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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE VALSARTAN CAPSULES BY USING CROSCARMELLOSE SODIUM

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ABSTRACT

Valsartan is a BCS class II antihypertensive drug whose bio availability is dissolution rate limited. Various capsule formulations of valsartan were prepared using croscarmellose sodium 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 croscarmellose sodium and sodium lauryl sulfate was studied by non-thermal methods like HPLC and IR.

KEYWORDS

Bioavailability, Valsartan, Croscarmellose Sodium, Sodium lauryl sulfate and Compatibility.

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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 As a consequence, it can exhibit low and variable bio availability 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 CCS 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 solubility⁶. 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 CCS and SLS was studied by non-thermal I.R and HPLC methods proposed by Serajuddin *et al*⁷.

MATERIAL AND METHODS

Material

Valsartan (VAL) (Bafna pharmaceuticals, Chennai, India), Ethanol, Croscarmellose sodium (CCS) 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 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 CCS

Solvent deposited systems of Valsartan and CCS (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 CCS 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: CCS 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, CCS 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 No.1.

Phase Solubility Studies

Phase solubility studies on Valsartan were performed by the method of Higuchi and Connors⁸. 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°C. Subsequently these systems were allowed to equilibrate for 24 hours at 37°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 250nm⁹.

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 valsartan⁹.

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 50⁰C 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 50⁰C in an oven before recording its I.R spectra⁷.

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 50⁰c for 30 minutes. The samples were analyzed after 30 minutes by HPLC at 250nm⁹.

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 37.5⁰C 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

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 No.2. Hence presence of SLS in a formulation will lead to increased wetting, solubility and dissolution rate of Valsartan in G.I fluids Table No.3 summarizes the results of percent of Valsartan dissolved at various time intervals. Dissolution rate testing parameters determined are given in Table No.4. 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 = 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 FTIR 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 CCS and SLS are compatible with Valsartan. 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 CCS and SLS are compatible with Valsartan. Had there been any interaction, new peaks would have been observed as in forced degradation studies discussed below.

From Table No.3 it is clear that solvent deposition of Valsartan on CCS (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,

CCS 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 CCS 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 t90 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. The flow properties of the best formulation **J** was found to have an angle of repose of 30° by open end cylinder method. This indicates that it has satisfactory flow properties for filling into capsules on a large scale.

Table No.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	CCS, 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

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

Table No.2: Phase solubility studies of Valsartan

S.No	% SLS	Valsartan Dissolved in g/ 1000ml	SLS moles/litre	Valsartan dissolved in moles/litre	log % SLS moles/litre	log Valsartan dissolved moles/litre
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 No.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
2	10	15.2	93.3	96.7	16.3	6.6	18.1	31.1	71.2	63.8	73.5
3	20	17.7	97.3	97.7	29.7	11.9	45.7	76.7	85.3	91.8	95.6
4	30	32.2	95	96.3	42.7	22.5	62	91.6	91.3	93.8	95.2
5	45	55.5	93.3	93	52.7	48.8	83	95.5	95.8	97.1	97.4
6	60	75.5	94.7	92	63.3	57.8	90.5	100	100	100	99

Table No.4: Comparative Dissolution Rate Testing Parameters of All Formulations of Valsartan

S.No	Parameters	A	B	C	D	E	F	G	H	I	J
1	T50	40.0	6	6	40	48	22	14	7	7	11
2	T90	72.1	10	9	56	113	54	29	27	20	46
3	DE10	51.7	47.2	82.1	59.4	56.7	53.0	42.1	68.4	46.9	54.5
4	DE30	49.5	81.3	86.9	61.3	38.4	50.0	54.2	70.6	70.9	64.1
5	DE60	46.0	90.8	92.7	41.4	45.7	61.7	72.7	79.5	82.2	73.0

T50 = Time taken for 50 % of the drug to dissolve, T90 = Time taken for 90 % of the drug to dissolve,
 DE10 = Dissolution efficiency in first 10 minutes, DE30 = Dissolution efficiency in 30 minutes,
 DE60 = Dissolution efficiency in 60 minutes

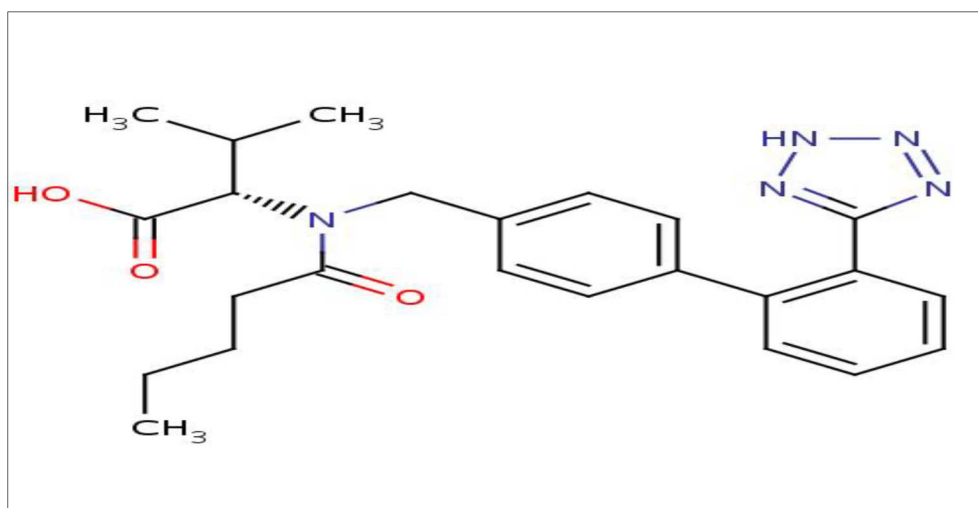


Figure No.1: Structure of Valsartan

CONCLUSION

Valsartan was found to be compatible with CCS and SLS by FT IR method. 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 t90 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.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Mehatap Saydam, Sevgi Takka. Bioavailability File: Valsartan, *FABAD J. Pharm. Sci*, 32(1), 2007, 185-196.
2. Park Y J, Lee H K, Im B, Lee W, Han H K. Improved pH-Independent Dissolution and Oral Absorption of Valsartan via the Preparation of Solid Dispersion, *Arc. Pharm. Res*, 33(8), 2010, 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*, 6(1), 2009, 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*, 29(3-4), 2006, 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*, 68(2), 2008, 330-337.
6. Horter D, Dressman J B. Influence of Physicochemical Properties on Dissolution of Drugs in the Gastrointestinal Tract, *Adv. Drug. Del. Rev*, 46(1-3), 2001, 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 Compatibility Testing, *J. Pharm. Sci*, 88(7), 1999, 696-704.
8. Higuchi T and Connors K A. Phase Solubility Diagram, *Adv. Anal. Chem. Instr*, 4(1), 1965, 117-212.
9. Government of India. Ministry of health and family welfare. Indian Pharmacopoeia Vol I and II, *The Controller of publication, New Delhi*, 6(3), 2010, 2286.
10. Remington. The Science and Practice of Pharmacy: Gennaro A R, *Lippincott, Williams and Wilkins*, 21st edition, 2005, 867-868.

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