American Journal of Advanced Drug Delivery

www.ajadd.co.uk

Original Article

Immediate Release Formulation of Valsartan Capsule and Evaluation of its Compatibility by Nonthermal Methods

Sudhir. Maddela[1]*, Eswar Gupta. Maddi[2] and Ramarao. Nadendla[3]

[1]Dept of Pharmaceutics,Nirmala College of Pharmacy, Atmakur, Mangalagiri, Guntur district, A.P., India.522503
[2]Dept of pharmaceutics,Sir CR Reddy college of Pharmacy, Eluru, A.P.India
[3]Chalapathi Institute of Pharmaceutical Sciences, Guntur, A.P, India.

Date of Receipt- 01/06/2013
Date of Revision- 08/06/2013
Date of Acceptance- 05/07/2013

Address for Correspondence
Dept of Pharmaceutics,Nirmala College of Pharmacy, Atmakur, Mangalagiri, Guntur district, A.P., India.522503
E-mail:
sudhir.spark@gmail.com

ABSTRACT

Valsartan is a BCS class II antihypertensive drug whose bioavailability is dissolution rate limited. Various capsule formulations of valsartan were prepared using micro crystalline cellulose and sodium lauryl sulfate. Their dissolution profiles were compared with commercial marketed formulations. Formulation **J** was found to have similar $t_{90\ values}$ to marketed brands statistically. Influence of sodium lauryl sulfate on the solubility of valsartan was studied and was found to increase with the concentration of sodium lauryl sulfate. Compatibility of valsartan with micro crystalline cellulose and sodium lauryl sulfate was studied by non-thermal methods like HPLC and IR.

Keywords: Bioavailability, Valsartan, Micro crystalline cellulose, Sodium lauryl sulfate, Compatibility.

INTRODUCTION

Valsartan is usually considered the angiotensive II receptor antagonist of choice for anti-hypertensive effects. It is indicated in conditions where hypertension therapy is likely to be beneficial. Valsartan is a BCS class II drug having low solubility and high permeability[1]. As a consequence, it can exhibit low and/or variable bioavailability after oral administration. Therefore, a well designed formulation must be capable of presenting a therapeutically effective amount of the hydrophobic drug to the desired absorption site, in an absorbable form There are various approaches to improve solubility and dissolution rate of BCS class II drugs like solid dispersion technique, micronization, melt granulation, co-precipitation, and liquisolid compaction. Solid dispersions of valsartan have been prepared using polaxomer 407 and gelucire-50/13 to improve its dissolution rate and oral bioavailability[2,3]. Till date, no one has attempted solvent deposition of valsartan on MCC to improve its in vitro dissolution rate.

Hence an attempt was made in this direction to prepare immediate release capsules. Capsules are relatively simple dosage forms than tablets requiring less number of excipients.

Drugs having poor aqueous solubility are generally not readily wetted and have poor dissolution rate in G.I fluids. Hence a number of workers have used sodium lauryl sulfate (SLS), as a wetting agent in formulations for increasing the dissolution rate of several poor water soluble drugs[4,5]. Hence SLS was also included in the formulation of valsartan capsules to improve its dissolution rate.

One important factor which influences the dissolution rate of a drug is its aqueous solubility[6]. Hence the influence of SLS on solubility of valsartan was studied.

Interaction of drugs with excipients creates stability problems in the formulations; hence interaction of valsartan with MCC and SLS was studied by non thermal I.R and HPLC methods proposed by Serajuddin et al[7].

MATERIALS AND METHODS

Materials

Valsartan (VAL) (Hetero drugs, Hyderabad, India), Ethanol, micro crystalline cellulose (MCC) and sodium lauryl sulfate (SLS) (Qualigens fine chemicals Mumbai, India). All other materials used in the study were of analytical or pharmaceutical grade.

Methods

Preparation of Pure drug Capsules of Valsartan

40mg of valsartan was accurately weighed and transferred manually in to hard gelatin capsules. They were coded as formulation A.

.Commercial Tablets of Valsartan

Commercial tablets of valsartan used for comparison are Valent 40mg (Lupin Pharmaceuticals), and Valzaar 40mg (Torrent Pharmaceuticals). They were purchased from local market and are coded as B and C respectively.

Preparation of Solvent Deposited Systems of Valsartan on MCC

Solvent deposited systems of valsartan and MCC (Formulation D and E) were prepared by the spraying technique. Valsartan was dissolved in 5 ml of ethanol and was sprayed with a syringe onto MCC spread in a mortar with intermittent mixing. The solvent was allowed to evaporate for 30 minutes at room temperature. The dried powder was triturated thoroughly and powder equivalent to 40 mg of valsartan was filled into capsules manually. Valsartan: MCC in formulation D and E are 1:1 and 1:5 on a weight basis. These capsules were subjected to assay and dissolution studies.

Preparation of Physical Mixtures

Physical mixtures (PM) of valsartan, MCC and SLS were prepared by geometric dilution method using a mortar and pestle. Then, powder equivalent to 40mg of valsartan was filled into capsules manually. These capsules were subjected to assay and dissolution studies.

The formulae of the various capsule formulations are given in Table 1.

Phase Solubility Studies

Phase solubility studies on valsartan were performed by the method of Higuchi and Connors[8]. One percent standard solution of SLS was prepared in pH 6.8 phosphate buffer. This standard SLS solution was subsequently diluted with buffer to get a series of SLS solutions having a concentration of 0.05, 0.1, 0.15, 0.2, 0.25, 0.5, 0.75, and 1 %. 500mg of valsartan was taken in 20 ml of

these solutions and were placed in water bath shaker for 24 hours at 37^{0}C. Subsequently these systems were allowed to equilibrate for 24 hours at 37^{0}C so that valsartan in undissolved form is in equilibrium with the dissolved form. The systems were filtered using whatmann paper; the filtrate was suitably diluted and analyzed spectrophotometrically at 250nm[9].

Assay of Capsules

The contents and the shells of one capsule was taken in a 100 ml volumetric flask, 20 ml ethanol and 20 ml of pH 6.8 Phosphate buffer was added and the contents were sonicated for 10 min. Later it was made up to the mark with pH 6.8 phosphate buffer. This solution was filtered and suitably diluted with pH 6.8 phosphate buffer and was assayed at 250nm for valsartan[9].

Drug Excipient Interaction Studies by IR Spectroscopy

400mg of samples of valsartan, excipients and blends of valsartan and excipients in ratio 1:1 were taken in open glass vials, they were placed in a plastic box (l = 30cm, b = 8cm, h = 8cm). Along with these samples, a beaker containing saturated potassium sulfate solution was taken in the box. This solution provided 96% relative humidity in the box. The box was closed and sealed by cellophane tape and was placed in an oven at 50^{0}C for 3 days. The samples were analyzed before and after the above stress condition by FT-IR. If any of the samples showed signs of water sorption, they were dried at 50^{0}C in an oven before recording its I.R spectra[7].

