Research Article

Valsartan Fast Dissolving Tablets: Formulation and *in vitro* Characterization

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ABSTRACT

Valsartan as an angiotensin II receptor antagonist widely used in the management of hypertension. The present research work was aimed to develop a fast dissolving tablet (FDT) of Valsartan. The FDT was formulated using different concentration (1, 2, and 4 %) of superdisintegrants like croscarmellose sodium, crospovidone, sodium starch glycolate and PVP K-30, using Avicel PH -102 using as diluents. The drug excipients interaction was examined by using FTIR and DSC. The drug excipient blend was examined for flow properties. All the batches of FDT were prepared by direct compression method and were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time, dissolution study, in vitro drug release kinetics and stability study. FTIR and DSC studies showed no evidence of interactions between drug and excipients. The IPQC parameters evaluation results for FDT for all batches were found to be acceptable according to standard limits of I.P. From the data of regression R2, it was concluded that optimized formulations followed first order drug release kinetic. Amongst all FDT formulations, formulation F8 prepared by using drug with 2% Crospovidone showed least disintegrating time of 21±0.31 s and greater dissolution (100.38 %). From the above studies, it was concluded that fast dissolving tablet of Valsartan prepared by crospovidone as superdisintegrant is most acceptable for safe management of hypertension.

Keywords: Valsartan, Crospovidone, Fast dissolution, Crosscarmellose, Disintegration time.

INTRODUCTION

Oral Disintegrating tablets are novel types of tablets that disintegrate rapidly in saliva. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients[1]. The benefits in terms of patient compliance, rapid onset of action, increased bioavailability and good stability. The oral disintegrating tablets are also known as fast dissolving tablets, melt-in-mouth tablets, rapid melts, porous tablets, oro-dispersible tablets, quick dissolving or rapidly disintegrating tablets[2, 3].

FDTs are prepared by various techniques, mainly direct compression, lyophilization and moulding. The superdisintegrants are added to a drug formulation to facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly than in absence of disintegrants[4, 5].

Valsartan is an orally active Angiotensin II receptor type 1 antagonist which causes reduction in blood pressure and is used in treatment of hypertension. Valsartan exert effects on blood pressure (BP) reduction, as well as decreases vascular smooth muscle contraction, inhibits sympathetic outflow, improves renal function and also leads to reduction in progression of atherosclerosis lesions[6, 7].

Valsartan is rapidly absorbed orally. After oral administration of Valsartan 80mg capsule and solution formulation in 12 healthy volunteers, maximum plasma concentrations (Cmax) of Valsartan (1.64mg/l and 3.25 mg/l) were respectively reached in ~ 1-2 h. Plasma levels and the area under the plasma concentration time curve were not linearly related to dose, indicating a saturable first pass metabolism[8].

The aim of the present study was to design, development, preparation and characterization of fast dissolving tablets of Valsartan using various superdisintegrants for rapid dissolution of drug and absorption, which may produce rapid onset of action in the management of hypertension.

MATERIALS

The Valsartan was procured as gift sample for analytical purpose from Macleod Pharmaceutical Ltd., Sikkim. The superdisintegrants crospovidone, croscarmellose and sodium starch glycolate were procured from S.D. Fine Chemical, Mumbai. All other chemicals were procured from authorized dealer and were of analytical grade.

METHODOLOGY

Fourier transforms infrared spectroscopy (FT-IR) studies

The FT-IR (Shimadzu IR spectrophotometer, model 840, Japan) was used for these IR analysis in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution. Pure drug and different super disintegrates were selected separately and palletized in KBr using IR press. The IR peaks of pure valsartan were analyzed and were compared with the peaks of the obtained formulations[9].

