



Research Article

FORMULATION AND IN-VITRO EVALUATION OF MOUTH DISSOLVING TABLETS OF VALSARTAN**B. Deepika*, K. Naga Raju, M. Chinna Eswaraiah**

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Abstract: Mouth dissolving tablets of Valsartan drug were prepared by using three different superdisintegrants like Cross carmellose sodium, Sodium starch glycolate and Cros-povidone. Each superdisintegrant was used in three different concentrations like 2.5 % w/w, 5 % w/w and 7.5 % w/w. Total 9 formulations were developed and optimized for nature and concentration of superdisintegrants in tablets with respective to disintegration time, wetting time, water absorption ratio and in-vitro drug release. In the present study, it was proved that the formulations containing Sodium starch glycolate have shown good in-vitro results compared to other formulations. However the formulations containing 7.5 % w/w concentration of any superdisintegrants have shown better optimum results, hence selected as best formulations in this study.

Key words: Mouth dissolving tablet, Valsartan, superdisintegrants, in-vitro drug release

INTRODUCTION

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self-medication, pain avoidance, versatility, high levels of patient compliance. Tablets and capsules are the most popular dosage forms but one important drawback of such dosage forms is 'Dysphagia' or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This leads to poor patient compliance in patients especially in geriatrics and pediatrics. So the technologies for improved patient compliance have achieved enormous demand³.

There are so many drugs with poor bioavailability through oral route. This may be because of drug degradation or pre-systemic metabolism of drugs in gastro-intestinal environment. All these problems associated with gastro-intestinal environment are derived from physicochemical properties of drugs. In order to overcome these drawbacks, two approaches can be followed, one is to modify the chemical structure of drug and developing the new chemical entity and another is to develop the new drug delivery systems for existing drugs. To develop a new chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced patient compliance, efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects³.

Mouth dissolving tablet (MDT) is a promising option for improved patient compliance in geriatrics and pediatrics and also for improved bioavailability of orally less efficient drugs. It is a tablet that disintegrates and dissolves rapidly in the saliva within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15sec to 3min. Most of the MDTs contain certain superdisintegrants and taste masking agents⁴.

Valsartan is an angiotensin II receptor antagonist and chemically it is N-(1-Oxopentyl)-N-[[2'-(1H-tetrazol-5-yl) [1, 1'-biphenyl]-4-yl] methyl]- L-Valine. It is used in the treatment of high blood pressure, congestive heart failure or post-myocardial infarction. The oral bioavailability of Valsartan is only 25% due to pre-systemic metabolism¹. In the present study, Valsartan was formulated as mouth dissolving tablets, in order to provide the fast drug therapy for geriatrics and in order to increase the bioavailability of drug by facilitating the drug absorption through buccal mucosa and mucosa of pharynx before swallowing. The effect of three different superdisintegrants in three different concentrations on disintegration time, wetting time, water absorption ratio and in-vitro drug release, was studied.

MATERIALS AND METHODS**Materials:**

Valsartan was gifted from Aurabindo Pharma, Hyderabad, other chemicals like Sodium Starch Glycolate, Cross Carmellose Sodium, Cros-povidone, Microcrystalline cellulose, Magnesium

stearate, Talc, Potassium dihydrogen ortho phosphate, Sodium hydroxide, Aspartame and Mannitol were purchased from Himedia Laboratories.

Methods:

1. Preformulation study

Preformulation studies were primarily performed to investigate the physicochemical properties of drug and to establish its compatibility with superdisintegrants and other excipients. Fourier Transform Infrared (FTIR) spectrophotometer was used for infrared analysis of samples to interpret the interactions of drug with superdisintegrants and other ingredients. The powder sample along with KBr was used for FTIR studies¹². The IR spectrum of a) pure Valsartan, b) physical mixture containing drug, Cross Carmellose Sodium and other excipients, c) physical mixture containing drug, Sodium Starch Glycolate and other excipients, d) physical mixture containing drug, Cros-povidone and other excipients, were taken, interpreted and compared with each other.