Drug Excipient Interaction Studies by HPLC

Valsartan solution (100µg/ml), excipient solutions (100µg /ml) and blends of valsartan and excipient solutions in ratio of 1:1 were prepared with HPLC water. These solutions were taken in a conical flask and were placed in a water bath shaker at 50^{0}C. The samples were analyzed after 30 minutes by HPLC at 250nm[7,9].

Forced Degradation Studies

Acid and alkali forced degradation studies were conducted on valsartan in 2M HCl and 2M NaOH. One ml of standard valsartan solution (1000 µg / ml) was made up to 20 ml using 2M HCl / 2M NaOH. These solutions were taken in 25 ml conical flasks and were placed in a water bath shaker at 50^{0}C for 30 minutes. The samples were analyzed after 30 minutes by HPLC at 250nm[9].

Dissolution Rate Studies

Dissolution rate studies of valsartan from various capsule formulations were performed according to the IP method, using apparatus II with the paddle rotating at 50 rpm in 900 ml of pH 6.8 phosphate buffer solutions, at 37.5^{0}C using sinker9. A copper wire was used as a sinker to prevent the floating of capsules. The capsule was placed inside the sinker and was added to the dissolution fluid. The diameter and length of copper sinker coil are 1cm and 2.5cm respectively. At different time intervals, 5 ml samples were withdrawn through a filter and an equivalent amount of dissolution fluid was added back. The amount of valsartan in the samples was determined by UV analysis at 250nm. All dissolution studies were carried out in triplicate.

RESULTS AND DISCUSSION

A graphical plot showing the influence of SLS on solubility of valsartan is shown in figure 1. The solubility of valsartan increased with the concentration of SLS. This is due to increased wetting of the valsartan by SLS and due to micellar solubilisation and results are given in table 2. Hence presence of SLS in a formulation will lead to increased

wetting, solubity and dissolution rate of valsartan in G.I fluids.

Table 3 summarizes the results of percent of valsartan dissolved at various time intervals. Comparative graphical plots of percent valsartan dissolved at versus time is given in figure 2. Dissolution rate testing paramters determined are given in table 4.

The FT-IR spectra of valsartan, excipients and their blends are presented in figure (3-9). The FT – IR spectra of valsartan showed characteristic peaks at 3393cm^{-1} (N-H stretching), 2981cm^{-1} (C- H stretching of aromatics), 2931cm^{-1} (O-H stretching of carboxyl group), 1695 cm^{-1} (C = O stretching of ketones), 1653cm^{-1} (C $\underline{=}$ N stretching), 1214cm^{-1} (C-O stretching of carboxyl group), 1100cm^{-1} (C-N stretching) and 753cm^{-1} (C-H bending of aromatic). On comparing the FT-IR spectra of the various samples before and after stress treatment, there was a slight shift in the characteristic peaks with no differences in overall spectrum, hence it is concluded that MCC and SLS are compatible with valsartan.

The HPLC chromatograms of valsartan, excipients and their blends are presented in figure (10-14). The chromatograms of the various solutions before and after stress treatments showed only the peak due to valsartan. No new additional peaks were produced. Hence it is concluded that MCC and SLS are compatible with valsartan. Had there been any interaction, new peaks would have been observed as in forced degradation studies discussed below.

The HPLC chromatograms obtained in acid and alkali degradation studies are shown in figure (15,16). They showed new peaks with the disappearance of the peak due to valsartan degradation. This indicates that valsartan is unstable in strong acidic and alkali media.

Assay results indicated that all the formulations contained valsartan within 100 $\underline{+}$ 5%.

From the one way ANOVA of the t_{90} values of various valsartan formulations in table 5, it was concluded that there is a significant difference between the formulations. One or more formulations may differ from each other with respect to t_{90} values. Hence they were divided into groups by LSD procedure at 5% level of significance[10] .As per LSD procedure, it was found that if formulations T_{90} values differ by more than 4.3 minutes, there is statistically significant difference between the formulations. Accordingly they have been divided into different groups as shown in Table 6.

From Table 3 it is clear that solvent deposition of valsartan on MCC (formulation D and E) did not improve the dissolution rate. They do not have SLS as wetting agent in the formulation. As this approach failed in improving dissolution rate of valsartan, physical mixtures containing valsartan, MCC and SLS were prepared (formulations F, G, H, I, J). As SLS content increased valsartan dissolution rate increased and from the table it can be concluded that formulation **J** is similar to commercial formulations **B** and **C.**

Formulation J contained 40mg valsartan, 35mg MCC and 175mg SLS which released 90 % of drug in first 10 minutes as the commercial products. As content of SLS in the capsules varied from 50 to 175mg the t_{90} values also varied from 107 minutes to nine minutes. Hence by varying the amount of SLS in capsules we can vary the dissolution rate of valsartan.

Table 6 indicates that the formulation J is similar to the marketed products of formulation B and C.

The flow properties of the best formulation J was found to have an angle of repose of 30^0 by open end cylinder method. This indicates that it has satisfactory flow properties for filling into capsules on a large scale.

CONCLUSION

Valsartan was fond to be compatible with MCC and SLS by HPLC and FT IR methods. A two fold increase in solubility of valsartan was observed with the use of 1% SLS. Formulation J was statistically similar to commercial products B and C with respect to t_{90} values. Formulation J was found to have satisfactory flow properties for filling into capsules on a large scale. Hence a capsule formulation of valsartan prepared by a simple physical mixing method was developed.

ACKNOWLEDGEMENTS

The authors are thankful to Hetero Drugs, Hyderabad for gift sample of valsartan and to the Chairman and Principal of Chalapathi Institute of Pharmaceutical Sciences, Guntur, for providing necessary facilities and support to carry out the research work.

