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Formulation and evaluation of orodispersible valsartan tablets

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ABSTRACT

The rationale of the study was to formulate orodispersible tablets of Valsartan for improving its poor oral bioavailability and with the aim of alleviating administration to patients facing problems with swallowing. Drug and excipients were characterized by infrared spectroscopy and differential scanning calorimetry. Valsartan tablets were formulated by using mannitol, methyl carboxy cellulose, croscarmellose sodium, crospovidone, sodium starch glycolate, aspartame, sodium bicarbonate, and citric acid and magnesium stearate. The formulations were characterized for their physical properties, weight variation, disintegration time, binding efficiency, wetting properties, content uniformity, and in-vitro dissolution. F1 showed the disintegration time of 20 sec and in-vitro drug release 93.43% within 20 min. The similarity factor (f2) is found to be 52.74 for the F1 formulation in which the release is greater to that of the marketed product (Diovan). The promising formulation (F1) was found to be stable during the stability studies conducted as per ICH guidelines, as it showed no significant changes in the physicochemical properties, disintegration time and in-vitro drug release.

Keywords: Fast dissolving, Valsartan, disintegration, binding efficiency

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INTRODUCTION

Fast dissolving tablets are the tablets dissipating upon contact with the damp mucosal surfaces of the oral cavity and rapidly release their components without mastication or water before swallowing [1,2]. The chief benefit of the fast dissolving tablets is meliorated patient compliance due to ease of swallowing and no need for water. Difficulties with resistance to tablet taking are common in all patient groups but are particularly prevalent in geriatric, pediatric, and psychiatric patients [3]. Physical problems with swallowing can aggravate compliance problems and undermine treatment efficacy. Other benefits of fast dissolving tablets include accuracy of dosage, rapid onset of action, and increase in bioavailability. The increased bioavailability of some fast dissolving tablets compared to conventional tablets may be due to the dispersion of drug in saliva and pregastric absorption. This pregastric absorption avoids first pass metabolism and can be a capital advantage in drugs that go through a big deal of hepatic metabolism [4,5,6]. However, many fast dissolving tablets showed nearly superposable plasma concentration profiles as conventional tablets but with the zealous advantage of convenience [7].

Valsartan is an angiotensin II receptor antagonist used in the management of hypertension [8]. It meliorates symptoms and quality of life in patients with chronic heart failure [9]. Valsartan treatment had no demonstrable negative effects on growth and development and is used safely as an antihypertensive agent in children less than 6 years old [10]. Valsartan is quickly absorbed following oral administration. It has a systemic availability of 25%, which is reduced to about 15% by food. It is 95% protein bound and is mostly excreted as unchanged drug via the bile [11]. It is given in doses of 40-320 mg once daily; this dosage is reduced in hepatic impairment, intravascular volume depletion, and renal impairment [12]. The drug is available commercially as conventional tablets 40, 80, 160 and 320 mg. Trials were done to formulate valsartan as a transdermal dosage form to overcome its low oral bioavailability [13].

The present work is concerned with the formulation and characterization of valsartan fast dissolving tablets for oral administration. Different drug compatible excipients were tried as fillers and binders.

MATERIALS AND METHODS

Materials

Valsartan was obtained as a gift from Torrent Pharma, India. Mannitol, methyl crystalline cellulose, and sodium bicarbonate were obtained as gift sample from SD-Fine-Chem Pvt, Mumbai. Croscarmellose sodium was gifted by Lobachemie Pvt Ltd, Mumbai. Crospovidone, sodium starch glycolate were obtained as gift from Arihant Trading Co., Mumbai. Aspartame was obtained as a gift sample from Sun and Kingly Pharma Pvt. Ltd., Satara, India. Magnesium stearate was gifted by Otto chemika biochemika, Reagents, Mumbai. All other chemicals are of either analytical or Pharmacopoeial grade.

Melting point determination:

Melting point of the drug sample was determined by capillary method by using melting point apparatus and was reported as shown in the table 1.

Determination of solubility:

The solubility of the Valsartan was determined by adding excess amount of drug in the solvent and equilibrium solubility was determined by taking supernatant and analyzing it on Lab India, double beam spectrophotometer and was reported as shown in the table 1.

Table no. 1: Characterization of Valsartan (API)

S. No	API characterization	Results
1	Physical appearance	It is a white to practically white fine powder.
2	Melting point	215 ºC
3	Solubility	It is soluble in ethanol and methanol and slightly soluble in water.

