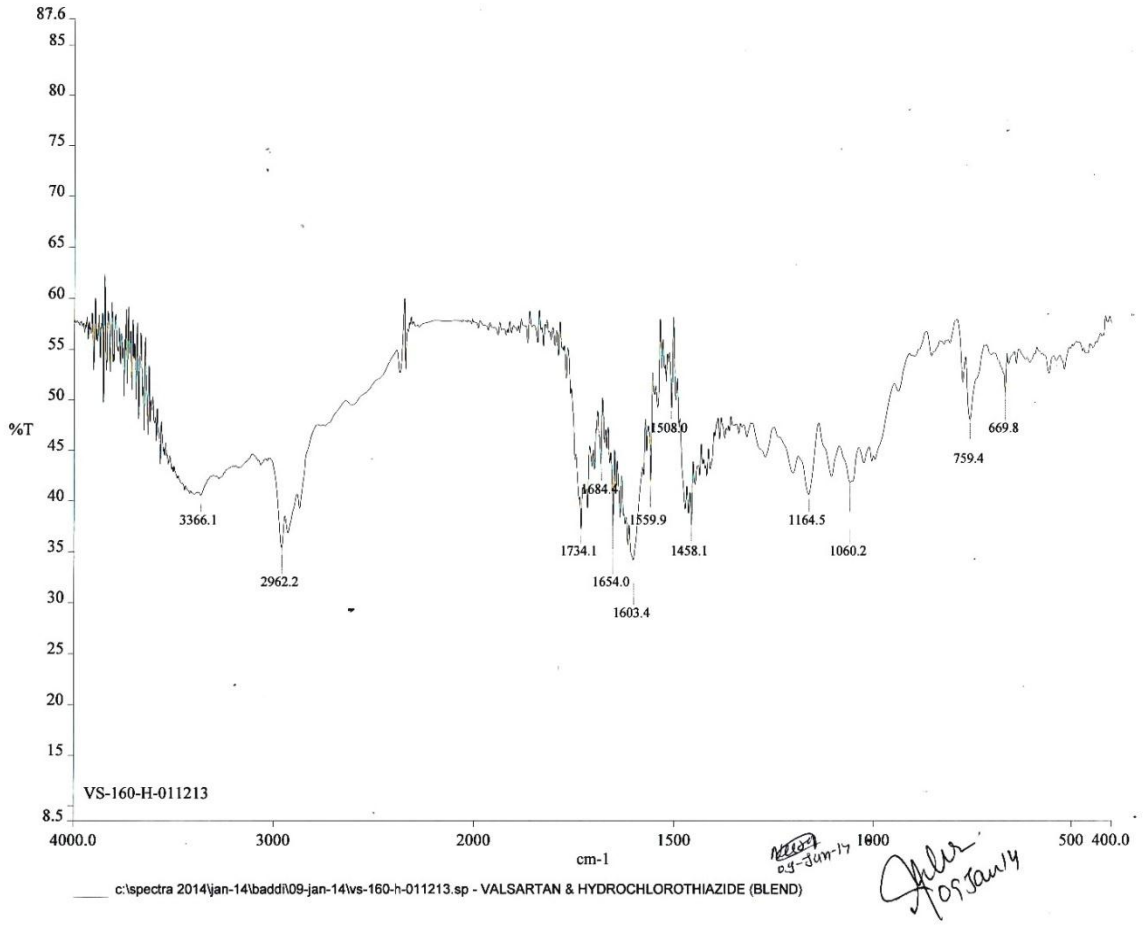


Figure 8 FTIR spectroscopy of Valsartan &Hydrochlorothiazide Blend.

Table 14
Interpretation in FTIR spectrum of Valsartan Hydrochlorothiazide Blend**.**

Remarks	**Peak (Wave number) cm^{-1} (Observed)**	**Peak (Wave number) cm^{-1} (Standard)**
Carboxyl carbonyl stretching	1710-1720	1700-1720
Amide carbonyl stretching	1600-1620	1600-1620
C-H stretch	2833.5-2943.8	2700-3300
O-H bending	1243-1520	1200-1500