REFERENCES

1. Mehatap Saydam, Sevgi Takka**.** Bioavailability File: Valsartan. *FABAD J. Pharm. Sci*., 2007; 32(1): 185-196.
2. Park YJ, Lee HK, Im B, Lee W, Han HK. Improved pH-Independent Dissolution and Oral Absorption of Valsartan via the Preparation of Solid Dispersion. *Arc. Pharm. Res.*, 2010; 33(8): 35-40.
3. Shrivastava, Agnivesh R, Ursekar, Bhalchandra, Kapadia, Chanda J. Design, Optimization, Preparation and Evaluation of Dispersion Granules of Valsartan and Formulation into Tablets. *Cur. Drug. Del.*, 2009; 6(1): 28-37.
4. Jennifer J. Shenga, Nehal A. Kasima, b, Ramachandran Chandrasekharana, and Gordon L. Amidon**.** Solubilization and Dissolution of Insoluble Weak Acid Ketoprofen: Effects of pH Combined with Surfactant. *Eur. J. Pharm. Sci.*, 2006; 29(3-4): 306-314.
5. Markus Vogt, Klaus Kunath, and Jennifer B. Dressman. Dissolution Improvement of Four Poorly Soluble Drugs by Co Grinding with Commonly Used Excipients. *Eur. J. Pharm*. Biopharm.**,** 2008; 68(2): 330-337**.**
6. D Horter, J.B Dressman. Influence of Physicochemical Properties on Dissolution of Drugs in the Gastrointestinal Tract. *Adv. Drug. Del. Rev*., 2001; 46(1-3): 75-87.
7. ABU T. M. Serajuddin, Ajit B. Thakur, Rabin N. Ghoshal, Micheal G. Fakes, Sunanda A. Ranadive, Kenneth R. Morris, and Sailesh A. Varia. Selection of Solid Dosage Form Composition through Drug Excipient Compatability Testing. *J. Pharm. Sci*., 1999; 88(7): 696-704.
8. T. Higuchi and K. A. Connors. Phase Solubility Diagram. *Adv. Anal. Chem. Instr*., 1965; 4(1): 117–212.
9. Government of India. Ministry of health and family welfare. Indian PharmacopoeiaVol I & II.The Controller of publication, New Delhi, 2010; 6(3), 2286.
10. Remington, The Science and Practice of Pharmacy: Gennaro A.R. (eds). 21st ed., Lippincott, Williams & Wilkins, , 2005: 867-868.

Table 1. Formulae of Valsartan Capsules

S. NO.	Material	A	B	C	D	E	F	G	H	I	J
1	Valsartan , mg	40	40	40	40	40	40	40	40	40	40
2	MCC, mg	-	-	-	40	200	160	135	110	60	35
3	SLS, mg	-	-	-	-	-	50	75	100	150	175
4	Method	-	CP	CP	SD	SD	GD	GD	GD	GD	GD
1	Valsartan , mg	40	40	40	40	40	40	40	40	40	40

CP is Commercial Product, SD is Solvent Deposition, and GD is Geometric Dilution.

Table 2. Phase solubility studies of valsartan

S.No.	% SLS	Valsartan Dissolved in g / 1000ml	SLS moles/litre	valsartan dissolved in	log %SLS moles/litre	log valsartan dissolved
1	0	0.86	0	$1.974x10^{-3}$	-	$0.29x10^{-3}$
2	0.5	0.86	$1.73x10^{-3}$	$1.974x10^{-3}$	$0.23\ x10^{-3}$	$0.29x10^{-3}$
3	1	0.89	$3.34x10^{-3}$	$2.057x10^{-3}$	$0.53x10^{-3}$	$0.31x10^{-3}$
4	1.5	1.01	$5.20x10^{-3}$	$2.296x10^{-3}$	$0.71x10^{-3}$	$0.34x10^{-3}$
5	2	1.16	$6.93x10^{-3}$	$2.665x10^{-3}$	$0.83x10^{-3}$	$0.41x10^{-3}$
6	2.5	1.38	$8.62x10^{-3}$	$3.188x10^{-3}$	$0.93x10^{-3}$	$0.49x10^{-3}$
7	5	1.56	$17.3x10^{-3}$	$3.489x10^{-3}$	$1.23x10^{-3}$	$0.53x10^{-3}$
8	7.5	1.53	$26.0x10^{-3}$	$3.514x10^{-3}$	$1.41x10^{-3}$	$0.54x10^{-3}$
9	10	1.64	$34.6x10^{-3}$	$3.784x10^{-3}$	$1.53x10^{-3}$	$0.56x10^{-3}$

Table 3. % of Valsartan Dissolved from Various Capsule Formulations (average of three trials)

S.NO	Time in Minutes	A	B	C	D	E	F	G	H	I	J
1	0	0	0	0	0	0	0	0	0	0	0
3	10	15.2	93.3	96.7	16.3	6.6	18.1	31.1	71.2	63.8	73.5
4	20	17.7	97.3	97.7	29.7	11.9	45.7	76.7	85.3	91.8	95.6
5	30	32.2	95	96.3	42.7	22.5	62	91.6	91.3	93.8	95.2
6	45	55.5	93.3	93	52.7	48.8	83	95.5	95.8	97.1	97.4
7	60	75.5	94.7	92	63.3	57.8	90.5	100	100	100	99

Table 4. Comparative Dissolution Rate Testing Parameters of All Formulations of Valsartan

Parameters	A	B	C	D	E	F	G	H	I	J	K
T_{50}	40.0	6	6	40	48	22	14	7	7	11	6
T_{90}	72.1	10	9	56	113	54	29	27	20	46	6
DE_{10}	51.7	47.2	82.1	59.4	56.7	53.0	42.1	68.4	46.9	54.5	81.9
DE_{30}	49.5	81.3	86.9	61.3	38.4	50.0	54.2	70.6	70.9	64.1	84.2
DE_{60}	46.0	90.8	92.7	41.4	45.7	61.7	72.7	79.5	82.2	73.0	90.8

T_{50} = Time taken for 50 % of the drug to dissolve
T_{90} = Time taken for 90 % of the drug to dissolve
DE_{10} = Dissolution efficiency in first 10 minutes
DE_{30} = Dissolution efficiency in 30 minutes
DE_{60} = Dissolution efficiency in 60 minutes

Table 5. One Way ANOVA of T_{90} Values of Valsartan Formulations

Formulation	Count	Sum of t_{90} values	Average of t_{90} values	Variance
A	3	212	70.66	2.64
B	3	29	9.66	0.33
C	3	28	9.33	0.33
D	3	167	55.66	12.33
E	3	323	107.66	25.33
F	3	164	54.66	1.33
G	3	80	26.66	6.33
H	3	83	27.66	1.33
I	3	59	19.66	2.33
J	3	29	9.66	0.33

Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	28617.39	10	2861.739	510.6657	1.22E-23	2.296694
Within Groups	123.2867	22	5.603939			
Total	28740.68	32				