Solubility data of Valsartan in various solvent media:

These values of concentrations indicate the solubility of Valsartan in different solvents. It was observed that the solubility of Valsartan in acidic media is very low and it shows better solubility profile in ph 6.8 buffer. The results were shown as in table 2.

Table 2: Solubility data of Valsartan

Solvent media	Solubility(mg/ml)
Water	0.137
0.1 N HCl	0.011
pH 3.0 buffer	0.090
pH 4.5 buffer	0.894
pH 6.8 buffer	1.303
pH 7.2 buffer	1.284

RESULTS AND DISCUSSION

Drug–Excipient Compatibility Study

This study was done by FTIR and DSC (Fig 1 – 4) to evaluate the compatibility of valsartan with pharmaceutical excipients of common use as diluents and superdisintegrants. Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR. The instrument was calibrated by using polystyrene film.

Fourier Transformation Infra-red (FTIR) analysis:

Infra-red spectroscopy analysis was performed by Fourier Transformation Infrared Spectrophotometer Alpha Brooker FTIR (Tokyo, Japan). The instrument was calibrated by using polystyrene film.

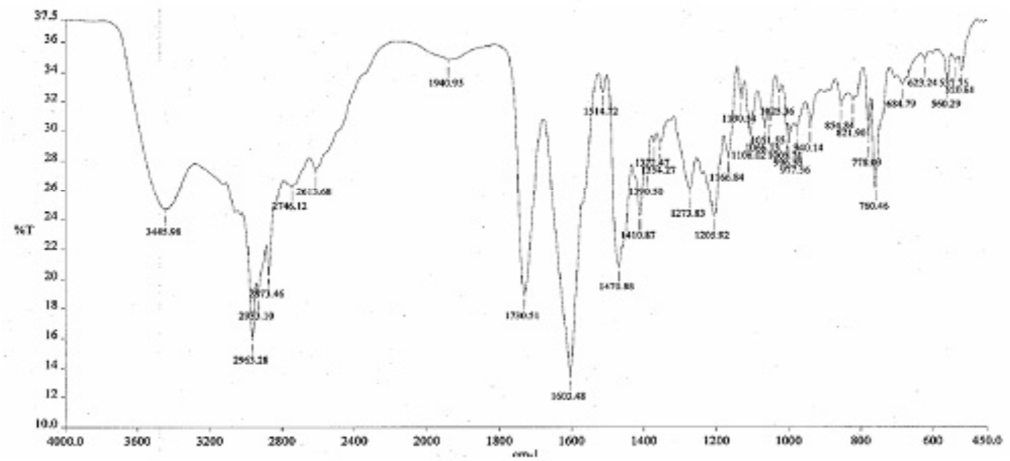


Fig 1: Infrared spectra of Valsartan drug

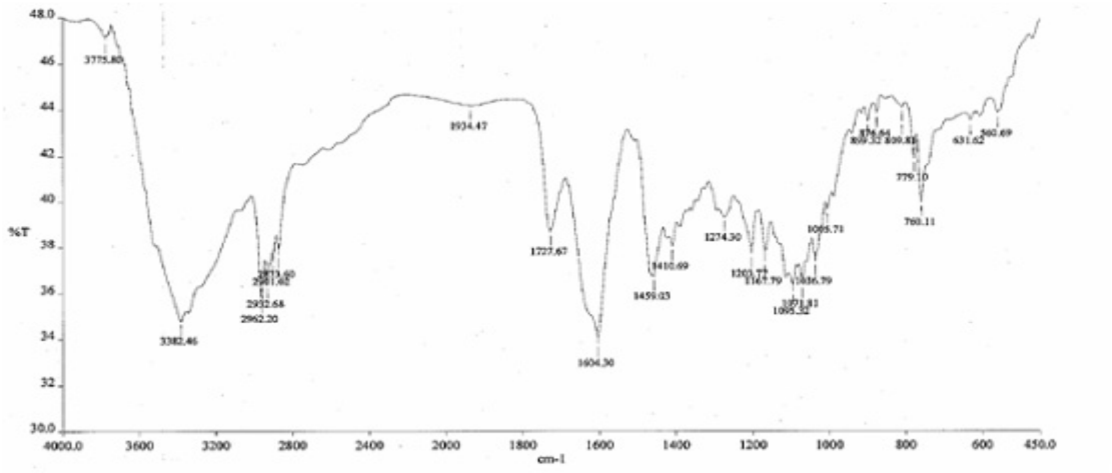


Fig 2: Infrared spectra of Valsartan + excipients

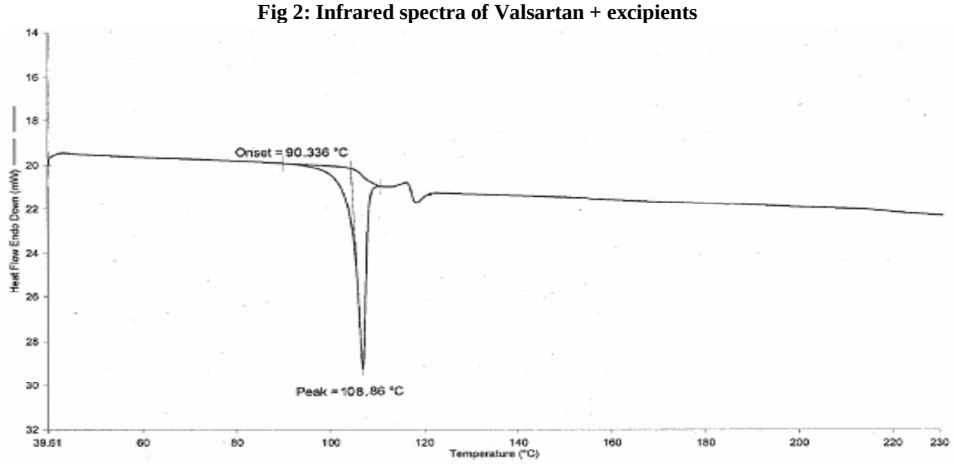


Fig 3: DSC of Valsartan

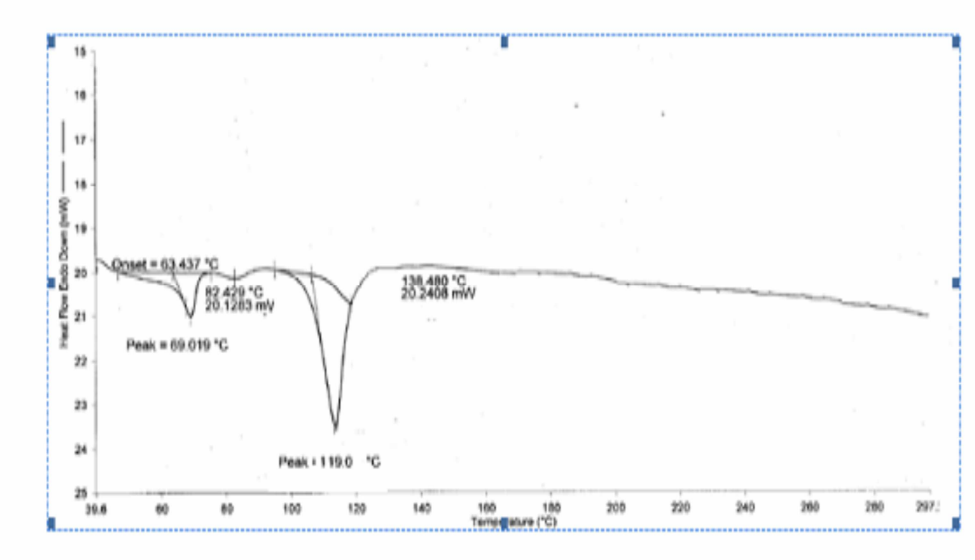


Fig 4: DSC of Valsartan + excipients

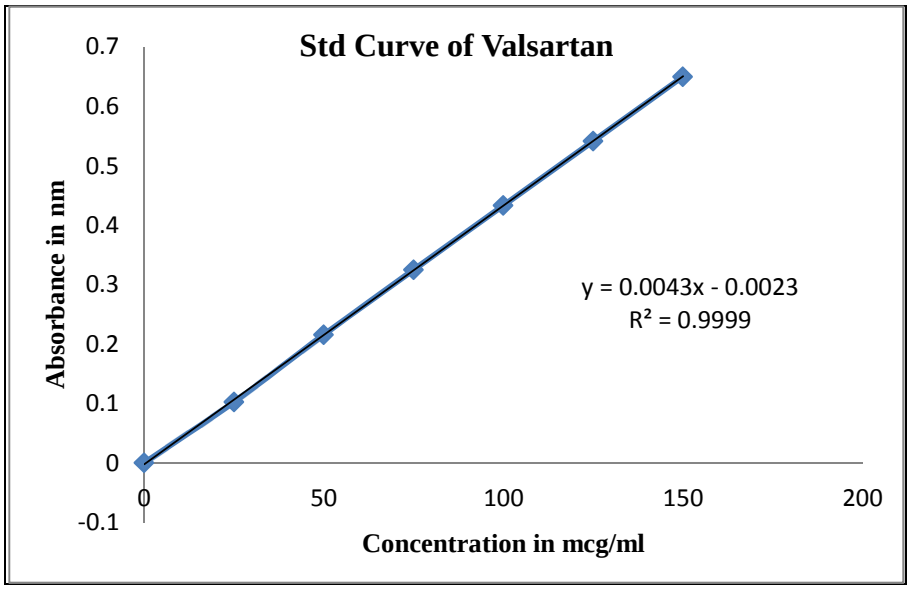
Calibration curve for Valsartan