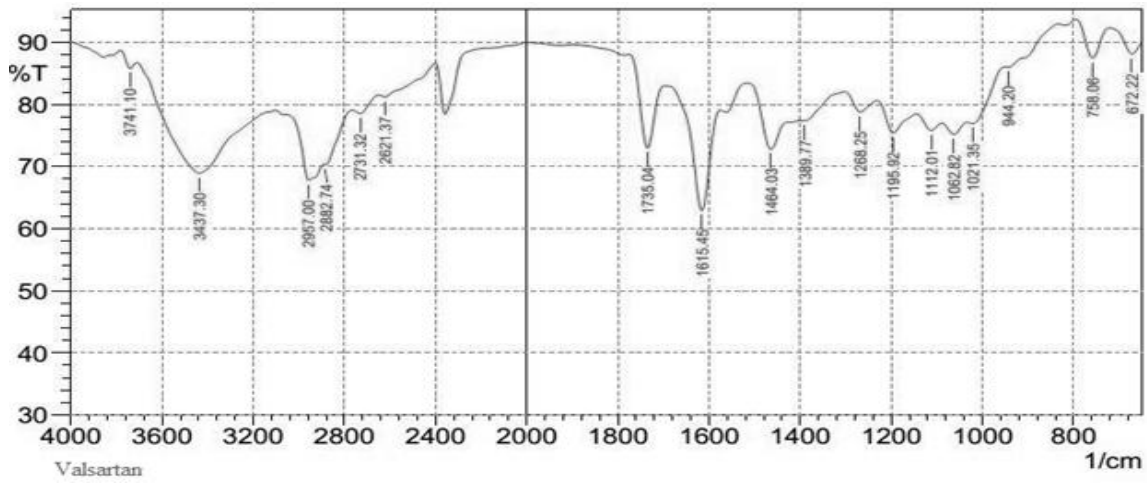

Figure 1: FTIR data (Graph) of Valsartan in the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution.

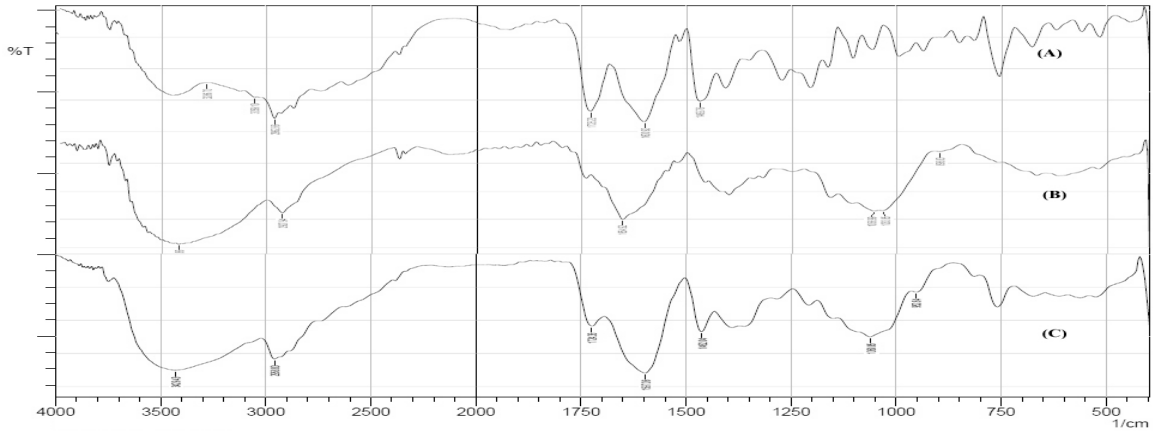

Figure 2: FTIR data of various Valsartan fast dissolving tablet formulations (A – Valsartan+SSG, B – Valsartan+Crosscarmellose and C – Valsartan+Crossprovidone).

Differential Scanning Colorimetric (DSC) studies

DSC was performed on a Shimadzu DSC-60 (Shimadzu, Japan). A 1:1 ratio of drug and excipient was weighed into aluminium crucible and sample was analyzed by heating at a scanning rate of 100°C/min over a temperature range 200-3000°C under a nitrogen flow of 40 ml/min[10].