Table 6. Grouping of Formulations As per LSD Procedure

S.NO.	Groups	Formulations
1	I	B, C, J
2	II	I
3	III	G, H
4	IV	D
5	V	A
6	VI	E

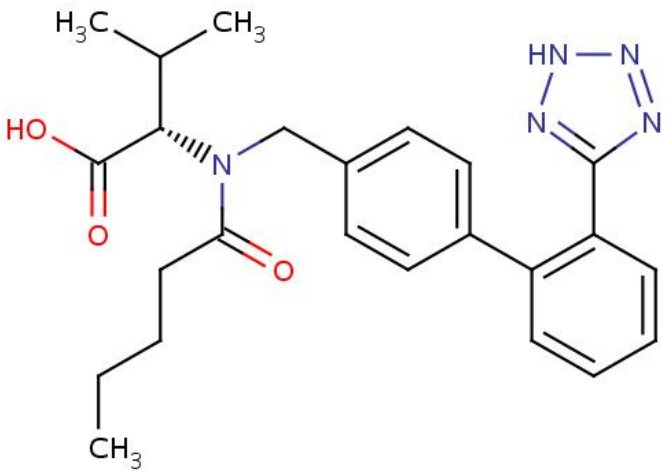

Figure.1. Structure of valsartan

 ISSN-2321-547X

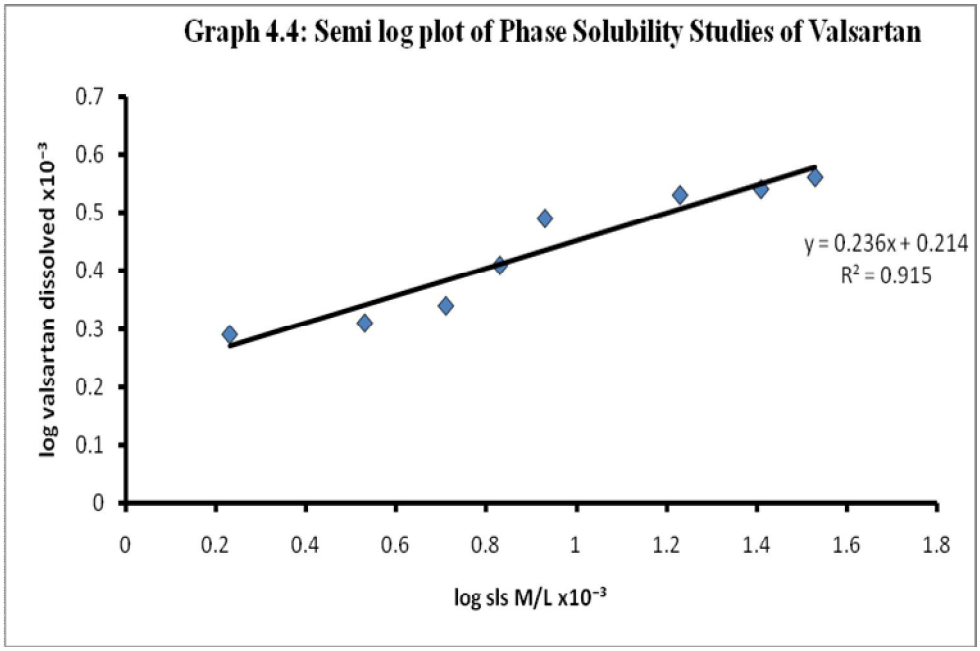

Figure.2. Phase solubility studies of Valsartan with SLS

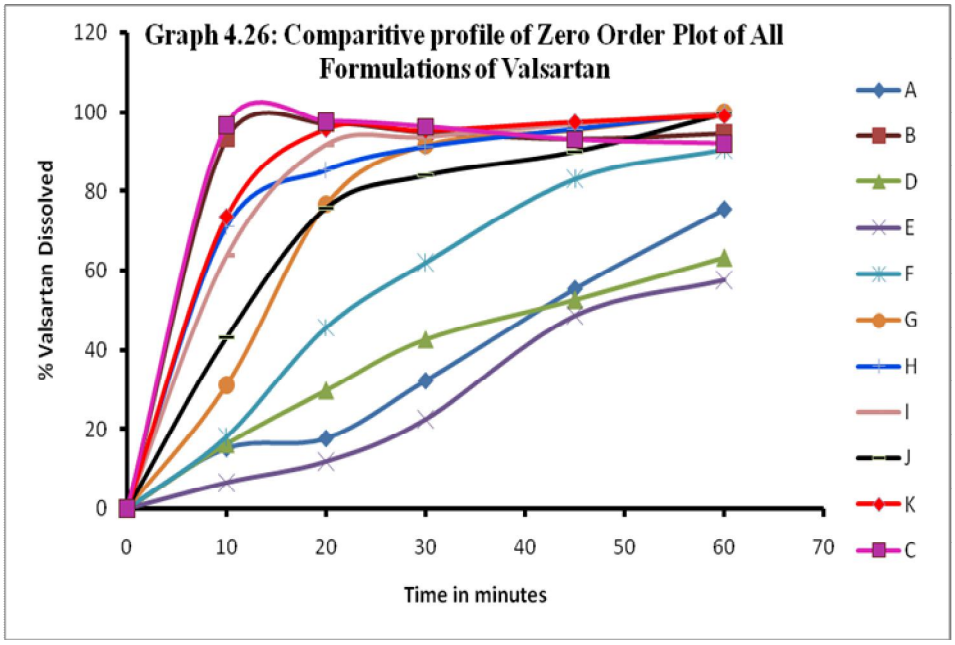