2. Mouth dissolving tablets preparation

Valsartan was mixed manually in polybags with different super disintegrants like cross carmellose sodium or sodium starch glycolate or cross povidone individually (Table 1). Mannitol and microcrystalline cellulose were added as diluents and mixed for 10 mins. The Aspartame was added and mixed to mask the bitter taste. The blend was lubricated with magnesium stearate for 3-5mins and talc was added as glidant. The mixed blend was then compressed into tablets by direct compression method using 9 mm punches on a single station tablet punching machine.

3. Evaluation of Mouth Dissolving Tablets

A) Characterization of tablets for physicochemical parameters

The prepared mouth dissolving tablets were evaluated for their physicochemical parameters like weight variation, hardness, thickness, friability and drug content.

B) In vitro disintegration time

The disintegration test was performed using an USP disintegration apparatus, with distilled water at $37\pm 0.5^\circ\text{C}$. The time required to obtain complete disintegration of six tablets were recorded and average was reported⁷.

C) Wetting time

A piece of tissue paper folded twice was kept in a petridish (internal diameter 5.5cm) containing 6ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded^{7,8}.

D) Water absorption ratio⁹

A piece of tissue paper folded twice was kept in a petridish (internal diameter 5.5cm) containing 6ml of purified water. The pre-weighed tablet was placed on the tissue paper and allowed to wet completely. The wetted tablet was removed and reweighed. Water absorption ratio, R was determined according to the following equation-

$$R = 100 (W_a - W_b) / W_b$$

Where W_b and W_a are the weight before and after water absorption, respectively.

E) In vitro drug release study

The drug release rate from mouth dissolving tablets was studied using the USP type II dissolution test apparatus. The dissolution test was performed using 900 ml of phosphate buffer (pH 6.8) as the dissolution medium at 50 rpm and $37 \pm 0.5^\circ\text{C}$. 5 ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 250 nm¹⁵.

F) Characterization of drug in mouth dissolving tablets

FTIR studies were conducted for characterization of drug in tablets of selected optimized formulations (F3, F6, and F9). The mouth dissolving tablets were compressed and powdered. The pelletized powder along with KBr was used for FTIR studies. The IR spectra were recorded using Fourier Transform Infrared spectrophotometer. The IR spectrum of pure Valsartan and pelletized powder of tablets were taken, interpreted and compared with each other⁸.

RESULTS AND DISCUSSION

1. Preformulation study

In IR spectrum of pure Valsartan (Figure 1), the presence of peaks at 1602.40 cm^{-1} ($>\text{C}=\text{N}$ stretching), 3433.98 cm^{-1} ($-\text{N}=\text{H}$ stretching), 1732.40 cm^{-1} ($>\text{C}=\text{O}$ group), 2963.75 cm^{-1} ($-\text{OH}$ stretching), $1205.90, 1274.26\text{ cm}^{-1}$ ($\text{C}-\text{N}$ -stretching) were characteristic to that of the pure drug and all of them remained unaltered in the IR spectra of physical mixtures containing drug, superdisintegrants and other ingredients (Figure 2, 3 and 4). IR analysis revealed that there was no known chemical interaction of drug with superdisintegrants and other ingredients.

Table 1: Formulation of Valsartan mouth dissolving tablets

Formulation	% w/w of super disintegrant	Drug	Cross carmellose sodium	Sodium starch glycolate	Cross povidone	MCC	Aspartame	Mannitol	Mg stearate	Talc
F1	2.5%	80mg	5mg	-	-	76mg	6mg	30mg	1mg	2mg
F2	5%	80mg	10mg	-	-	71mg	6mg	30mg	1mg	2mg
F3	7.5%	80mg	15mg	-	-	66mg	6mg	30mg	1mg	2mg
F4	2.5%	80mg	-	5mg	-	76mg	6mg	30mg	1mg	2mg
F5	5%	80mg	-	10mg	-	71mg	6mg	30mg	1mg	2mg
F6	7.5%	80mg	-	15mg	-	66mg	6mg	30mg	1mg	2mg
F7	2.5%	80mg	-	-	5mg	76mg	6mg	30mg	1mg	2mg
F8	5%	80mg	-	-	10mg	71mg	6mg	30mg	1mg	2mg
F9	7.5%	80mg	-	-	15mg	66mg	6mg	30mg	1mg	2mg