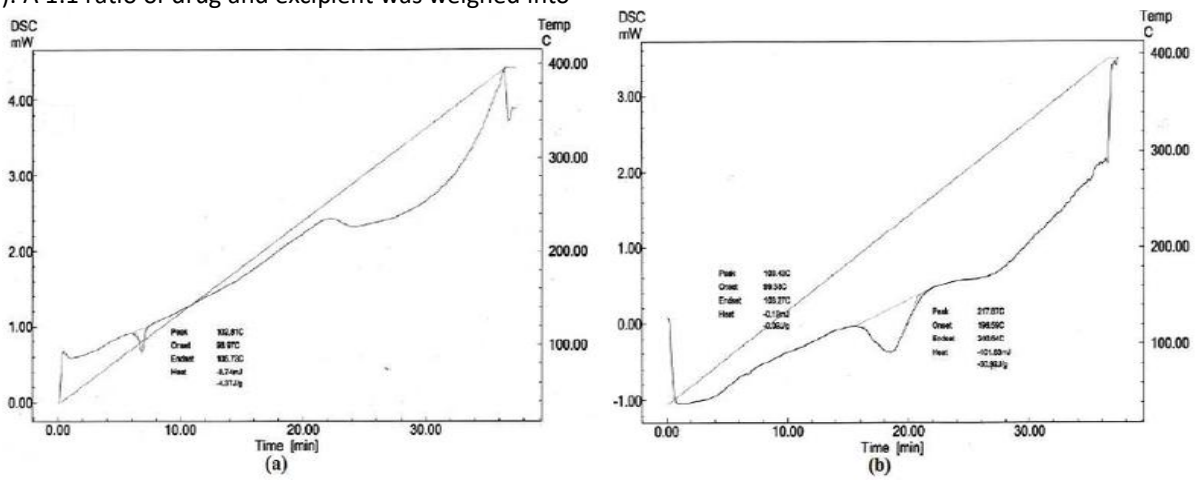

Figure 3: DSC chromatogram of Valsartan (a) drug and Valsartan optimized (F8) (b) fast dissolving tablets.

Formulation Design and Preparation FDT of Valsartan:

The different formulations each containing 80 mg of pure drug were prepared using Avicel pH 1.2 as diluent and sodium starch glycollate, cross carmellose sodium (Ac-Di-Sol), cross povidone and poly vinyl pyrrolidine K-30 as superdisintegrants. To impact good mouth peel properties lemon flavor and sweetener sodium saccharine was incorporated. All the ingredients were passed through mesh 60 separately. Required quantity of each ingredient was taken for each specified formulation (depicted in the Table 1) and blended[11].

Table 1: Formulation design of valsartan fast dissolving tablets.

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Drug	80	80	80	80	80	80	80	80	80	80	80	80
MCC	91	88	82	91	88	82	91	88	82	91	88	82
SSG	3	6	12	--	--	--	--	--	--	--	--	--
Ac-Di-Sol	--	--	--	3	6	12	--	--	--	--	--	--
Ac-Di-Son	--	--	--	--	--	--	3	6	12	--	--	--
PVP (K-30)	--	--	--	--	--	--	--	--	--	3	6	12
Sod. Starch	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mg Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Lemon flavor	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total wt.	180	180	180	180	180	180	180	180	180	180	180	180

MCC - Microcrystalline Cellulose, SSG - Sodium starch Glycolate, Ac-Di-Sol – Crosscarmellose, Ac-Di-Son – Crosprovidone.

Flow Properties

The powder blend was evaluated for flow properties such as bulk density, tapped density, compressibility index and Hausner ratio to assure weight and dose accuracy during compression for commercial aspect. The angle of repose was determined by fixed funnel method. The blend were tapped using bulk density apparatus (Excel Enterprises, Kolkata) for 1000 taps in a cylinder and the change in volume were measured. Carr index and Hausner ratio were calculated by the formula[12, 13]:

Carr index (%) = $(D_f - D_0) \times 100 / D_f$ ..... (1)

Hausner ratio = D_f / D_0 ..... (2)

Where, D_f is poured density; D_0 is tapped density. All the experimental units were studied in triplicate (n=3).