Figure.3. Comparitive dissolution profile of valsartan f all formulations

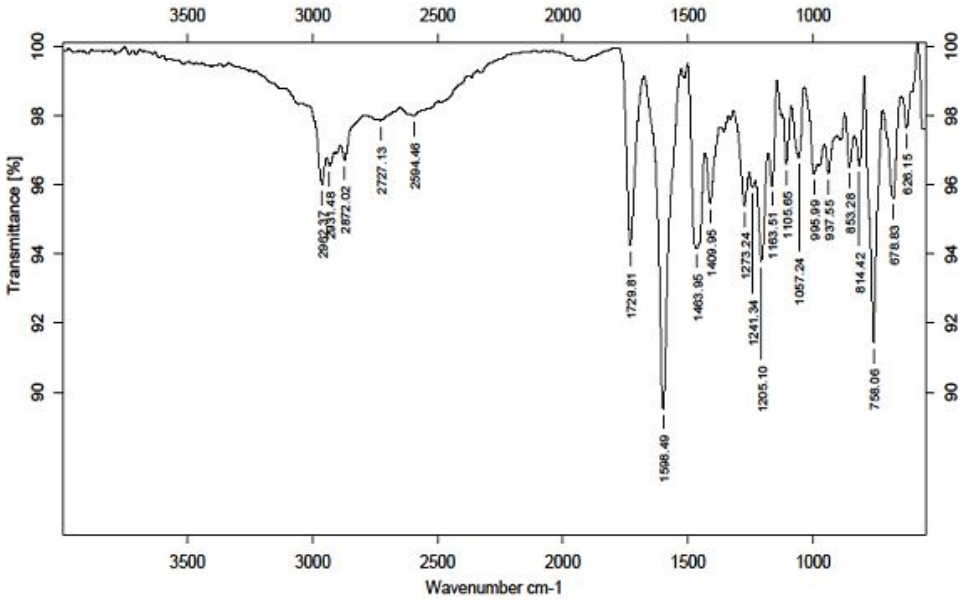

Figure.4. FT-IR spectra of valsartan

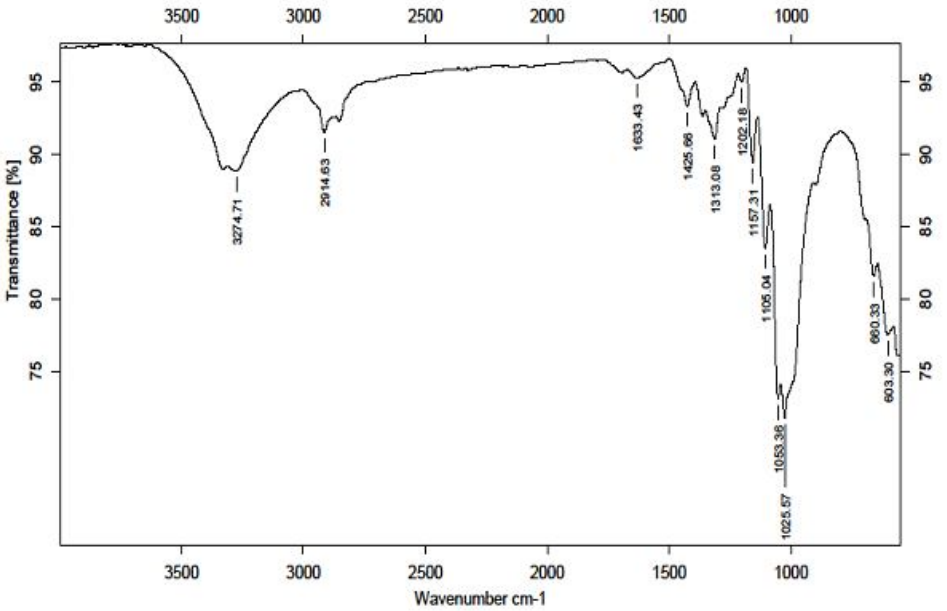

Figure.5. FT-IR spectra of mcc

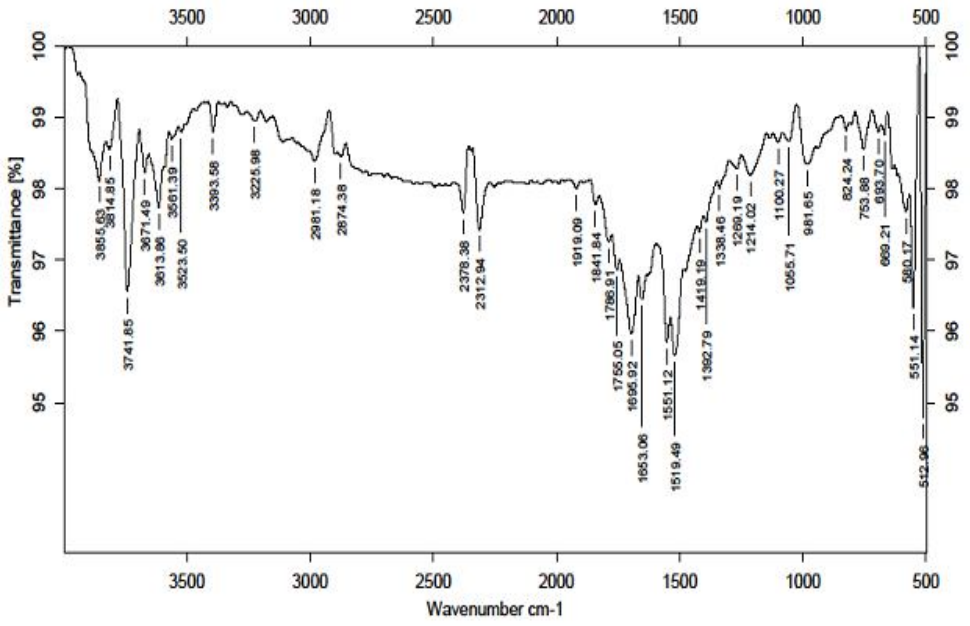

Figure.6. FT-IR spectra of sls

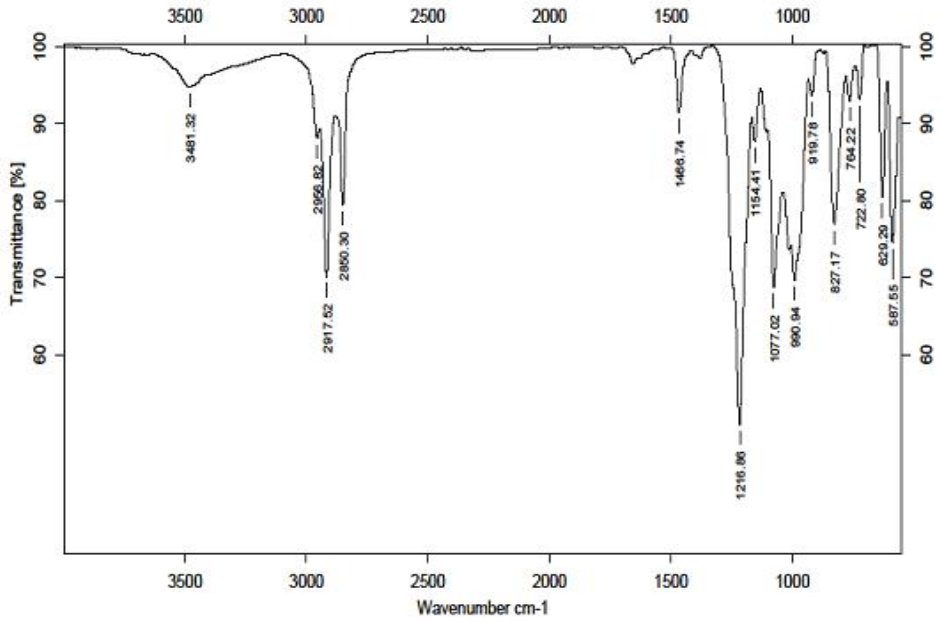