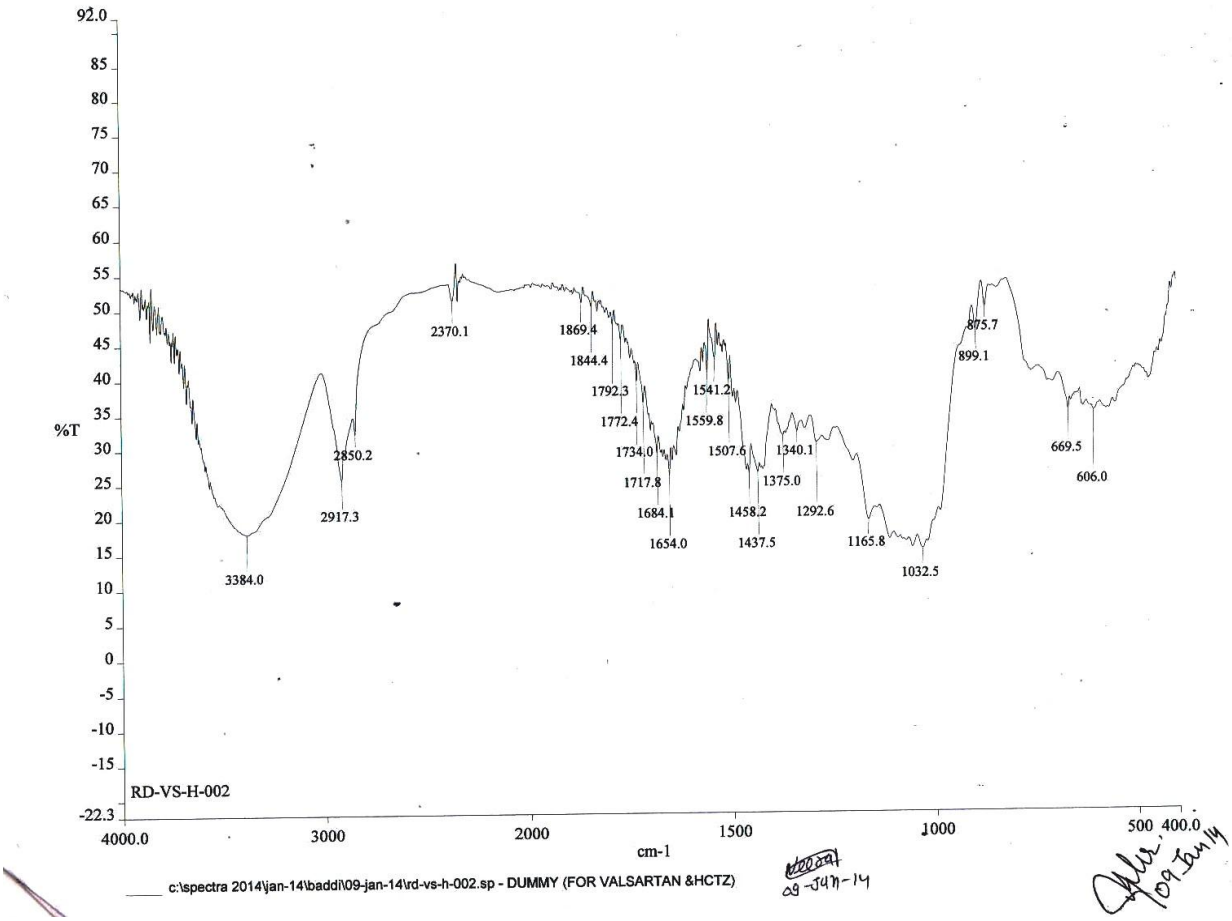


Figure 9 FTIR spectroscopy of Valsartan &Hydrochlorothiazide Dummy.

Table 15

Interpretation in FTIR spectrum of Hydrochlorothiazide dummy.

Remarks	**Peak (Wave number) cm^{-1} (Observed)**	**Peak (Wave number) cm^{-1} (Standard)**
Carboxyl carbonyl stretching	1710-1720	1700-1720
Amide carbonyl stretching	1600-1620	1600-1620
C-H stretch	2833.5-2943.8	2700-3300
C=O	3300-3600	3300-3600
O-H bending	1243-1520	1200-1500
N-H	700-900	700-900

Given IR ranges of different medication excipients blends demonstrated that there is no cooperation among tranquilize and excipients. The noticeable pinnacles of the medication

appeared in Table were not influenced. In this way, no collaboration was seen between the medication and excipients. Along these lines, sedate excipients similarity was built up.

5) Solubility study

From the consequences of dissolvability study it was seen that, Valsartan has extremely low solvency in water and 0.1 N HCl, yet high solvency in 6.8 pH phosphate buffer. Because of high dissolvability of medication in 6.8 pH phosphate buffer, further analytical studies were conducted in this solvent and the solubility study of hydrochlorothiazide.

Table 16 Solubility data in different solvents

Solvent	**Valsartan**	**Hydrochlorothiazide**
Water	0.89 mg/ml (Practically insoluble)	733 mg/ml
0.1 N HCl	3.17 mg/ml (Slightly soluble)	3.87 mg/ml
pH 6.8Phosphate buffer	268.97 mg/ml (Freely soluble)	288.97 mg/ml (Freely soluble)

4.2 Development of Analytical Method

Valsartan

The linear relationship for Valsartan between concentration and absorbance was in range of 10 to 50 μg/ml for 6.8 pH phosphate buffer at 250 nm.

Table 17

Standard Curve of Valsartan in 6.8 pH phosphate buffer

Sr.no.	**Conc.(mcg/ml)**	**Absorbance**
1	0	0
2	10	0.229
3	20	0.381
4	30	0.480
5	40	0.664

6	50	0.754

Calibration curve in pH6.8 Phosphate buffer

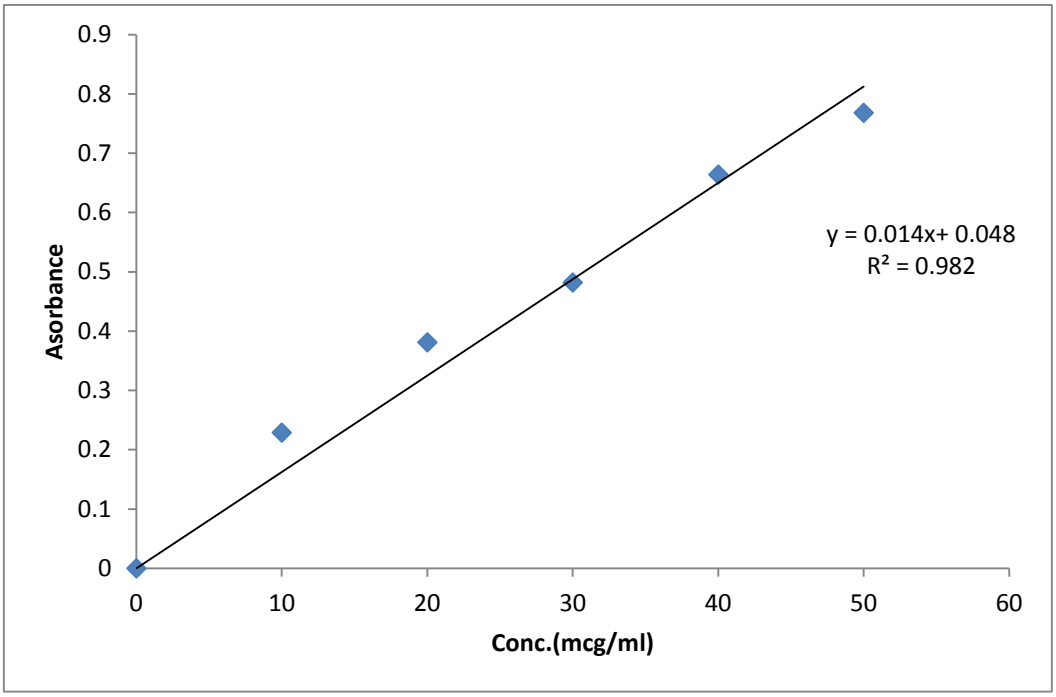


Figure 10 Standard curve of Valsartan in 6.8 pH phosphate buffer.