Compression of tablets

The mixed blend of drug-excipient (Magnesium stearate) was compressed using an 8 mm, biconcave punch in a single-stroke by using eight station rotary machines (The Rimek Mini Press-1) to produce biconvex faced tablets weighing 180 mg each. A minimum of 40 tablets were prepared for each batch and were kept in air tight closed container for further study[14].

Evaluation of Physicochemical parameters of FDT tablets

The tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution study as per the standard specification of I.P.

Thickness uniformity

The crown thickness of individual tablet (Six tablets from each formulation) was measured by using vernier caliper, which permits accurate measurements and provides information on the variation between tablets[15].

Hardness

The strength of tablet is expressed as tensile strength (Kg/cm2). The tablet crushing load, which is the force required to break a tablet into halves by compression .It was measured by taking 6 tablets from each formulation using a tablet hardness tester (Monsanto Hardness Tester) [15, 16].

Friability

The friability of sample of six tablets ware measured using a Roche Fribilator. Six pre-weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fine's using 60 mesh screens and the percentage of weight loss was calculated by using equation[16],

Friability (%) = (Loss in weight / Initial weight) × 100 ..... (3)

Uniformity of weight

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight[16, 17].

Drug content uniformity

Twenty tablets were powdered, and 10 mg equivalent weight of losartan tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of simulated gastric fluid 0.1N HCl (pH 1.2) was added and shaken for 10 min. Then, the volume was made up to 100 ml with 0.1N HCl. The solution in the volumetric flask was filtered, diluted suitably and drug content was analyzed using UV-Visible spectrophotometer (Shimazu UV/Vis spectrophotometer) at λ_{max} 206 nm[16, 17].

Wetting time and water absorption ratio

A piece of paper folded twice was kept in a Petri dish (internal diameter 5.5 cm) containing 6 ml of purified water. A tablet having a small amount of Rosaline dye powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. The same procedure without Rosaline dye powder was followed for determining the water absorption ratio (R) was determined according to the following equation[18],

$$R = [(Wa - Wb)/Wb] \times 100 \quad (4)$$

Where, Wb and Wa are the weights of the tablet before and after use.

Disintegration time

Disintegration time was measured in 900 ml artificial simulated gastric fluid i.e. 0.1N HCl (pH 1.2) according to the USP 24 method without disc at 37 ± 0.1°C temperature. The disintegration time of 6 individual tablets from each formulation were recorded and the average was reported[18].

In vitro dissolution study

The release of losartan from FDTs was determined using USP dissolution testing apparatus 2 (paddle method; Veego Scientific, Mumbai) [19]. The dissolution test was performed using 900 ml of artificial simulated gastric fluid i.e. 0.1N HCl (pH 1.2) at 37 ± 0.1°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at different time intervals and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to suitable concentration with artificial gastric fluid i.e. 0.1N HCl (pH 1.2). Absorbance of these solutions was measured at λ_{max} 206 nm using a UV-Visible spectrophotometer. Cumulative percentage drug release was calculated using regression equation obtained from a standard curve.

In vitro drug release kinetics

In order to study the exact mechanism of drug release from microspheres, drug release data was analyzed according to Zero order kinetics[20], first order kinetics[21] and Koresmeyer model[22]. The criterion for selecting the most appropriate model was chosen on the basis of goodness of fit test.

Stability studies

Stability studies for optimized FDTs formulation was carried out at 25±2°C, 60±5% RH and 40±2°C, 75±5% RH for 60 days for optimized formulation. The stability study was done as per ICH guidelines[23].

Statistical analysis

All the results obtained during evaluation, were verified with different statistical methods like mean, standard deviation, standard error mean[24-26].