2. Evaluation of mouth dissolving tablets

A) Characterization of physicochemical parameters of tablets

The weight variation and the thickness of the tablets (Table 2) were within the limits of uniformity. The mass ranged from 201.22 to 210.75 mg with SD values 0.54–1.02. Thickness ranged between 2.50 and 2.59 mm with SD values of 0.24 to 1.08. The mass and thickness of all compressed tablets were within the limits as per

USP. The hardness of all prepared tablets was in the range of 3.5 to 4 kgs. The drug content ranged from 84.83± 0.86% in formulation F1 to 90.88 ± 0.92% in formulation F3, 88.98 ± 1.01% in formulation F4 to 88.71 ± 0.96 in formulation F6 and 87.96±0.88 in formulation F7 to 99.76±1.27 in formulation F9 (Table:13). The friability was ranged from 0.38 to 0.76. Friability and assay of all compressed tablets were within the limits as per USP.

Table 2: Weight variation, thickness, friability and assay

Formulation	Mass (mg) Mean ± SD	Thickness (mm) Mean ± SD	Friability (%)	Assay (%)
F1	201.22 ± 1.02	2.57 ± 0.24	0.72	84.83 ± 0.86
F2	206.31 ± 0.54	2.57 ± 0.26	0.54	87.21 ± 0.98
F3	206.35 ± 0.59	2.50 ± 0.47	0.64	90.88 ± 0.92
F4	206.57 ± 0.60	2.59 ± 1.08	0.76	88.98 ± 1.01
F5	208.47 ± 1.08	2.54 ± 0.67	0.56	87.71 ± 0.85
F6	208.21 ± 0.78	2.52 ± 0.54	0.47	88.71 ± 0.96
F7	210.75 ± 0.85	2.52 ± 0.85	0.56	87.96 ± 0.88
F8	212.44 ± 0.96	2.58 ± 0.96	0.38	84.17 ± 0.96
F9	208.76 ± 1.00	2.56 ± 1.01	0.45	99.76 ± 1.27

B) In vitro disintegration time

All formulations showed disintegration time less than 60 sec. Among the three super disintegrants used, Sodium Starch Glycolate showed less disintegration time followed by Cross Carmellose Sodium and Cros-povidone. The probable reason may be high gelling tendency of Cross Carmellose Sodium and Cros-povidone than Sodium Starch Glycolate which causes of tablet mass with subsequent retardation of disintegration. Besides the type, the concentration of super disintegrant used also affected the disintegration time. In case of all tablets an increase in concentration of super disintegrant resulted in definite decrease in disintegration time (Table 3).

C) Wetting time and Water absorption ratio

Wetting time is used as an indicator of the ease of the tablet disintegration in mouth cavity. It was observed that wetting time of tablets was in the

range of 18 to 35 sec (Table 3). It was observed that the type of the disintegrant affected the wetting time of the tablets. On comparing super disintegrants the formulation containing Cross-povidone has taken more wetting time than Cross carmellose sodium and Sodium Starch Glycolate. Wetting is related to the inner structure of the tablets and hydrophobicity of the components.

Water absorption ratio ranged from 51.53% to 80.20 % (Table 3). Super disintegrants performs their disintegrating action by wicking through capillary action and fibrous structure respectively. The relative ability of various disintegrants to wick water into the tablets was studied by water absorption ratio. Tablets containing Sodium Starch Glycolate quickly wicks water and were more hydrated as compared with tablets prepared with Cros-povidone and Cross Carmellose Sodium. The centers of the tablets with Cross Carmellose Sodium and Cros-povidone remained dry and hard.

Table 3: Disintegration time, wetting time and water absorption ratio

Formulation	Disintegrations time (sec)	Wetting time (sec)	Water absorption ratio
F1	30 sec	27sec	66.16%
F2	28 sec	25sec	68.50%
F3	22 sec	22sec	69.03%
F4	40 sec	35 sec	74.48%
F5	25 sec	20 sec	78.50%
F6	15 sec	18 sec	80.20.%
F7	35 sec	30 sec	51.53%
F8	30 sec	28 sec	55.32%
F9	28 sec	25 sec	62.50%

D) In vitro drug release study

In vitro dissolution study of the prepared mouth dissolving tablets was performed in pH 6.8 phosphate buffer using USP type 2 dissolution apparatus. The dissolution rate was found to increase linearly with increasing concentration of superdisintegrants (Figure 3). This was marked by decreased disintegration time values for tablet formulations containing higher proportions of super disintegrant. Formulations F1, F2, F3 containing Cross carmellose sodium have given maximum release at the end of 40min (Table 4). Formulations F4, F5, F6 containing sodium starch glycolate have given better release than formulations with Cross carmellose sodium and Cros-povidone. Formulation F4 with 2.5%w/w of sodium starch glycolate has given only 45.36% release.