Table 18 Characteristic of calibration curve of Valsartan

Sr. No.	**Parameters**	**Values**
i.	Correlation coefficient (r^2)	0.982
ii.	Slope	0.014
iii.	Intercept	0.048
iv.	Equation	y= 0.014x + 0.048

b)Hydrochlorothiazide

The linear relationship for Hydrochlorothiazide between concentration and absorbance was found 5 to 25 µg/ml in phosphate buffer of pH6.8. All the dilutions were made in phosphate buffer.

Table 19Standard Curve of Hydrochlorothiazide in 6.8 pH phosphate buffer

Sr. No.	**Conc.(mcg/ml)**	**Absorbance**

1	0	0
2	5	0.195
3	10	0.354
4	15	0.560
5	20	0.684
6	25	0.874

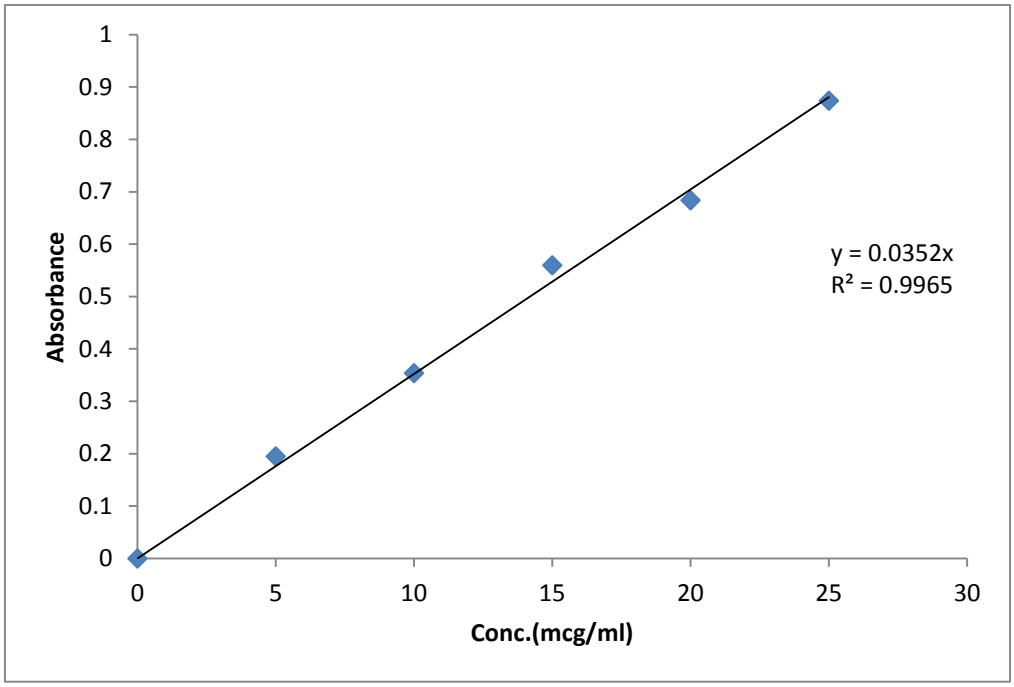


Figure 11Standard curve of Hydrochlorothiazide in Phosphate buffer.

Table 20Characteristic of calibration curve of Hydrochlorothiazide

Sr. No.	**Parameters**	**Values**
i.	Correlation coefficient (r^2)	0.9965
ii.	Slope	0.0352
iii.	Intercept	0.0096
iv	Equation	y= 0.0352x + 0.0096

4.3 Evaluation of granules

Table 21 Pre compression parameters

Formulations	**Bulk Density**	**Tapped Density**	**Hausner's Ratio**	**Angle of Repose**	**Loss on Drying**	**Carr's Index**
F1	0.417±0.02	0.4830±0.02	1.17±0.01	32.18±0.19	1.89%±0.27	14.54±0.13
F2	0.397±0.04	0.4870±0.09	1.25±0.03	38.9±0.27	2.07%±0.45	21.5±0.25
F3	0.418±0.03	0.4790±0.04	1.14±0.02	34.42±0.23	1.68%±0.34	12.56±0.14
F4	0.438±0.03	0.4971±0.04	1.13±0.02	31.37±0.24	1.98%±0.32	11.72±0.12
F5	0.427±0.04	0.4907±0.03	1.14±0.02	32.29±0.22	1.17%±0.32	12.92±0.14
F6	0.423±0.02	0.4842±0.02	1.14±0.03	31.19±0.18	1.85%±0.32	12.59±0.13
F7	0.418±0.03	0.495±0.02	1.14±0.03	31.24±0.14	1.90%±0.32	16.32±0.14
F8	0.41±0.01	0.475±0.04	1.13±0.01	31.29±0.12	1.95%±0.28	12.76±0.09
F9	**0.429**±0.01	**0.489**±0.02	**1.14**±0.01	**31.40**±0.12	**1.80%**±0.23	**12.50**±0.06

The micrometrics study of the granules was performed and all the parameters were calculated. The bulk density of different formulation was found to be 0.39 to0.45 range and the CI in the range of 1.1 to 1.24 range, HR was found 1to2.3%. The AR was found in the range of 30 to 34.The CI index was found in 11to 21.

Bulk Density

The bulk density of different granules were studied and all the parameters was found within range. Among all formulation the f9 shows very good result .The bulk density of f9 was found to be 0.429±0.01.

Tapped Density

The test of tapped density was performed for all formulation. The f9 formulation shows the best result .

Hausner's ratio (HR). The values of Hausner's ratio shows the excellent flow properties. The formulaton F9 shows the HR 1.14±0.1.which came in the range of good flow properties.

*Angle of repose (AR***)** of granules has showed good results. This test was performed for all formulation.