RESULTS AND DISCUSSIONS

The direct compression method was found to be efficient method for successful manufacture of FDTs. After interpretation of the FTIR data, the formulation samples gave exact absorbance peaks for major functional groups with standard pure drug (Valsartan) hence the drug is compatible with other polymers and excipients as evident from Fig 1 and 2, thus there was no physical incompatibility between drug and excipients (superdisintegrants)[27,28]. The angle of repose were found in the range of 23.48±0.19 to 26.36±0.26°, Carr's index of the prepared blends falls in the range of 8.459 to 14.09 % and this is also supported by Hausner ratio values which were in the ranges of 1.089 to 1.161 (Table 2). Hence the prepared blends possessed good flow properties, thus during compression of blend into tablets, the weight variation and dose inaccuracy problem might not come [29-31].

Physico-chemical behavior of the designed tablets

The measured hardness of the tablets of each batches of FDT formulations were ranged between 3.5±0.09 to 4.8±0.03 Kg/cm^2. This ensures good handling characteristics. The friability of the tablets was within the 0.12±0.11 to 0.77±0.19 %, which was less than 1 %, thus considered acceptable as per I.P. The minimum friability value was exhibited by FDT formulation F8. The maximum and minimum average thickness of tablets was found to be 2.96±0.12 and 3.08±0.14 mm respectively. Almost all FDTs were having uniform thickness. The average weight of all FDT formulations ranges from 178±0.91 and 182±0.69 mg respectively, thus all tablets were of uniform weight which primarily assured that dose shall be accurate in all tablets. The minimum and maximum percentage of drug content from all the formulations was found to be 97.2±0.98 and 101.1±0.95 % respectively. All tablet formulations exhibited satisfactory drug content. Disintegration time of prepared FDTs was in the ranges of 21±0.31 to 46±0.18 s and the order was Crospovidone < Ac-Di-Sol < SSG < PVP K30. It was observed that wetting time of tablets was in the range of 22±0.42 to 38±0.81 s.

On comparing superdisintegrants, the formulation containing SSG take more wetting time than Ac-Di- Sol, Crospovidone and PVPK-30. It was observed that water absorption ratio of tablet formulations was in the ranges of 102±0.29 to 148±0.29 %. All formulations exhibited uniformity of dispersion.

Table 2: Flow properties of powder blend containing valsartan.

Formulation code	Bulk Density (g/cc) (X±S.D.)	Tapped density (g/cc) (X±S.D.)	Carr's index	Hausner ratio	Angle of repose (°) (X±S.D.)
F1	0.417±0.09	0.468±0.05	10.88	1.120	25.31±0.17
F2	0.423±0.08	0.475±0.06	10.35	1.117	24.88±0.31
F3	0.432±0.06	0.474±0.07	9.262	1.112	23.48±0.19
F4	0.422±0.09	0.466±0.06	9.459	1.109	26.36±0.26
F5	0.396±0.08	0.438±0.08	9.345	1.107	25.44±0.22
F6	0.402±0.07	0.442±0.05	8.619	1.091	26.11±0.18
F7	0.414±0.05	0.467±0.08	11.08	1.124	24.18±0.15
F8	0.423±0.06	0.462±0.06	8.459	1.089	25.29±0.22
F9	0.427±0.08	0.471±0.05	9.351	1.104	24.52±0.14
F10	0.501±0.08	0.571±0.04	12.33	1.141	23.50±0.34
F11	0.522±0.08	0.592±0.10	11.88	1.133	23.51±0.29
F12	0.551±0.09	0.641±0.12	14.09	1.161	24.66±0.28

All values are represented as mean ± standard deviation (n = 3). Standard error means (SEM) < 0.423.

From the dissolution study it was found that, all FDT formulations showed satisfactory drug release profile. The minimum and maximum drug release were exhibited by FDT formulations F1 (67.558) and 100.38 % respectively. The formulations F7, F8 and F9 (crospovidone 2, 3 and 4%) showed cumulative percentage drug released profile of 97.165, 100.38 and 97.966 % respectively. Among all the FDT formulations, the order of drug release irrespective to superdisintegrant used are in the following order of Crosprovidone > Ac-Di-sol > SSG> PVPK-30.