Standard solutions in the range of 50 to 150 µg/ml (Table 3 and Fig 5) were prepared and absorbance values were recorded at 265 nm against the reference. From this data, the standard curve of Valsartan was obtained by plotting absorbance on y-axis against concentration on x-axis.

Table 3: Standard Curve for Valsartan

S. No	Concentration (µg/ml)	Absorbance (265 nm)
1	0	0
2	50	0.2166
3	75	0.3248
4	100	0.4331
5	125	0.5414
6	150	0.6497

Fig 5: Standard curve of Valsartan



Preparation and Characterization of Valsartan Fast dissolving Tablets
Method of preparation of tablets
All the ingredients (table 4) except magnesium stearate are weighed and sieved through # 44 mesh separately. After sieving they were thoroughly mixed by geometrical order for 10 min. Finally, the magnesium stearate was added to the above blend and mixed for 2 min. The above lubricated blend is compressed by using 8 mm round punches.

Evaluation of precompression parameters:
Angle of Repose:
20gm of the sample was taken. The sample was passed through the funnel slowly to form a heap. The height of the powder heap formed was measured. The circumference formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

Table 4: Composition of Valsartan Tablets

INGREIDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Valsartan	40	40	40	40	40	40	40	40
Mannitol	135	135	135	135	135	135	125	125
Methyl carboxy cellulose	50	50	50	50	50	50	50	50
Croscarmellose sodium	20	-	-	10	10	-	-	-
Cross povidone	-	20	-	10	-	10	-	-
Sodium starch glycolate	-	-	20	-	10	10	-	-
Sodium-bi-carbonate	-	-	-	-	-	-	20	20
Citric acid	-	-	-	-	-	-	10	10
Aspartame	3	3	3	3	3	3	3	3
Magnesium stearate	2	2	2	2	2	2	2	2
Total Weight	250	250	250	250	250	250	250	250