Formulations F5 and F6 with 5%w/w and 7.5%w/w of sodium starch glycolate have given maximum release at the end of 20min and 10min respectively (Table 4). In case of formulations F7, F8 and F9 the drug release were 37.25%w/w, 67.5%w/w and 87.89%w/w at the end of 40min respectively (Table 4).

The relative efficiency of different super disintegrants to improve the dissolution rate of tablets was in the order of Sodium Starch Glycolate>Cros-carmellose Sodium>Cros-povidone at 5%w/w and 7.5%w/w concentrations. At 2.5%w/w concentration the relative efficiency was in the order of Cros-carmellose sodium>Cros-povidone>Sodium Starch Glycolate. In comparative study of all formulations F5 and F6 showed good release with in less time.

Table 4: In-vitro release profiles of formulations

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	7.99 ± 0.62	6.08 ± 0.75	16.42 ± 0.48	3.10 ± 0.54	30.85 ± 0.57	46.75 ± 0.67	11.53 ± 0.45	13.24 ± 0.47	11.33 ± 0.96
4	20.00 ± 1.07	17.61 ± 0.23	19.16 ± 0.94	3.62 ± 1.35	53.67 ± 0.32	72.95 ± 0.96	13.09 ± 0.53	16.89 ± 0.38	20.71 ± 0.63
6	22.46 ± 0.54	25.32 ± 0.62	28.26 ± 0.48	6.44 ± 0.64	73.58 ± 0.26	91.15 ± 0.48	14.03 ± 0.47	24.21 ± 0.46	26.55 ± 0.39
8	25.32 ± 0.47	31.44 ± 0.94	34.66 ± 1.41	8.90 ± 0.47	89.64 ± 0.45	96.40 ± 1.28	26.75 ± 0.64	27.07 ± 0.57	35.86 ± 0.65
10	43.05 ± 0.36	34.07 ± 0.40	43.09 ± 0.36	9.86 ± 0.85	95.17 ± 0.67	126.93 ± 0.29	17.93 ± 0.77	32.20 ± 0.69	43.57 ± 0.32
15	41.14 ± 0.97	51.72 ± 0.71	61.78 ± 0.62	23.30 ± 0.76	99.50 ± 0.89	-	24.13 ± 0.86	53.11 ± 0.76	54.30 ± 0.45
20	50.64 ± 0.71	58.56 ± 0.36	65.71 ± 0.62	25.16 ± 0.84	100.57 ± 0.62	-	28.62 ± 0.44	44.84 ± 0.64	64.20 ± 0.62
25	62.57 ± 0.48	73.70 ± 0.48	81.97 ± 0.36	29.54 ± 0.65	-	-	32.88 ± 0.76	51.66 ± 0.37	70.64 ± 0.38
30	68.02 ± 1.29	87.14 ± 0.23	94.17 ± 0.23	34.70 ± 1.20	-	-	37.25 ± 1.02	54.54 ± 0.65	75.77 ± 0.48
40	82.80 ± 1.37	101.97 ± 0.54	105.78 ± 0.65	45.36 ± 1.28	-	-	51.04 ± 1.16	67.50 ± 1.05	87.89 ± 0.78