Carr's Index (CI)

The CI of all formulations was studied and found in the range of 12-16. They posses good flow properties.

Loss on drying (LD): The LOD was found to be less than 2 % which shows that they absorb less moisture from atmosphere. The best formulation shows 1.8%.

Friability test (FT): Pellet formulations achieved friability values less than 1% as per USP limit for tablets. Thus all tablets passed the USP friability test expect f2 formulation. The f9 formulation shows almost nill friability. It means the formulation can withstand strain and stress during handling.

Evaluation of Tablets

Table 22
Post compression parameters

Formulation	**Weight (mg)**	**Diameter (mm)**	**Thickness (mm)**	**Disintegration Time (NMT--Min)**	**Friability (%)**	**Hardness (NLT kg/cm^2)**
F1	300±0.3	9.8±0.03	3.9±0.29	8±0.25	0.19±0.23	4±0.4
F2	300±0.5	9.8±0.14	3.9±0.31	15±0.85	1.5 ±0.43	4±0.5
F3	300±0.4	9.8±0.10	3.9±0.25	4±0.24	0.11±0.21	4±0.3
F4	305±0.4	9.8±0.02	3.9±0.31	6±0.34	0.67±0.19	4±0.4
F5	310±0.45	9.8±0.14	3.9±0.29	8±0.40	0.54±0.42	4±0.3
F6	310±0.43	9.8±0.15	3.9±0.28	9±0.54	0.41±0.32	4±0.2
F7	300±0.36	9.8±0.13	3.9±0.27	6±0.43	0.24±0.34	4±0.3
F8	320±0.3	1.5x6.4±0.02	4.5±0.21	3.5±0.24	0.18±0.12	4±0.1
F9	**320±0.3**	**1.5x6.4±0.02**	**4.5±0.2**	**2.45±0.14**	**0.15±0.11**	**4±0.1**

The evaluation parameters of the different formulation was checked out . The formulation made by DC method shows capping and friability problems and when we increases hardness then it does not give the satisfactory D.T result so we give preference to wet granulation method the post compression parameters of all others formulation were calculated. Among all formulations result the result of f8 &f9 were good but f9 results were better(Ozakan et al;2001).

Table 23
Post Coating Tablet Parameter

Formulation	**Weight**	**Diameter (mm)**	**Thickness (mm)**	**D.T (Min)**
F1	306±0.52	9.85±0.2	4.2±0.2	10±0.58
F3	305±0.68	9.89±0.4	4.2±0.2	8±0.56
F4	315±0.65	9.91±0.3	4.0±0.2	9±0.32
F5	320±0.86	9.84±0.3	4.3±0.4	9±0.34
F6	320±0.74	9.85±0.3	4.3±0.3	8±0.24
F7	308±0.65	9.90±0.4	4.2±0.3	7±.32
F8	328±0.45	1.5x6.4±0.2	4.5±0.1	5.10±0.15

F9	329±0.51	1.5x6.4±0.2	4.5±0.1	4.50±0.10

Tablet weight variance Check

Of each set, 20 tablets were randomly selected and their average weight was determined. It can be contained within the boundaries. The method indicates variation in weight within limits.

Hardness Test

For the testing of the hardness of the prepared formulations Monsanto hardness tester was used .All the formulation shows good tensile strength so they can withstand different conditions.

Friability

The friability studies was carried out for the different formulation by using the Roche appartus . In this tablets allowed for 100 rotation and the weights of the tablets were calculated before and after test .The f2 formulation shows friability hence no further trial carried with this formulation. Others formulation also shows good results .F8 and f9 formulation having almost nil friability**.**

Assay

The assay of the F1-F9 Preparation of the Valsartan Hydrochlorothiazide was carried out to check the% drug quantity. The amount of%age purity of the drug was determined.The assay of the different formulation was in the range.The f9 formulation release the good drug amount. (chowdhary et al;2014)

Table 24Assay of Different formulations

FORMULATION	**VALSARTAN (%drug quantity)**	**HYDROCHLOROTHIAZIDE (% drug quantity)**
F1	93.5±0.45	96±0.45
F3	96.4±0.24	92±0.42
F4	92.4±0.42	94±0.42
F5	94.5±0.43	96.5±0.41
F6	93.2±0.41	95.2±0.45
F7	95±0.41	96.7±0.43
F8	99.3±0.5	97.82±0.42

F9	**104.16±0.5**	**98.82±0.45**

Form the above assay result the formulation f9 shows the best assay of both drugs Valsartan and Hydrochlorothiazide .which match with the innovator .so the f9 is the best formulation and it transfer further to the stability study.

In-Vitro Dissolution of Valsartan & Hydrochlorothiazide **.**

In-Vitro testing were done by utilizing USP (TDT 06L) Type II (paddle type) disintegration test mechanical assembly at 50 rpm utilizing pH 6.8 phosphate buffer as dissolution media kept up at the temperature of 37±0.5^{o} C. Tests were pulled back at explicit time interims and supplanted with new media and sifted. The measure of medication broke down was controlled by spectrophotometrically at 250 nm and 270 nm respectively. The experiments were conducted in triplicate.(Seitz et al;1991).