Figure.7. FT-IR spectra of valsartan-50^{0}C and95%RH – 72hrs

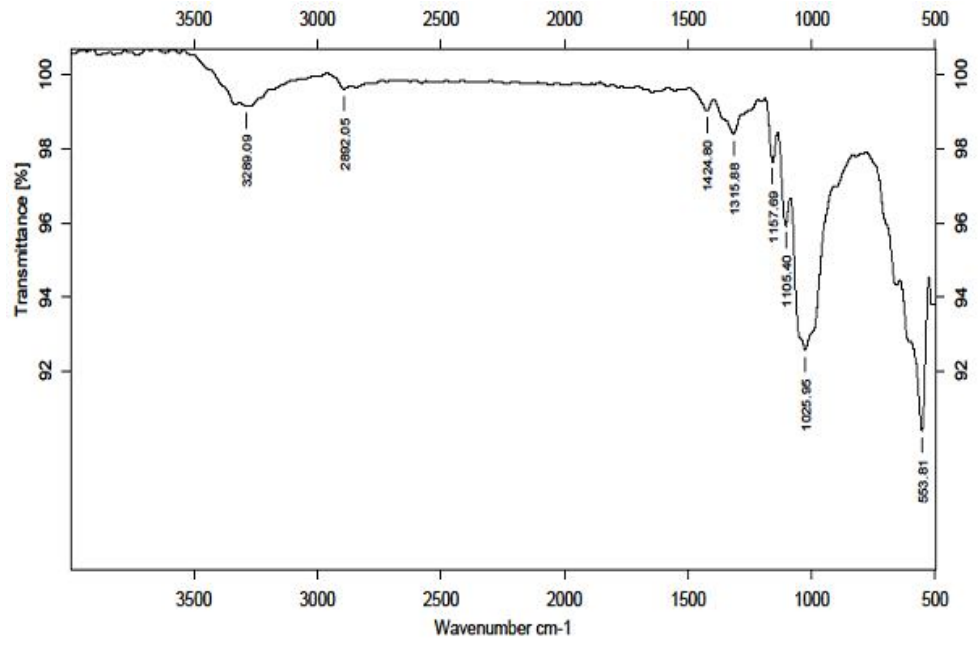

Figure.8. FT-IR Spectra of mcc-50^{0}C and 95% RH – 72hrs

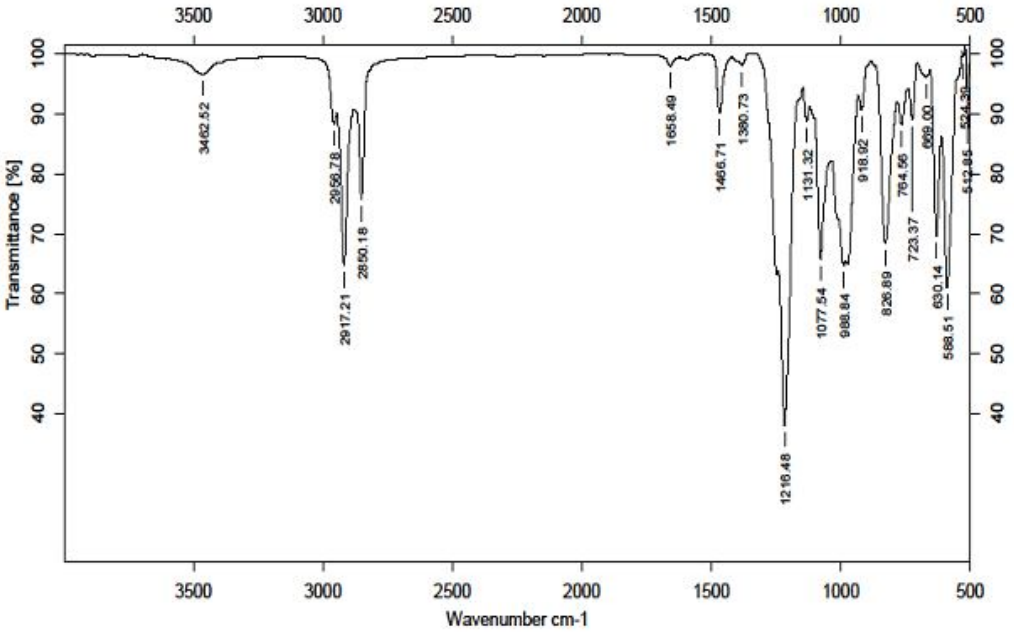

Figure.9. FT-IR spectra of sls-50^{0}C and 95% RH – 72hrs

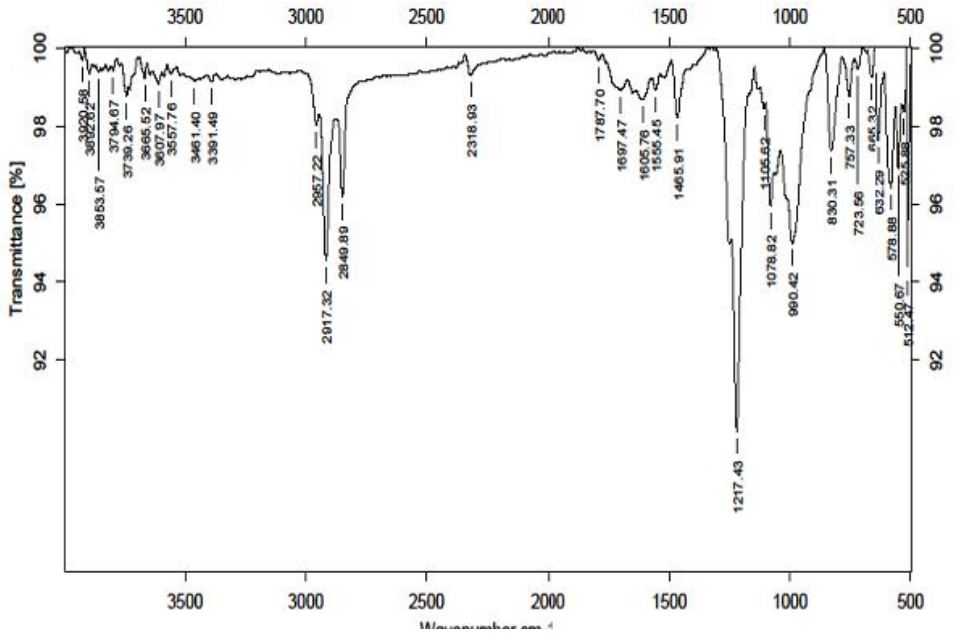