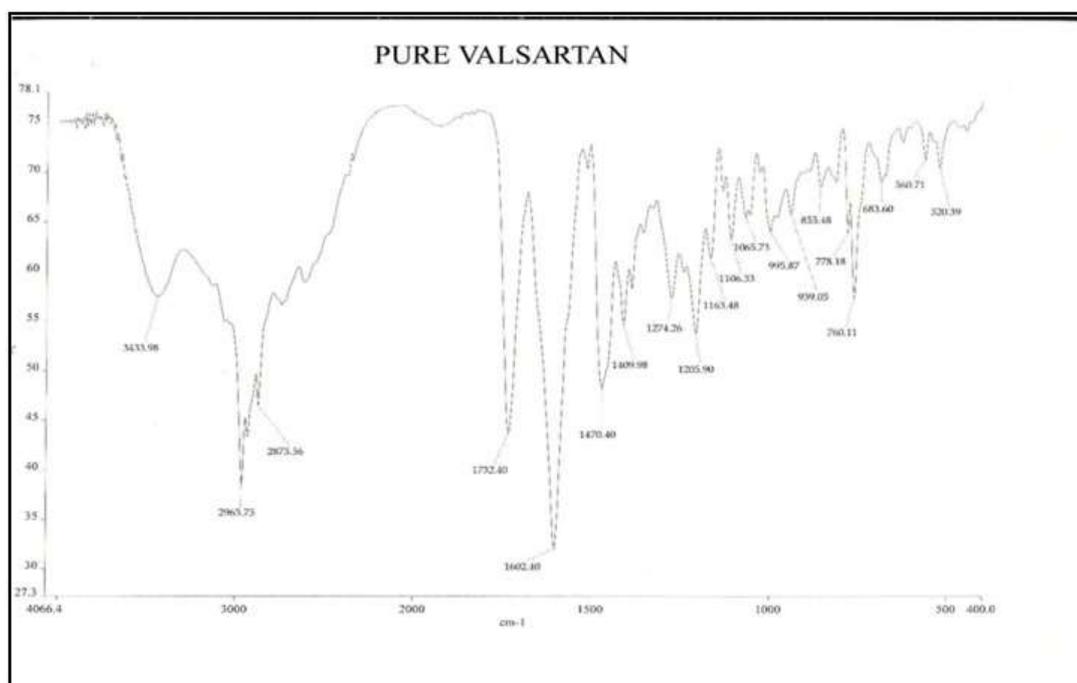


Figure 1: IR spectrum of pure Valsartan

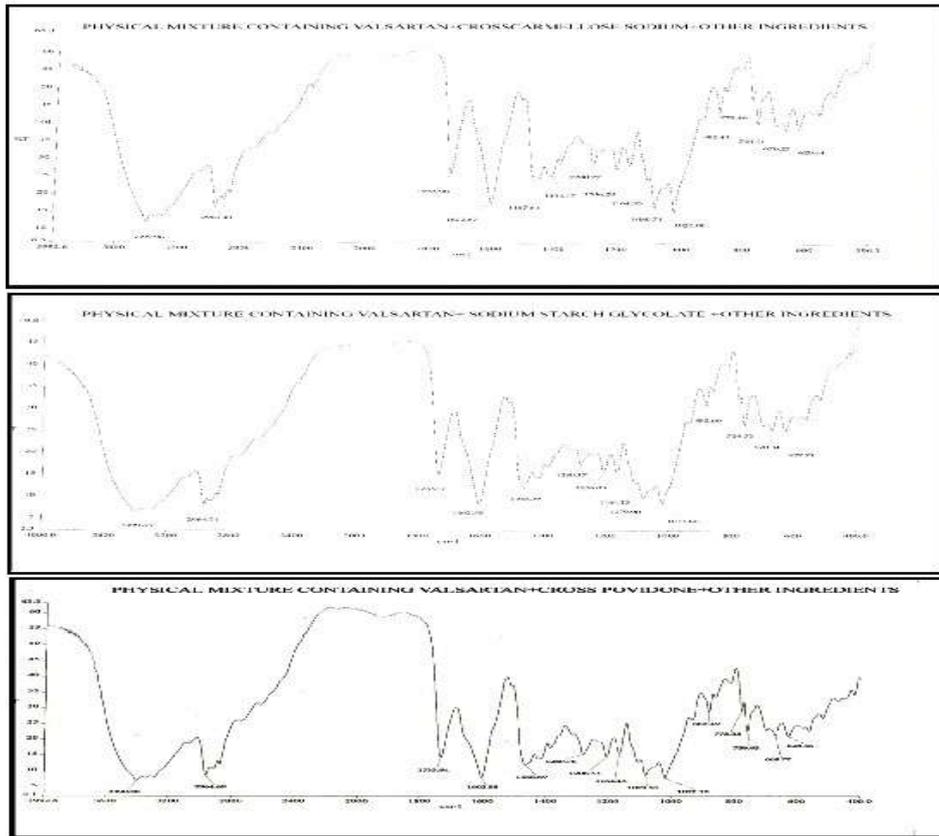


Figure 2: IR spectra of physical mixtures containing Valsartan+Super disintegrant+other ingredients