Bulk density:
Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder or through volume measuring apparatus in to cup.

Bulk density = M / V_0

Where M= mass of the powder; V_0=bulk volume of the powder.

Tapped density:
A known quantity of powder was transferred to a graduated cylinder and volume V0 was noted. The cylinder fixed to a density determination apparatus, tapped for 500 times then reading was observed. The density is achieved by mechanically tapped by a measuring cylinder containing the powder sample. After observing the initial volume the cylinder is mechanically tapped and volume reading were taken until little further volume changes is observed.

Tap density = M / V_r

Where M = mass of the powder, V_r = final tapping volume of the powder.

Compressibility index and Hausner's ratio:
While there are some variations in the method of determining the compressibility index and Hausner's ratio, the basic procedure is to measure the unsettled apparent volume, (V_O), and the final tapped volume, (V_f), of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner's ratio are calculated as follows:

Compressibility index = $100 \times Vo\text{-}V_f/Vo$
Hausner's ratio = Vo/V_f

Where, V_o = apparent volume, V_f = final tapped volume.

Alternatively, the compressibility index and Hausner's ratio may be calculated using measured values of bulk density and tapped density as follows:

Compressibility index = 100 × 1- (bulk density / tapped density)
Hausner's ratio = tapped density / bulk density

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping.