Table 3: Physico chemical behavior of the designed tablets.

Formulation	F_1	F_2	F_3	F_4	F_5	F_6
Hardness (Kg/cm^2) (X±S.D.)	4.6±0.09	4.8±0.03	4.4±0.08	3.8±0.05	4.3±0.08	3.7±0.07
Friability (%) (X±S.D.)	0.56±0.23	0.71±0.38	0.77±0.19	0.58±0.23	0.47±0.42	0.51±0.61
Thickness (mm) (X±S.D.)	2.99±0.12	3.03±0.09	3.01±0.11	2.99±0.15	3.02±0.13	2.98±0.17
DT (s) (X±S.D.)	40±0.23	36±0.19	28±0.23	39±0.11	35±0.21	28±0.28
WT (s) (X±S.D.)	35±0.49	37±0.66	38±0.81	32±0.41	36±0.56	35±0.65
CU (%) (X±S.D.)	97.2±0.98	99.1±0.86	101.1±0.95	100.6±1.06	98.1±0.97	97.5±0.89
WAR (%) (X±S.D.)	115±0.44	124±0.35	136±0.67	118±0.55	131±0.74	126±0.23
UOD (%) (X±S.D.)	pass	pass	pass	pass	pass	pass
Avg. Wt. (mg) (X±S.D.)	181±0.45	179±0.88	180±0.95	182±0.84	178±0.56	179±0.44

DT – Disintegration time, WT – Wetting time, CU – Content Uniformity, Water absorption ratio, UOD – Uniformity of dispersion. All values are represented as mean ± standard deviation (n = 3). Standard error means (SEM) < 0.569.

Table 4: Physico-chemical behavior of the designed tablets.

Formulation	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
Hardness (Kg/cm^2) (X±S.D.)	4.5±0.06	3.5±0.09	3.8±0.06	4.5±0.04	4.5±0.07	4.5±0.08
Friability (%) (X±S.D.)	0.47±0.14	0.12±0.11	0.28±0.17	0.41±0.15	0.35±0.18	0.34±0.11
Thickness (mm) (X±S.D.)	3.08±0.14	3.09±0.11	2.99±	2.96±0.12	2.98±0.19	3.06±0.21
DT (s) (X±S.D.)	30±0.27	21±0.31	29±0.29	36±0.22	46±0.18	41±0.21
WT (s) (X±S.D.)	28±0.43	22±0.42	28±0.37	35±0.54	38±0.45	31±0.33
CU (%) (X±S.D.)	98.72±0.97	99.16±0.86	99.09±1.03	98.74±0.91	98.76±1.08	97.38±1.13
WAR (%) (X±S.D.)	137±0.66	148±0.29	156±0.41	124±0.32	118±0.22	102±0.29
UOD (%) (X±S.D.)	pass	pass	pass	pass	pass	pass
Avg. Wt. (mg) (X±S.D.)	182±0.69	180±0.94	181±0.86	178±0.91	181±0.99	179±1.02

DT – Disintegration time, WT – Wetting time, CU – Content Uniformity, Water absorption ratio, UOD – Uniformity of dispersion. All values are represented as mean ± standard deviation (n = 3). Standard error means (SEM) < 0.652.

Table 5: *In vitro* drug release and kinetics study fast dissolving tablets of valsartan.

Formulation code	Cumulative % Drug release (0.5 h study)	Zero Order kinetics	First Order kinetics	Korsmeyer and Peppas equation	
		Regression co-efficient (r^2)			n
F1	67.558	0.983	0.963	0.996	0.415
F2	84.272	0.891	0.976	0.979	0.462
F3	91.773	0.886	0.993	0.969	0.487
F4	86.857	0.985	0.974	0.998	0.492
F5	89.222	0.971	0.981	0.998	0.417
F6	99.291	0.755	0.965	0.950	0.229
F7	97.165	0.771	0.982	0.991	0.357
F8	100.38	0.774	0.999	0.992	0.225
F9	97.966	0.857	0.949	0.953	0.459
F10	92.142	0.844	0.986	0.984	0.383
F11	89.555	0.947	0.994	0.994	0.425
F12	74.516	0.933	0.989	0.986	0.471

Table 6: Stability study of optimized FDT formulation (F8) of valsartan as per ICH guidelines.