Table 25

In vitro release profile of Valsartan

Time (Min)	**% Drug Release**							
	F1	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0
10	69.4±0.89	73.58±0.78	68.17±0.85	72.50±0.65	76.5±0.65	72.5±0.65	74.4±0.56	75.0±0.04
20	75.69±0.7	80.45±0.94	77.12±0.84	86.1±0.3	84.67±0.56	85.6±0.45	86.9±0.45	89.5±0.34
30	85.93±0.7	88.5±0.78	86.17±0.72	95.6±0.5	95.6±0.98	95.9±0.65	98.4±0.65	102.68±0.32

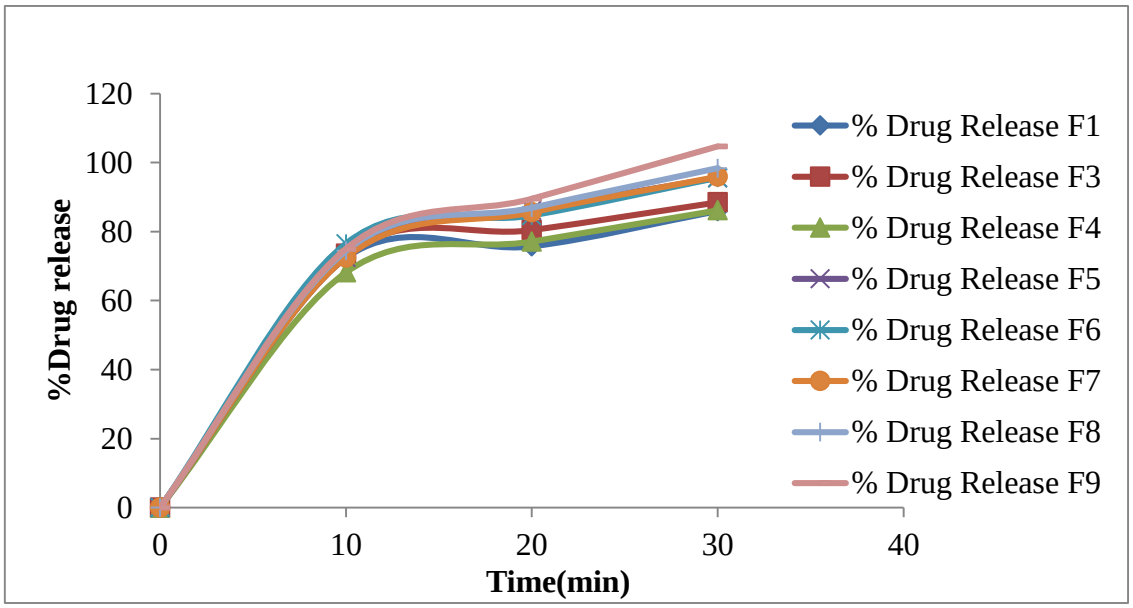


Figure 12 *In vitro* release of Valsartan f1-f9

Table 26*In vitro* release of Hydrochlorothiazide

Time (Min)	% Drug Release							
	F1	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0
10	72.4±0.45	68.4±0.65	65±0.67	72.50±0.56	73.5±0.65	70.5±0.54	77.4±0.54	79.4±0.52
20	78.69±0.56	76.45±0.56	77.12±0.49	84.1±0.54	84.67±0.64	86±0.53	88.4±0.52	89.6±0.51
30	85.93±0.45	84.5±0.54	88.4±0.57	93.8±0.53	92.2±0.56	95.8±0.45	98.4±0.51	99.6±0.49

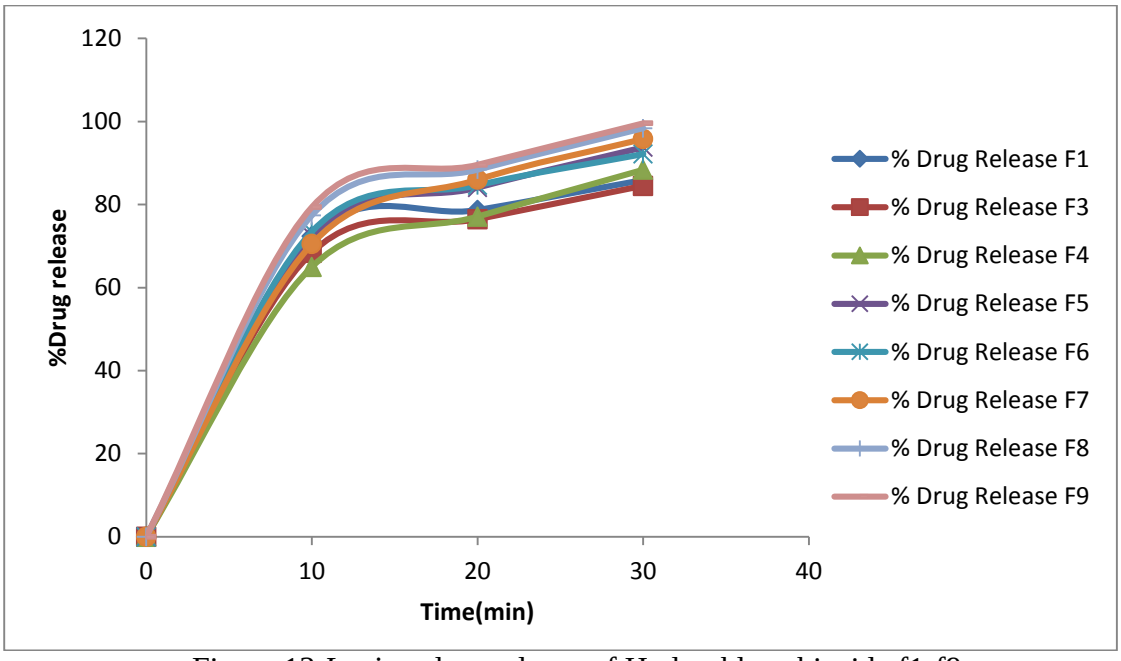


Figure 13 *In vitro* drug release of Hydrochlorothiazide f1-f9

The dissolution studies of different formulation made by wet granulation carried out .For the immediate release dosages form it should release the NLT 85% within the 30 minutes. From the *In vitro* dissolution result of different formulation the result of f9 formulation was very good which matches the marketed formulation result**.**