Table 5: Preformulation studies of blend of all formulation

Formulation code	Angle of repose(θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	21.5	0.5769	0.7500	23.076	1.3000
F2	20.1	0.5769	0.7500	23.076	1.3000
F3	19.6	0.5357	0.6818	21.428	1.2727
F4	20.1	0.5357	0.6250	14.285	1.1666
F5	21.3	0.5769	0.6818	15.384	1.1818
F6	19.5	0.4687	0.5769	18.750	1.2307
F7	19.2	0.5357	0.6250	14.285	1.1666
F8	17.5	0.5000	0.6818	26.666	1.3636

EVALUATION OF TABLETS (Post Compression Parameters):
The quantitative evaluation and assessment of tablets includes chemical, physical and bioavailability properties. These are important in the design of tablets and to monitor product quality. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

1. Physical Appearance:
The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. Five tablets from different batches were randomly selected and organoleptic properties such as size, shape, color, odor, and taste were evaluated. Appearance was judged visually.

Very good (+++), good (++), fair (+) poor (-), very poor (- -).

2. Diameter
It was measured by digital Vernier Calliper. It is expressed in mm.

3. Hardness [14]
The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2.

4. Thickness [14]:
It can be dimensionally described and controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value. It was determined by using digital Vernier Calliper. It is expressed in mm.

5. Friability [14]:
Ten tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked. Friability of the tablets was determined using Roche Friabilator. It is expressed in percentage. The percentage friability was determined by the formula:

% Friability = $(W_1-W_2) / W_1 \times 100$

$\mathbf{W_1}$ = Weight of tablets before test and $\mathbf{W_2}$ = Weight of tablets after test

6. Hardness-Friability ratio [15, 16]:
The hardness-friability ratio (HFR) provides a parameter for measuring tablet strength. Generally, the higher the HFR value, the stronger is the tablet. Alternatively, the hardness-disintegration ratio (HDR) can also be exploited to establish tablet strength.

7. Weight variation test [14]:
Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table 6: Post Compression parameters of fast dissolving Valsartan tablets

F. code	Diameter (mm)	Thickness (mm)	Friability (%)	Hardness Kg/cm^2	Hardness-Friability ratio	Binding efficiency (kg/sec)
F1	10.8	1.95	0.12	3.9	32.5	1.62
F2	10.9	1.85	0.15	3.6	24	1.33
F3	11.3	1.9	0.12	3.5	29.16	1.82
F4	11.2	1.91	0.14	4.1	29.28	2.44
F5	11.0	1.86	0.13	3.5	26.92	1.41
F6	10.9	1.92	0.12	3.3	27.5	1.61
F7	10.9	1.91	0.14	3.4	24.28	1.61
F8	11.1	1.93	0.16	3.8	23.75	1.82

8. Wetting time [17, 18]:

Five circular butter papers of 10-cm diameter were placed in a petridish with a 10-cm diameter. 10 ml of water at 37^0C $\pm$ 0.5^0C containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of butter paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Six tablets from each formulation batch were tested randomly and the average reading noted. Based on the following equation, the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders.

$$dl / dt = r \gamma \cos\theta / (4 \eta l)$$

where, l = length of penetration, r = capillary radius , γ = surface tension
η = liquid viscosity, t = time, θ = contact angle

9. Water absorption ratio [18]:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R, was determined using following equation,

$$\mathbf{R = W_a - W_b / W_b \times 100}$$

Where, W_a = weight of tablet after absorption and W_b = weight of tablet before absorption

10. Disintegration time:

To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2º C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. The basket containing the tablets is moved up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test, the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate the test is repeated using 12 tablets.

11. Content Uniformity:

Randomly 30 tablets were selected. 10 of these are assayed individually. The Tablet passes the test if 9 of the 10 tablets contains not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

Table 7: Post Compression parameters of fast dissolving Valsartan tablets

F. code		Weight	Wetting time	Water absorption	Disintegration	Content
F1	+++	250±0.11	15	24.95	20	99.98
F2	++	250±0.13	14	24.39	18	99.21
F3	+++	249±0.53	12	19.5	16	99.72
F4	+	249±0.69	8	16.82	12	99.54
F5	+	251±0.16	10	27.94	19	99.56
F6	++	250±0.17	12	16.36	17	99.62
F7	+	250±0.18	15	14.54	15	99.18
F8	+++	251±0.10	11	19.81	13	99.81