Figure.10. FT-IR spectra of val+mcc+sls-50^{0}C and 95% RH – 72hrs

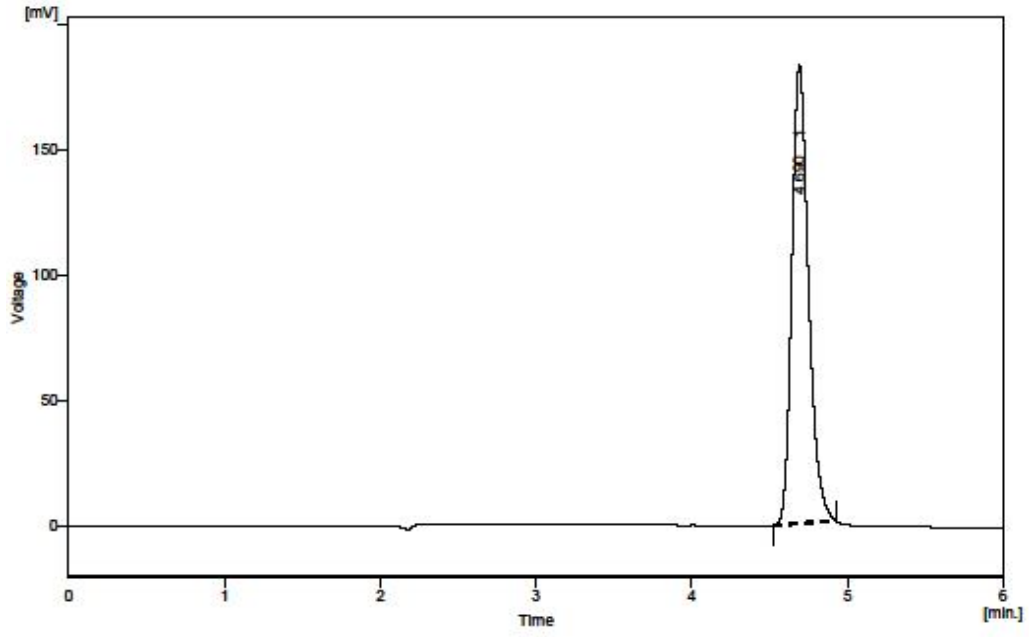

Figure.11. Chromatogram of valsartan

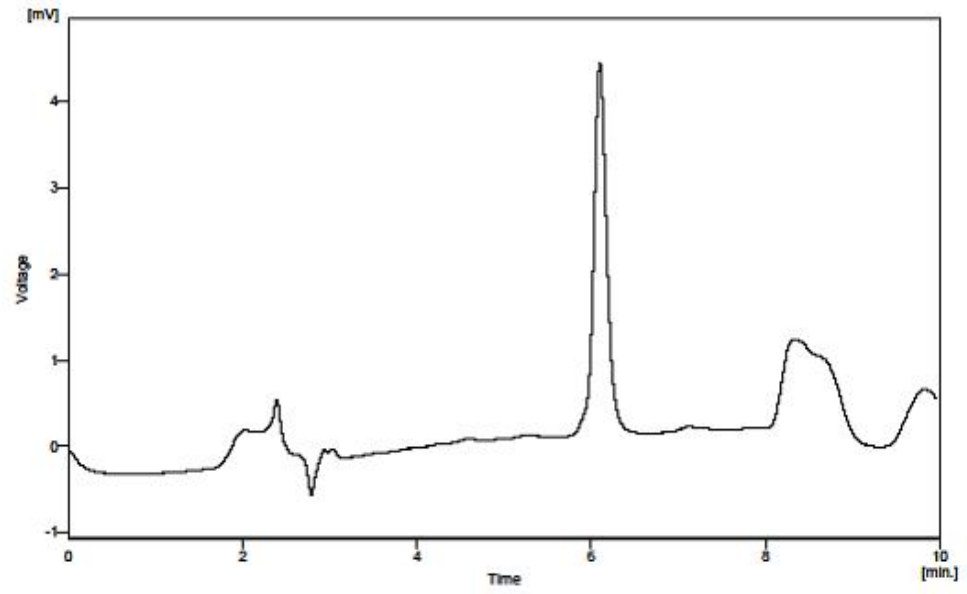

Figure.12. Chromatogram of mcc

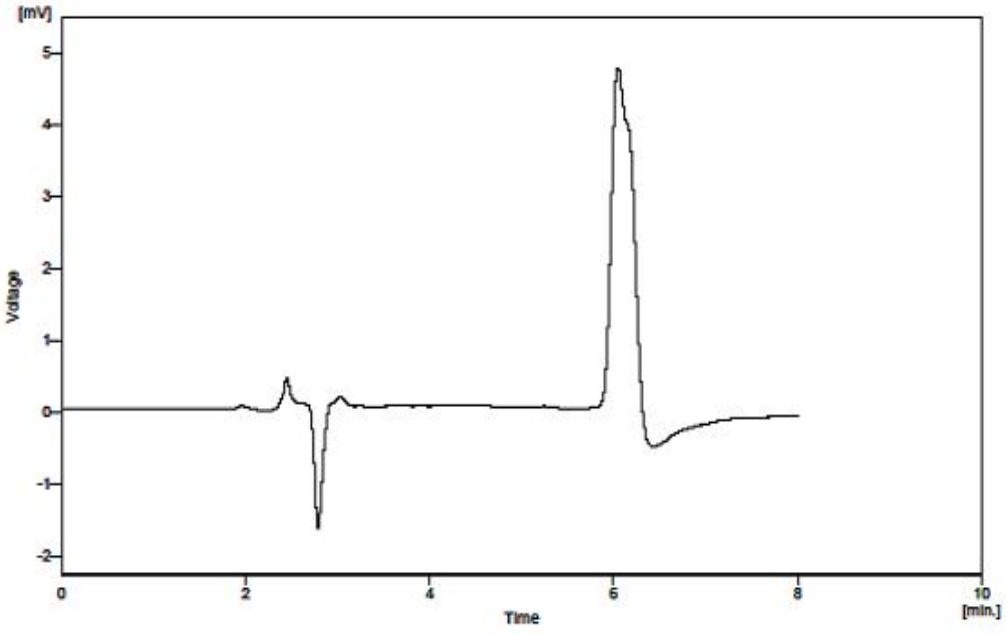

Figure.13. Chromatogram of sls

 ISSN-2321-547X

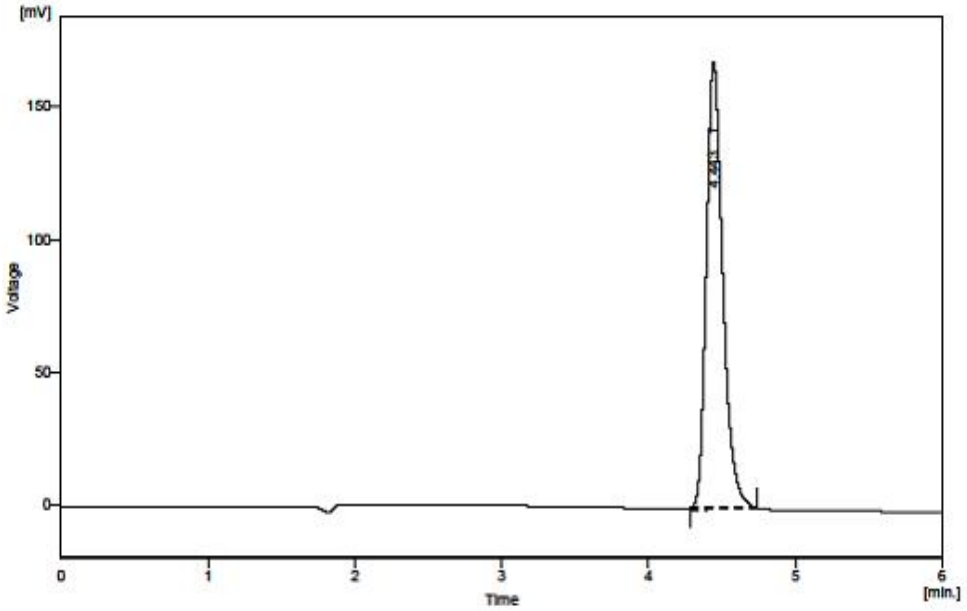