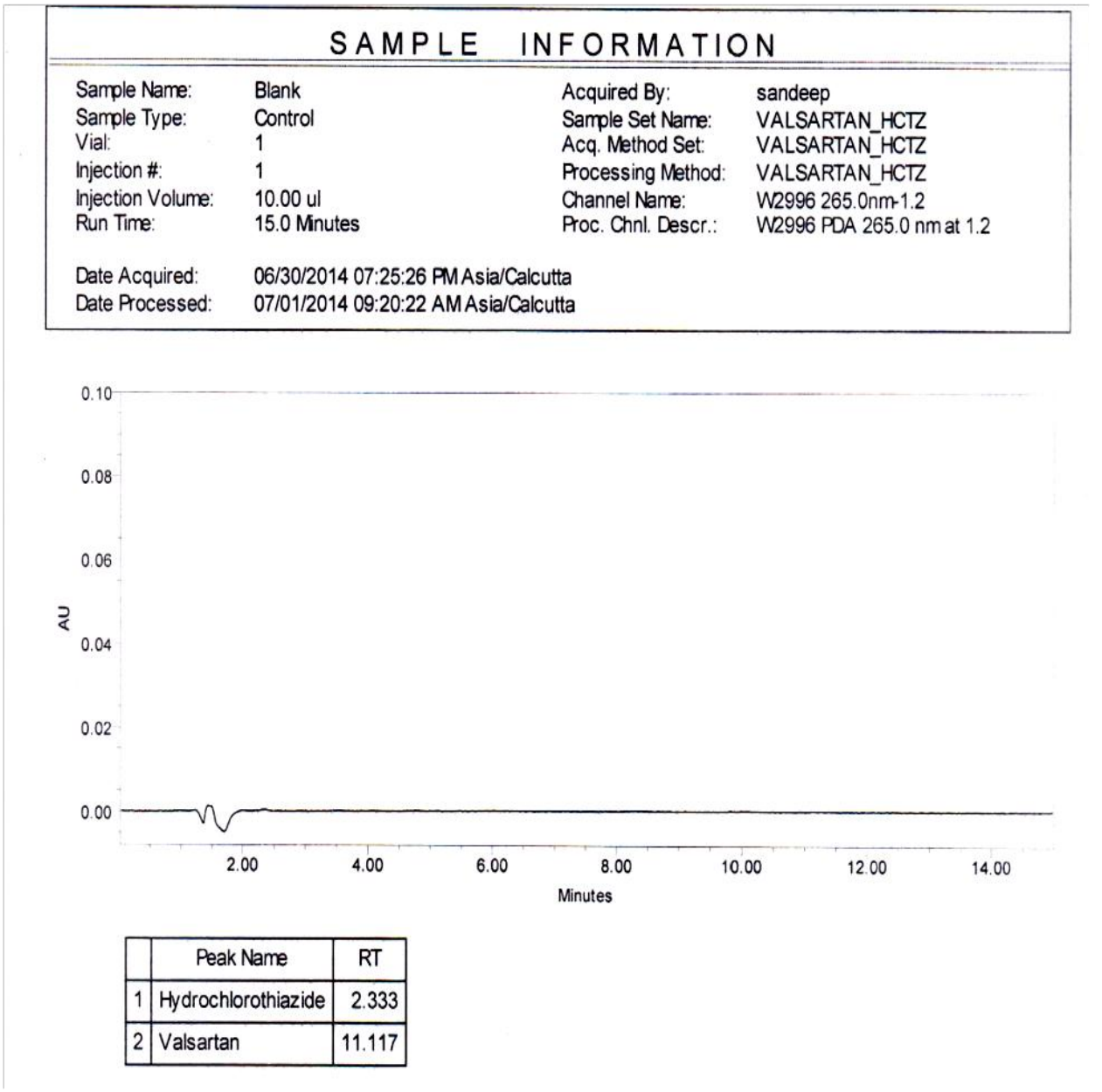
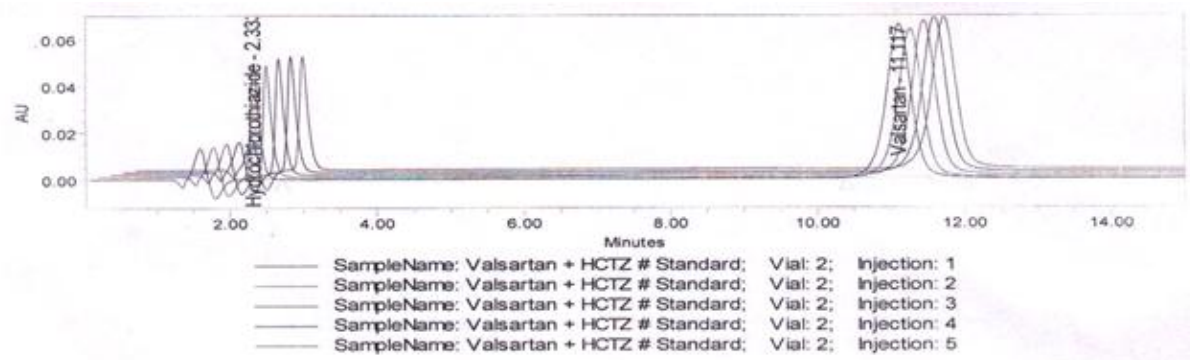


Figure 14 Blank for Valsartan hydrochlorothiazide



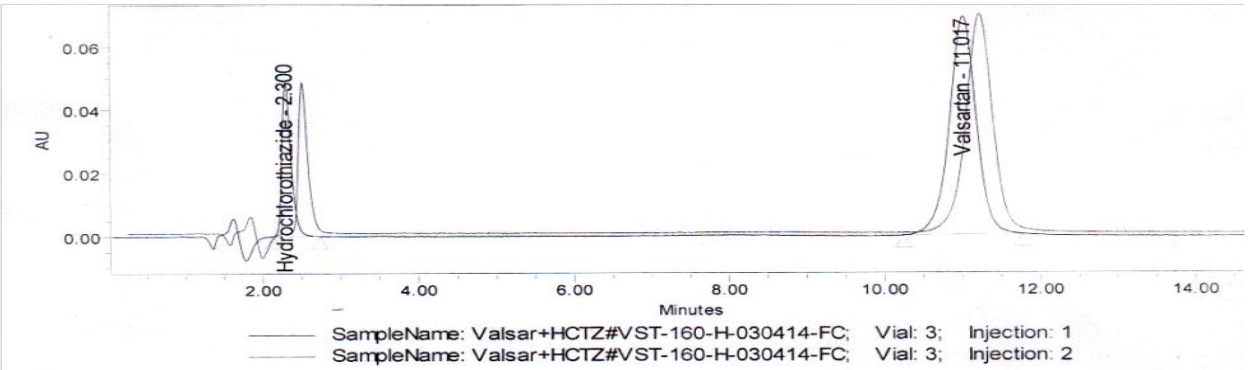
Component Summary Table
Name: Hydrochlorothiazide

