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Formulation And Evaluation of Immediate Release Tablets Of Valsartan

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The main objective was formulation and evaluation of immediate release tablets of valsartan. In the present study, valsartan 200 mg immediate release tablets were prepared by direct compression, considering amount of Croscarmellose sodium, Crospovidone and Sodium stearate as three independent variables and *in vitro* drug dissolution studies were performed to find out the drug release rate and patterns. *In- vitro* drug release was carried out using USP Type II dissolution test apparatus 37 °C ± 5 °C and 50 rpm in 750 ml of 0.1 N Hydrochloric acid for 2 hours and then the pH was charged to 6.8 by adding 250 ml of 0.2 M tri sodium orthophosphate for the rest of the dissolution duration. 5 ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid, then drug release percentage was estimated by spectrophotometer at 249nm. The all prepared formulas were tested for bulk density, tap density, angle of repose, hausner's ratio, thickness, weight variation, hardness, friability, drug content, in vitro dissolution test, floating time. Drug excipients compatibility was checked with the help of Fourier Transform Infrared Spectroscopy (FTIR). The drug content of all the formulations ranged from 98.5±0.1% to 98.4±0.7%. The formulation (F1) with Croscarmellose sodium was found to be best formulation with *In-vitro* drug release of about 99.5% at the end of 30 minutes. It can be concluded that the selected formula (F6) can be a promising formula for the preparation of immediate release of valsartan.

Introduction:

EImvamlueadtiiaotne, release tablets are invented to disintegrate and release their dosage form with no special rate controlling features, such as special coatings and other techniques. Immediate release tablets are those which disintegrate swiftly and get dissolved to release the medicaments [1]. The oral bioavailability of drug dependent on disintegration, dissolution and various physiological factors [2]. An immediate release dosage form helps a manufacturer to diversify market and simultaneously offering patients a convenient dosage form or dosage regimen.[3-10] Valsartan ($C_{24}H_{29}N_5O_3$) used to treat high blood pressure (hypertension). Valsartan is a new potent and orally active antihypertensive drug which selectivity act as angiotensin II antagonist acting on the AT1 receptor subtype. It is indicated for hypertension, heart failure and post-myocardial infarction [11-18]. The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. The drug is having low aqueous solubility of about 0.0213 mg/ml. The drug is rapidly absorbed after oral administration having bioavailability is 23% [5]. This compound belongs to the class of organic compounds known as biphenyl tetrazoles and derivatives. These are organic compounds containing a biphenyl attached to a tetrazole. A carbon atom of the biphenyl moiety is boned to a carbon or the nitrogen atom of the tetrazole moiety. Other techniques are like liposomes, emulsions, microemulsion, solid dispersion and inclusion complexation using cyclodextrins show sensible achiever, but they lack in universal applicability to all drugs [19-20]. These techniques are not applicable for those drugs which are not soluble in aqueous and organic solvents. .Recent advances in novel drug delivery system aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance, one such approach is nanosuspension[21-25].

MATERIALS AND METHODS

Materials:

Valsartan ($C_{24}H_{29}N_5O_3$) was obtained as free gift sample from Macleods Pharmaceutical Ltd.,

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Crospovidone, Croscarmellose sodium**,** , Talc and Lactose were obtained from Yarrowchem products, Mumbai. Sodium starch glycolate and magnesium stearate were obtained from S.d fine chem., Mumbai. All reagents and solvents used were of analytical grade satisfying pharmacopoeial standards.

Methods:

Pre formulation studies:

Pre-formulation may be defined as the application of biopharmaceutical principles to the physicochemical properties of the drug. It is a phase of R & D process.

Identification and compatibility studies: UV – Visible Spectroscopy:

UV and Vis Spectroscopy is a fast yet effective and simple process to identify the organic compounds containing conjugated dienes in their structure.

Stock solution preparation: 100 mg of Valsartan was accurately weighed and dissolved in 100 ml of methanol in volumetric flask to prepare stock solution. The resultant stock solution is of concentration of 1000 µg/ml. The sample is analysed in Shimadzu 1800 UV visible spectrophotometer in the range of 200-400nm. (Figure no. 2)

Calibration curve of Valsartan

To obtain the stock solution of concentration 1000 µg/ml, from this 10 ml was taken and diluted to 100ml using 0.1N NaOH (100
µg/ml) to obtain working stock solution of concentration. From the above solutions 0.2, 0.4, 0.6, 0.8 and 1ml was taken to dilute to 10ml Methanol to get series of solutions in concentration range from 2 to 10 µg/ml of valsartan. Absorbance was noted at λmax 250nm against a blank. (0.1 N NaOH).