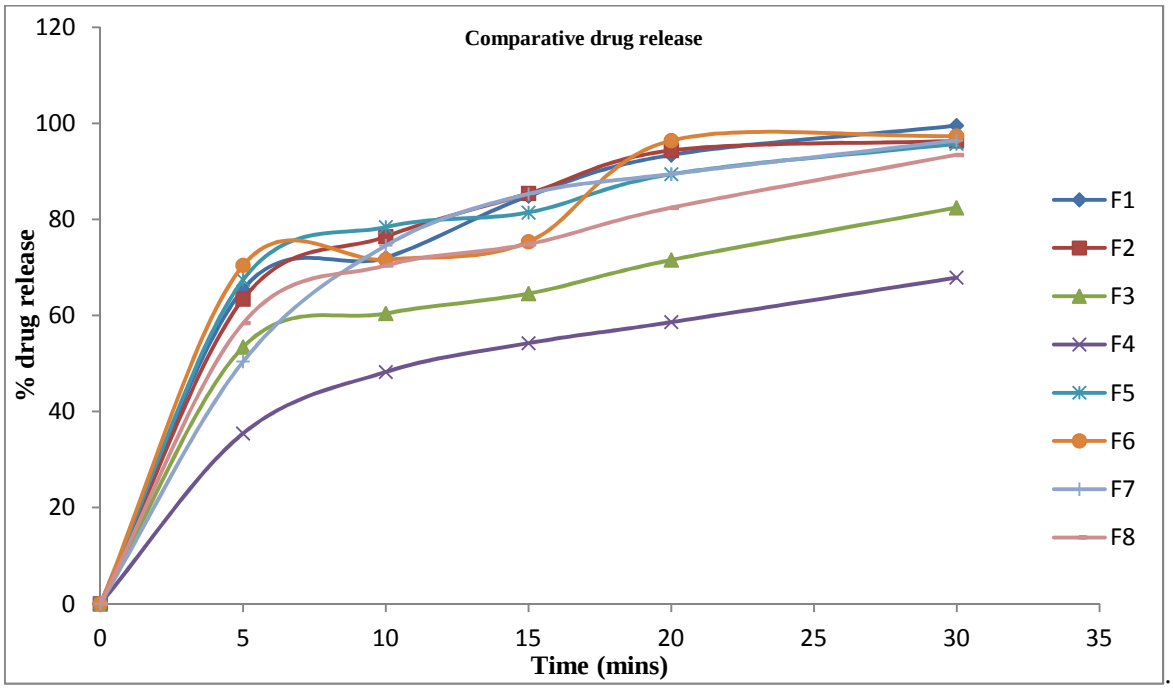
12. Drug release

The drug release from the Valsartan tablets was investigated in a USP-II (paddle) apparatus, 900 ml of 6.8 pH Phosphate buffer (50 rpm, 37°C). At predetermined time intervals, 5-ml samples were withdrawn and take 1ml sample and diluted to 10 ml and then analyzed with UV Spectrophotometry at λmax = 267 nm.

Table 8: Dissolution values of Formulations F1 - F8

Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	65.46	63.42	53.42	35.46	67.42	70.42	50.42	58.42
10	72.04	76.45	60.42	48.25	78.42	71.64	74.56	70.42
15	84.89	85.42	64.57	54.25	81.46	75.35	85.32	74.86
20	93.43	94.36	71.56	58.62	89.42	96.42	89.46	82.45
30	99.54	96.36	82.46	67.89	95.76	97.35	96.42	93.46

Fig. 6: Comparison of in-vitro release of various formulations



COMPARISON WITH MARKETED PRODUCT

Valsartan innovator product (Diovan) has shown 80.37% drug release in initial stage, after that it gradually increases to 92.4% drug release in 45mins. The results were shown in table 9.