	SampleName	Vial	Inj	Name	Retention Time (min)	Area (µV*sec)	% Area	USP Tailing
1	Valsartan + HCTZ # Standard	2	1	Hydrochlorothiazide	2.333	407627	20.28	1.40
2	Valsartan + HCTZ # Standard	2	2	Hydrochlorothiazide	2.333	394957	20.56	1.42
3	Valsartan + HCTZ # Standard	2	3	Hydrochlorothiazide	2.333	401313	20.21	1.40
4	Valsartan + HCTZ # Standard	2	4	Hydrochlorothiazide	2.317	404099	20.29	1.54
5	Valsartan + HCTZ # Standard	2	5	Hydrochlorothiazide	2.317	397378	20.35	1.38
Mean					2.327	401075		
Std. Dev.					0.009	5080.1		
% RSD					0.392	1.27		

Component Summary Table
Name: Valsartan

	SampleName	Vial	Inj	Name	Retention Time (min)	Area (µV*sec)	% Area	USP Tailing
1	Valsartan + HCTZ # Standard	2	1	Valsartan	11.117	1602193	79.72	0.94
2	Valsartan + HCTZ # Standard	2	2	Valsartan	11.100	1526246	79.44	0.93
3	Valsartan + HCTZ # Standard	2	3	Valsartan	11.100	1584754	79.79	0.96
4	Valsartan + HCTZ # Standard	2	4	Valsartan	11.083	1587285	79.71	0.92
5	Valsartan + HCTZ # Standard	2	5	Valsartan	11.033	1555608	79.65	0.95
Mean					11.087	1571217		
Std. Dev.					0.032	30277.8		
% RSD					0.289	1.93		

Figure 15 Standard for Valsartan hydrochlorothiazide



Component Summary Table
Name: Hydrochlorothiazide

	SampleName	Vial	Inj	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Valsar+HCTZ#VST-160-H-030414-FC	3	1	Hydrochlorothiazide	2.300	393327	19.25
2	Valsar+HCTZ#VST-160-H-030414-FC	3	2	Hydrochlorothiazide	2.283	392461	19.12
Mean					2.292	392894	
Std. Dev.					0.012	612.7	
% RSD					0.514	0.16	