FT-IR spectrophotometric studies Infrared Spectroscopy (FTIR)

IR spectra of Valsartan, was obtained by a Perkin-Elmer Fourier transform infrared Spectrophotometer using KBr pellets. IR spectra of pure Valsartan, polymer and combination of Valsartan with polymers were obtained by using Perkin-Elmer Fourier transform infrared spectrophotometer. The scanning range used was 4000 to 400cm^{-1}.

Valsartan was analysed by using FTIR within (400-4000 cm^{-1}) range and characteristic functional group peaks were shown in Figure no.4

Valsartan and all ingredients were analysed by using FTIR within (400-4000 cm^{-1}) range and characteristic functional group peaks were shown in Figure no.5

Pre-compression Parameters Tablets:

Various parameters like bulk density, tap density, angle of repose, Hausner's ratio were determined. (Table no. 4)

Bulk Density: It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below.

Db= M/Vb

It is expressed in g/ml and is given by Where, Db is the bulk density, M is the mass of powder and Vb is the bulk volume of the powder.

Tap Density: It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

Dt= M/Vt

Where, Dt is the bulk density, M is the mass of powder and Vt is the tapped volume of the powder.

Angel of repose:

Angle of repose was calculated using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated as per the formula-

$\theta = \tan^{-1}$ (h/r)

Where, θ is angel of repose, h is height of pile and r is radius of pile.

Hausner's Ratio:

Hausner ratio is a type of parameter to define the flowability of powders. It was calculated by the formula –

Hausner's Ratio = V0/Vf

Where, V0 is tapped density, Vf is bulk density.

Method of preparation of tablets:

Valsartan tablets were prepared by direct compression method using excipients and polymers to release the drug immediately after administration.

Accurately weighed quantities of excipients were placed in a mortar and gradually mixed with constant kneading to ensure homogenous mass. Then the homogenous powder was passed through sieve number 40 and the powder was directly compressed into tablets on a tablet punching machine.

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Table no. 1: Formulation of Tablets

S. No.	Ingredient	F1	F2	F3	F4	F5	F6
1	Valsartan	40	40	40	40	40	40
2	Lactose	125	125	125	125	125	125
3	Crospovidone	3	5	10	-	-	-
4	Croscarmellose sodium	-	-	-	3	5	10
5	SSG	18	16	11	18	16	11
6	Talc	7	7	7	7	7	7
7	Mg Stearate	7	7	7	7	7	7
	Total (mg)	**200**	**200**	**200**	**200**	**200**	**200**

Post-Compression Parameters of Tablets:

Post compression evaluation for weight variation, hardness, friability, and thickness were determined for compressed tablets.

Weight Variation:

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated.

$$\% \text{ Deviation} = \frac{W_{initial} - W_{final}}{W_{final}} \times 100$$

Where, % Deviation = Percentage deviation, Wfinal = Average weight of tablet, W initial = individual weight of tablet

Hardness:

The Mansanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. The scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. Hardness was expressed in kg/cm2. This parameter is important to know that the tablet has sufficient strength to withstand mechanical shocks of handling in manufacture, packaging and shipping.

$$\%\text{Friability} = \frac{(W_1 - W_2)}{W_2} \times 100$$

Where, % Friability = Percentage Friability, W1 = Initial weight of tablet, W2 = Final weight of tablet

Thickness:

Control of the physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

***In-vitro* dissolution study:**

In-vitro dissolution studies of Valsartan tablets were carried out in USP XXIII tablet dissolution test apparatus-II (figure 1) employing a paddle stirrer rotating at 50 rpm. The dissolution medium consisted of 750 ml of 0.1 N Hcl for 2 hours and then the pH was changed to 6.8 by adding 250 ml of 0.2 M tri sodium orthophosphate for the rest of the dissolution duration. The temperature of the dissolution medium was maintained at 37± 0.50 C throughout the experiment. 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn from the dissolution apparatus 5, 10, 15, 20, 25, and 30 minutes were filtered through 0.45µ membrane filter and drug content in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer at 249 nm, and cumulative percent drug release was calculated. The study was performed in triplicate. The results of dissolution studies were shown in figure 6.