Time Period (Days)	25±2°C, 60±5% RH			40±2°C, 75±5% RH		
	Content uniformity (mg) (X±S.D.)	Wetting Time (s) (X±S.D.)	DT (s) (X±S.D.)	Content uniformity (mg) (X±S.D.)	Wetting Time (s) (X±S.D.)	DT (s) (X±S.D.)
0	99.16±0.19	22±0.91	21±0.77	99.16±0.19	22±0.91	21±0.77
15	99.05±0.21	22±1.02	21±0.87	99.04±0.22	21±0.12	21±0.87
30	99.01±0.27	21±0.55	21±0.92	98.88±0.73	21±0.55	20±0.62
45	98.82±0.38	21±0.82	20±1.06	98.18±0.29	20±0.85	20±1.03
60	98.79±0.19	21±1.08	20±1.11	98.01±0.39	20±1.01	20±1.01

All values are represented as mean ± standard deviation (n = 3). DT – Disintegration time. Standard error means (SEM) < 0.641.

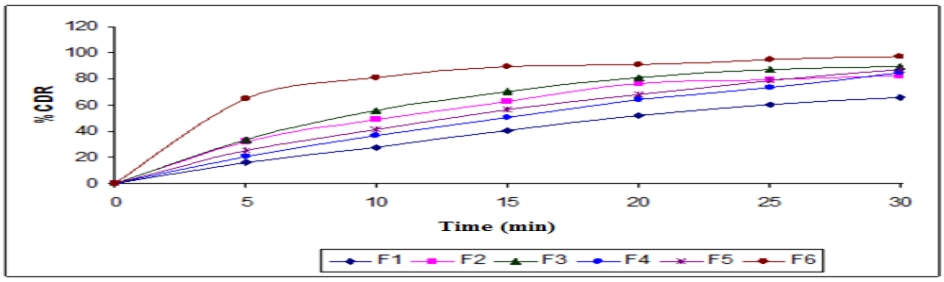

Figure 4: *In vitro* drug release pattern comparison of various FDT formulations F1 to F6.
CDR – Cumulative drug release.

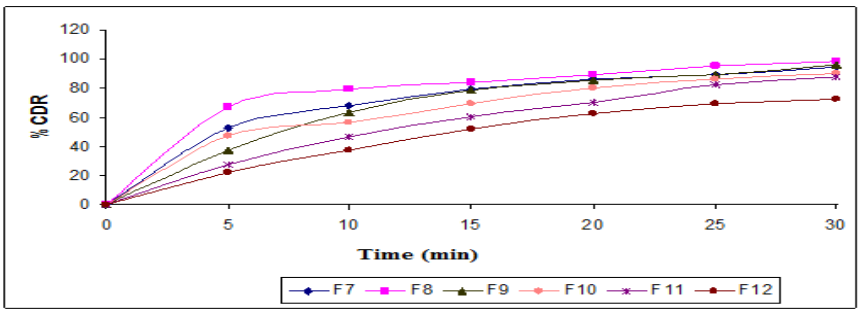

Figure 5: *In vitro* drug release pattern comparison of FDT formulations F7 to F12.
CDR – Cumulative drug release.

CONCLUSION

Amongst all formulations, formulation F8 prepared by drug with 2 % crospovidone showed least disintegrating time, least wetting time, greater water absorption ratio and faster dissolution. Thus crospovidone can be successfully used in the formulation of fast disintegrating tablets so formulation F8 was found to be the best formulation. From the above studies, it was concluded that fast dissolving tablet of Valsartan that formulation containing crospovidone is most acceptable. Further research emphasis has to be done over *in vivo* study and *in vitro – in vivo* correlations.

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