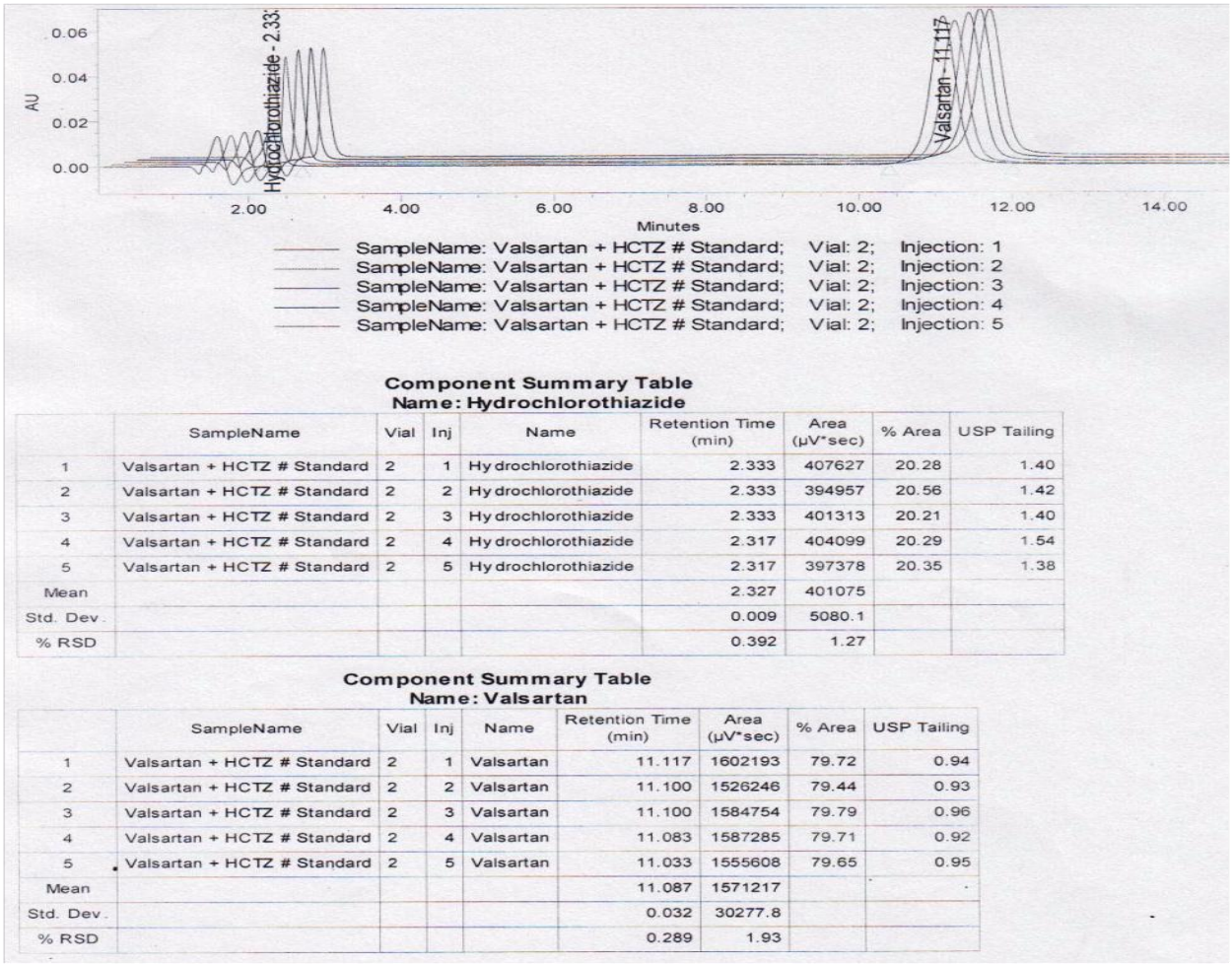
Component Summary Table
Name: Valsartan

	SampleName	Vial	Inj	Name	Retention Time (min)	Area (µV*sec)	% Area
1	Valsar+HCTZ#VST-160-H-030414-FC	3	1	Valsartan	11.017	1650010	80.75
2	Valsar+HCTZ#VST-160-H-030414-FC	3	2	Valsartan	11.000	1660378	80.88
Mean					11.008	1655194	
Std. Dev.					0.012	7331.3	
% RSD					0.107	0.44	

Figure 16 HPLC graph of final formulation assay.

Assay of Valsartan was 104.16%.

Assay of Hydrochlorothiazide was 99.82%.



Component Summary Table
Name: Hydrochlorothiazide

	SampleName	Vial	Inj	Name	Retention Time (min)	Area (µV*sec)	% Area	USP Tailing
1	Valsartan + HCTZ # Standard	2	1	Hydrochlorothiazide	2.333	407627	20.28	1.40
2	Valsartan + HCTZ # Standard	2	2	Hydrochlorothiazide	2.333	394957	20.56	1.42
3	Valsartan + HCTZ # Standard	2	3	Hydrochlorothiazide	2.333	401313	20.21	1.40
4	Valsartan + HCTZ # Standard	2	4	Hydrochlorothiazide	2.317	404099	20.29	1.54
5	Valsartan + HCTZ # Standard	2	5	Hydrochlorothiazide	2.317	397378	20.35	1.38
Mean					2.327	401075		
Std. Dev.					0.009	5080.1		
% RSD					0.392	1.27		

Component Summary Table
Name: Valsartan

	SampleName	Vial	Inj	Name	Retention Time (min)	Area (µV*sec)	% Area	USP Tailing
1	Valsartan + HCTZ # Standard	2	1	Valsartan	11.117	1602193	79.72	0.94
2	Valsartan + HCTZ # Standard	2	2	Valsartan	11.100	1526246	79.44	0.93
3	Valsartan + HCTZ # Standard	2	3	Valsartan	11.100	1584754	79.79	0.96
4	Valsartan + HCTZ # Standard	2	4	Valsartan	11.083	1587285	79.71	0.92
5	Valsartan + HCTZ # Standard	2	5	Valsartan	11.033	1555608	79.65	0.95
Mean					11.087	1571217		
Std. Dev.					0.032	30277.8		
% RSD					0.289	1.93		

Figure 17 HPLC graph of final formulation dissolution

4 Accelerated Stability Studies

In the evaluation of dosage forms, the consistency of the active ingredients should be a crucial factor in the determination of their rejection or acceptance. The stability of the drug may be specified as the time of manufacturing and delivery of the product until its efficacy is not less than the predetermined level of the labelled potency and the physical characteristics of the medication are not less than the predetermined level of the labelled(Naga et al;2013)

Table 27 Stability studies data

PARAMETERS	**TIME**			
	0 Days	**30 Days**	**60 Days**	**90 Days**

Average weight (mg)	328±0.3	328±0.3	329±0.3	330±0.3
Hardness (kg/cm^2)	4±0.2	4±0.2	3.9±0.2	3.9±0.2
Disintegration time	4min10sec	4min10sec	4min10sec	4min10sec
Dissolution Valsartan %DR	102.64±0.5	102.6±0.41	101.6±0.45	101.25±0.46
Dissolution Hydrochlorothiazide %DR	99.6±0.41	99.6±0.43	98.5±0.42	98.32±0.41

From the results of stability the results were very good and found in fulfilling all the limits. After the 3 month stability study no significant changes were takes place. The formulation f9 is quite stable after 3 month accelerated Stability Studies**.**

Weight Variation
After the 3month stability studies, no significant changes in weight were found. The weight of the tablets was estimated to be 330±0.3.
Hardness
The tablets showed good hardness. No significant changestakes place.
In vitro Dissolution
After the 90 days stability studies the formulation shows good drug release no significant changes takes place. It has 98.32 ±0.41of the Hydrochlorothiazide release and the amount of Valsartan is 101.25±0.46.

5.CONCLUSION

The oral delivery is the most efficient and favored method for the delivery of medications in s ystemic circulation due to ease of treatment, patient compliance and flexibility.The Valsartan - Hydrochlorothiazide tablet tends to film coated to prevent the drug from degradation. This formulation is immediate release formulation which produces the effective reduction in high blood pressure within sort span of time.The goal of this study was to establish and test Valsartan-Hydrochlorothiazide (160/12.5 mg) film-
coated tablets in order to reduce repeated dosing and to achieve a more active reduction in hy pertension.Preliminary examination with the excipients and the drug and their physical & chemical compatabilities were checked and the drugs and excipients were found to be compatible with each other.The wet granulation process was used to prepare tablets.. The trials also made on direct compression method but it showed capping and friability problems and complications. So wet granulation method was selected for further trails.

Various granule parameters are done for bulk size, tapped Carr Index density and Hausner Ra tio.The moisture contents in the granules were below 2%. The granules were compressed in to the tablets and film coated. Total nine formulation batches (f1- f9) were prepared. Prepared

formulations had also been tested for QC test and dissolution studies..The tested parameters were found within in the limits. Among all formulation the result of batch f9 has shown very good result in terms of friability, assay and the %age drug release profile.

It further subjected to accelerated stability study at 40±2ºC / 75±5% RH. From the reports of the stability studies, tablets were found to have an acceptable appearance and without any coating defect. After the 3 month stability study the result were very good.F9 is quite stable after 3 month of accelerated Stability Studies.

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