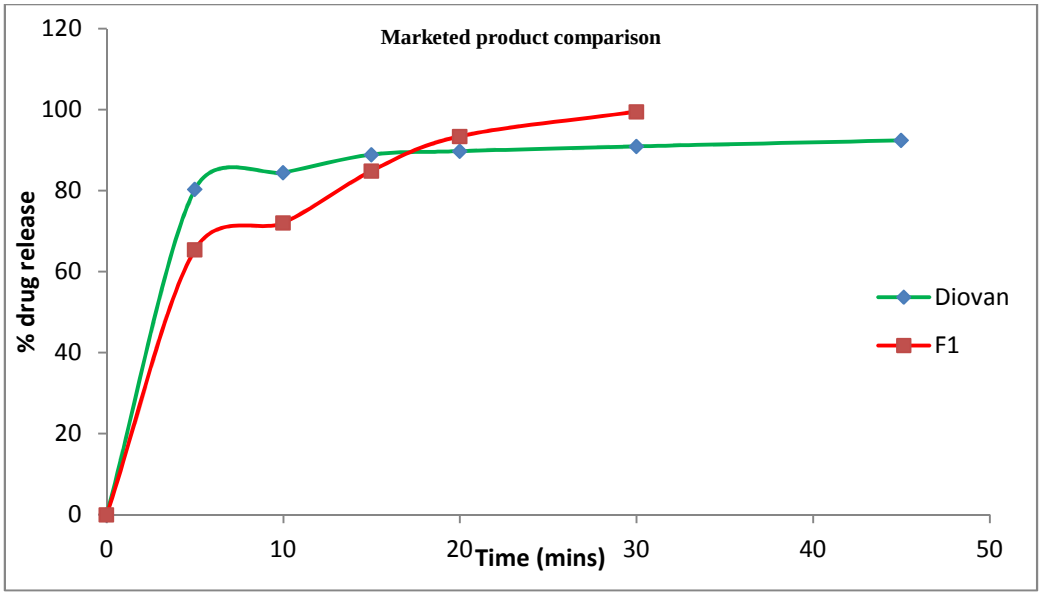
The *in-vitro* dissolution profile of formulation F1 was compared with the marketed formulation Diovan in the solvent pH 6.8 buffer. The similarity factor *f*2 was found to be 52.74 for the formulation F1 and the marketed formulation, indicating the release was faster than that of marketed product. The *f*2 factor is a logarithmic reciprocal square root transformation of the sum of squared error. The *f*2 factor was used to quantitate the agreement between two dissolution profiles. The similarity factor is calculated using PCP Disso Software. Dissolution tests were conducted under the same conditions. The value of *f*2 from 50 to 100 shows similarity in *in-vitro* release profiles. The similarity factor ($f2$) was found to be 52.74 for the formulation F1, which the release was greater to that of the marketed product Diovan.

$$f2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}[R_t - T_t]^2\right]^{-0.5} \times 100\right\}$$

Table 9: In-vitro drug release of formulation F1 with innovator product (Diovan)

Time (mins)	Innovator product (%) Diovan	F1 (%)
0	0	0
5	80.37	65.46
10	84.48	72.04
15	88.91	84.89
20	89.76	93.43
30	90.95	99.54
45	92.43	-

Figure 7: Cumulative % drug release of F1 Vs time profile of innovator product



STABILITY STUDIES OF PROMISING FORMULATION

Stability studies of batch F1 was carried out using the samples at 40^0C ± 2^0C and 75% ± 5% RH for a period of 3 months. The tablets are observed that there is no significant change in the release characteristics and physicochemical properties of the tablets. The results were shown in table below.

Table 10: STABILITY STUDY OF FORMULATION F1

PARAMETERS	Initial	1st Month	2nd Month	3rd Month
Physical appearance	White, smooth flat faced	White, smooth flat faced	White, smooth flat faced	White, smooth flat faced
Hardness(Kg/cm2)	3.9	3.9	3.9	4.0
Wetting Time (sec)	15	15	15	15
Disintegration Time (sec)	20	20	20	19
Drug content (%)	99.9	100.8	98.2	100.4
In-vitro release (%)	99.69	99.52	99.73	99.68

CONCLUSION

It can be concluded from the characterization of fast dissolving tablets, that formulation F1 containing methyl carboxy cellulose and croscarmellose sodium is most acceptable based on disintegration time, drug content and *in-vitro* data. It was also observed that to further increase the drug release from FDTs, solubility enhancement of valsartan is required. Under standard stability conditions, no significant changes were recorded with respect to appearance, hardness, wetting time, disintegration time, drug content and *in-vitro* drug release over a period of 3 months indicating a stable product. Since 65% release of the drug from the tablet was obtained within 5 minutes, the approach is suitable for the formulation of mouth-dissolving tablets. The similarity factor ($f2$) was found to be 52.74 for the promising formulation (F1) with that of the marketed product (Diovan). Further *in vivo* studies in animal models and human volunteers are required to correlate *in vitro* release data.

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