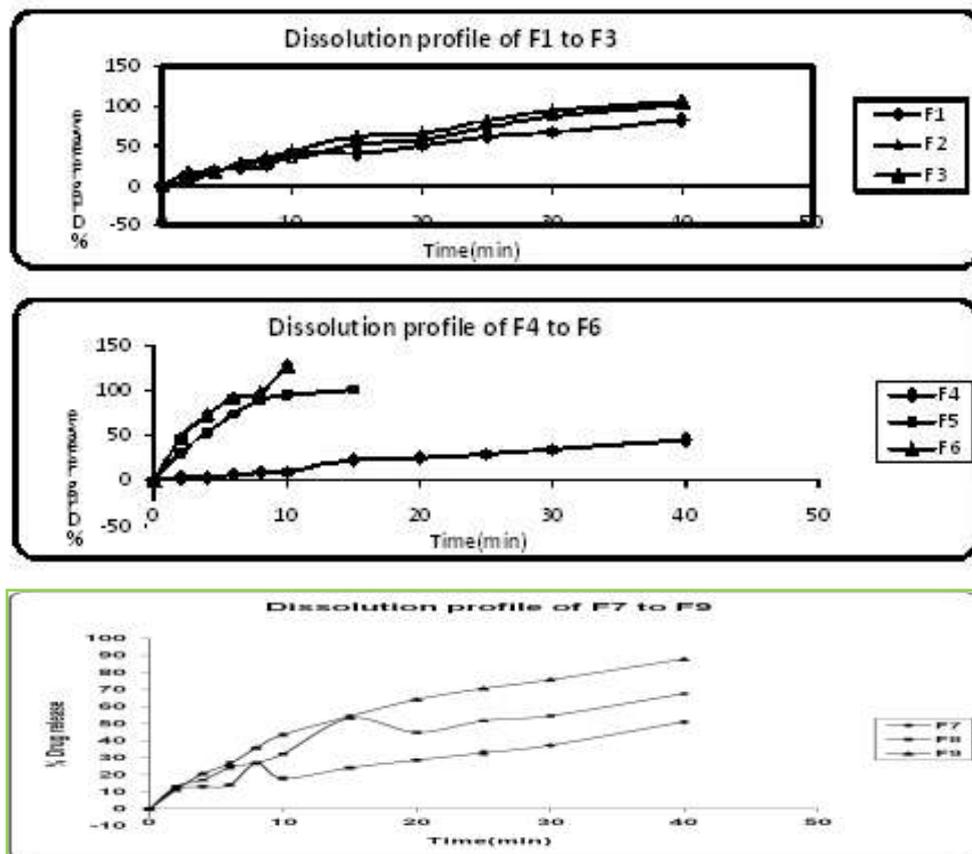


Figure 3: Comparison of dissolution profile of formulations

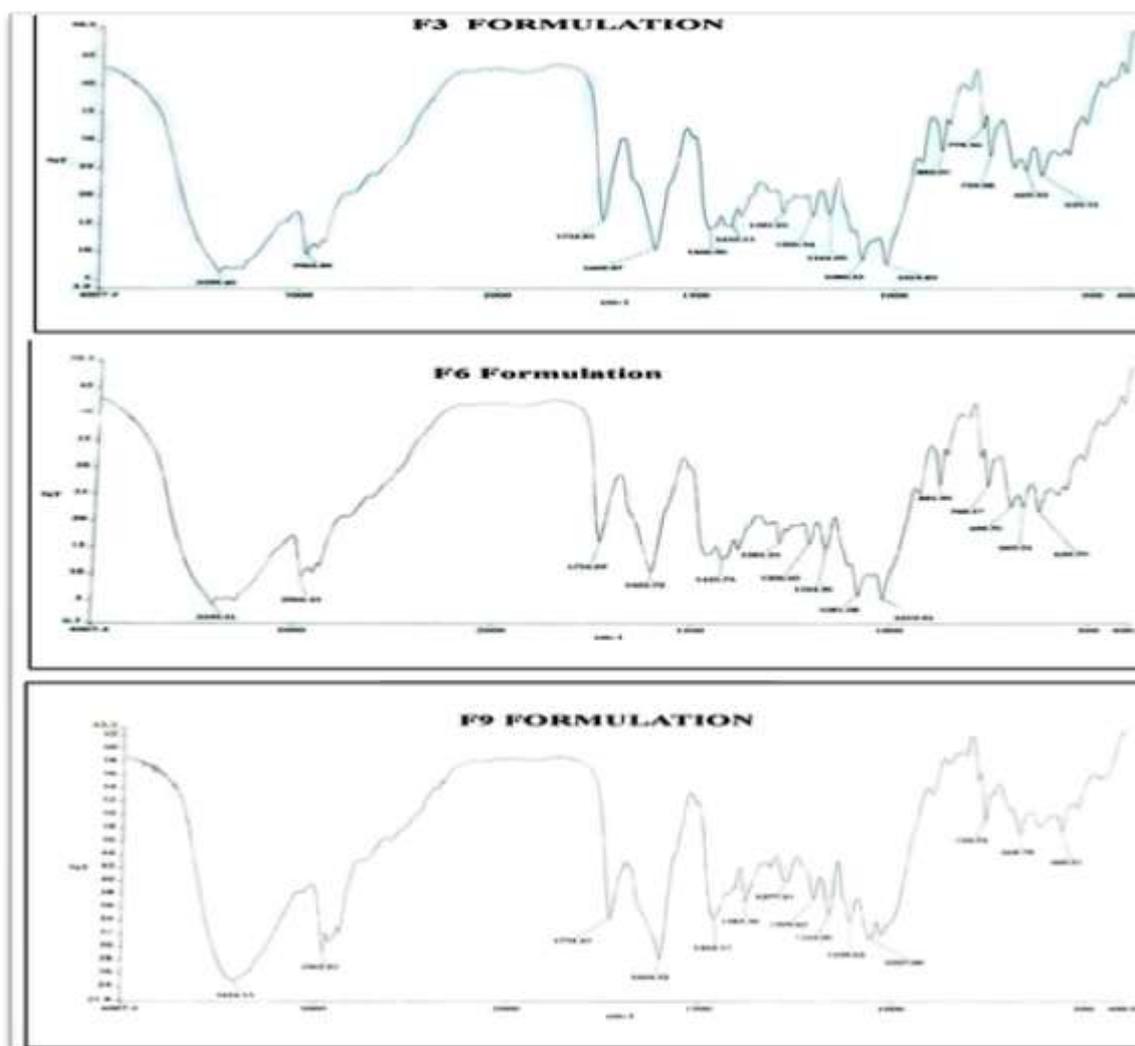


Figure 4: IR Spectra of F3, F6 and F9 formulations

F) Characterization of drug in mouth dissolving tablets

In IR spectrum of pure Valsartan (Figure 1) the presence of peaks at 1602.40 cm^{-1} ($>\text{C}=\text{N}$ stretching), 3433.98 cm^{-1} ($-\text{N}=\text{H}$ stretching), 1732.40 cm^{-1} ($>\text{C}=\text{O}$ group), 2963.75 cm^{-1} ($-\text{O}-\text{H}$ stretching), $1205.90, 1274.26\text{ cm}^{-1}$ ($-\text{C}-\text{N}$ stretching) were characteristic to that of the pure drug and all of them remained unaltered in the IR spectrum of powder sample of tablets (Formulations F3, F6, F9). IR analysis (Figure 4) revealed that there was no known chemical interaction of drug with super disintegrants and other ingredients in prepared Mouth dissolving tablets.

Conclusion:

In this study, it can be concluded that mouth dissolving tablets will give the promising

blood levels of Valsartan after administration. The first pass metabolism of Valsartan may be decreased due to rapid dissolution and absorption through mucosal layer of oral cavity and pharynx. Three super disintegrants at 7.5%w/w concentration have given good results for in vitro tests. Further work is needed to claim the same results in human volunteers by in vivo studies.

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