Figure.14. Chromatogram of val-50^{0}C and 95% RH – 72hrs

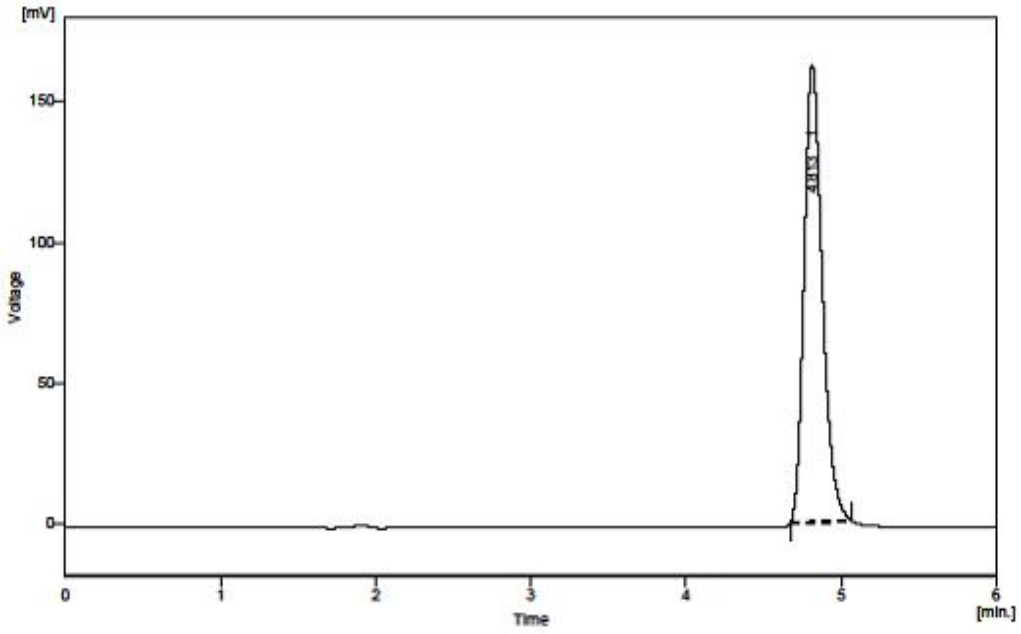

Figure.15. Chromatogram of val+mcc+sls -50^{0}C and 95% RH – 72hrs

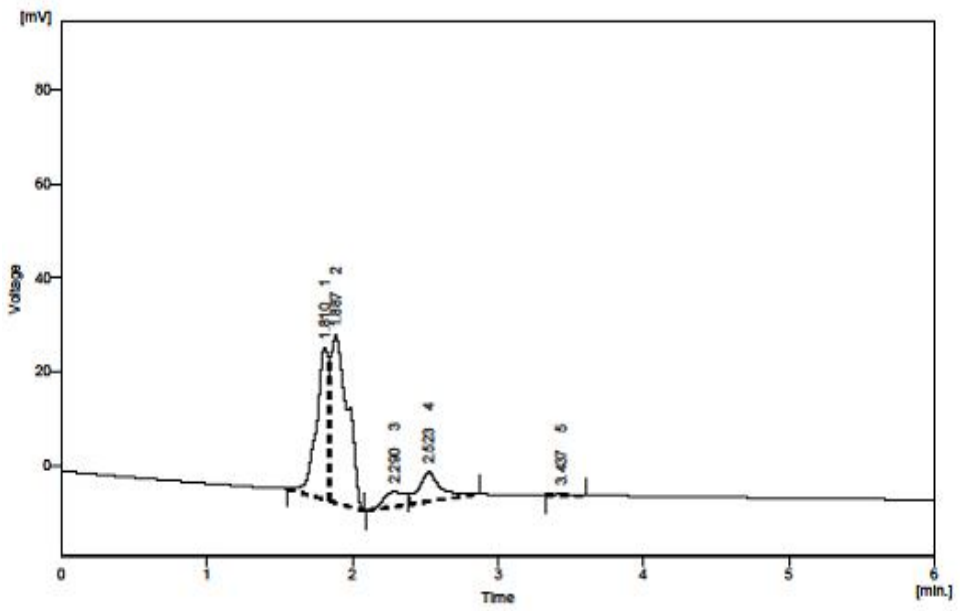

Figure.16. Chromatogram of acid degradation studies of val

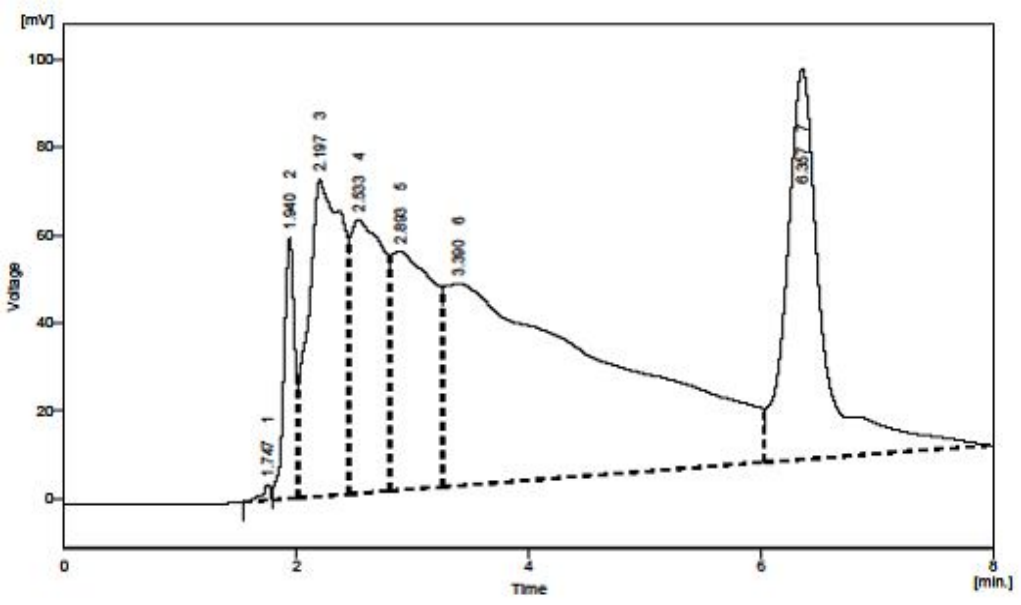

Figure.17. Chromatogram of alkali degradation studies of val