Friability:

Tablet strength was tested by Roche friabilator. Preweighed tablets were allowed for 100 revolutions (4min), taken out and were deducted. The percentage the weight loss was calculated by rewriting the tablets. Conventional compressed tablets that lose than 0.5 to 1.0% of their weight are generally considered acceptable.

The percentage release of valsartan was calculated. The observations for different batches were shown in Table no 7.

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Fig. 1 Dissolution test apparatus-II (Electrolab)

RESULT AND DISCUSSION:

Pre formulation studies:

The polysaccharide was characterized by various organoleptic properties such as colour, state, and LOD are shown in below table no. 2

Table no. 2: Preformulation study of drug sample (Valsartan)

S.No.	Parameter	Observations
1	Colour	White
2	State	Crystalline
3	Melting point	119.6ºC -121º C.

Identification and compatibility studies of Valsartan drug Uv- Spectroscopy:

UV spectra of drug were obtained by scanning drug solutions (1mg/ml) showed maximum absorption at 250nm.Reported absorbance maxima valsartan is λmax at 250 nm.

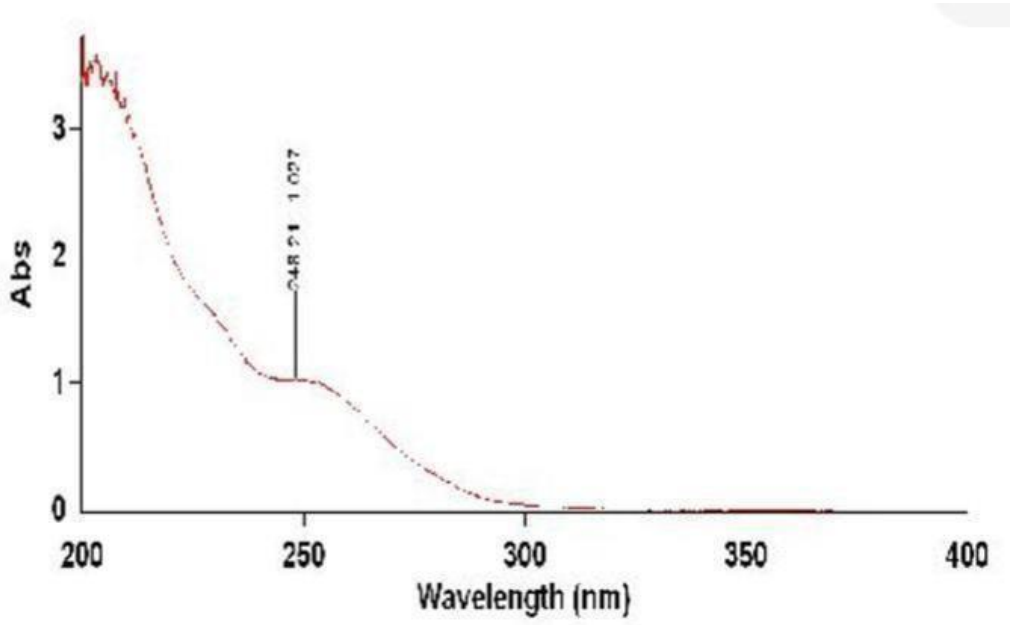

Fig. 2 UV spectrum of Valsartan

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Calibration curve

The calibration curves of valsartan were prepared in methanol by using Shimadzu 1800 UV visible spectrophotometer. A standard stock solution of valsartan was prepared by dissolving 1gm of drug in 100 ml of methanol (1000 µg/ml). From the above stock solution 10 ml was taken and transferred into a 100 ml volumetric flask and rest of the volume was made up with solvent to obtain a 100µg/ml of solution 0.1N NaOH from which further dilutions of 2-20 µg/ml were prepared. Absorbance was noted at λmax 250nm against a blank (0.1 N NaOH). (Table 3 and Fig. 3)

Table no. 3: Calibration curve of Valsartan

Sample No.	Concentration (µg/ml)	Absorption
1	0	0
2	2	0.2063
3	4	0.4129
4	6	0.619
5	8	1.0145
6	10	1.0238
7	12	1.2547
8	14	1.4449
9	16	1.6514
10	18	1.8577
11	20	1.8705

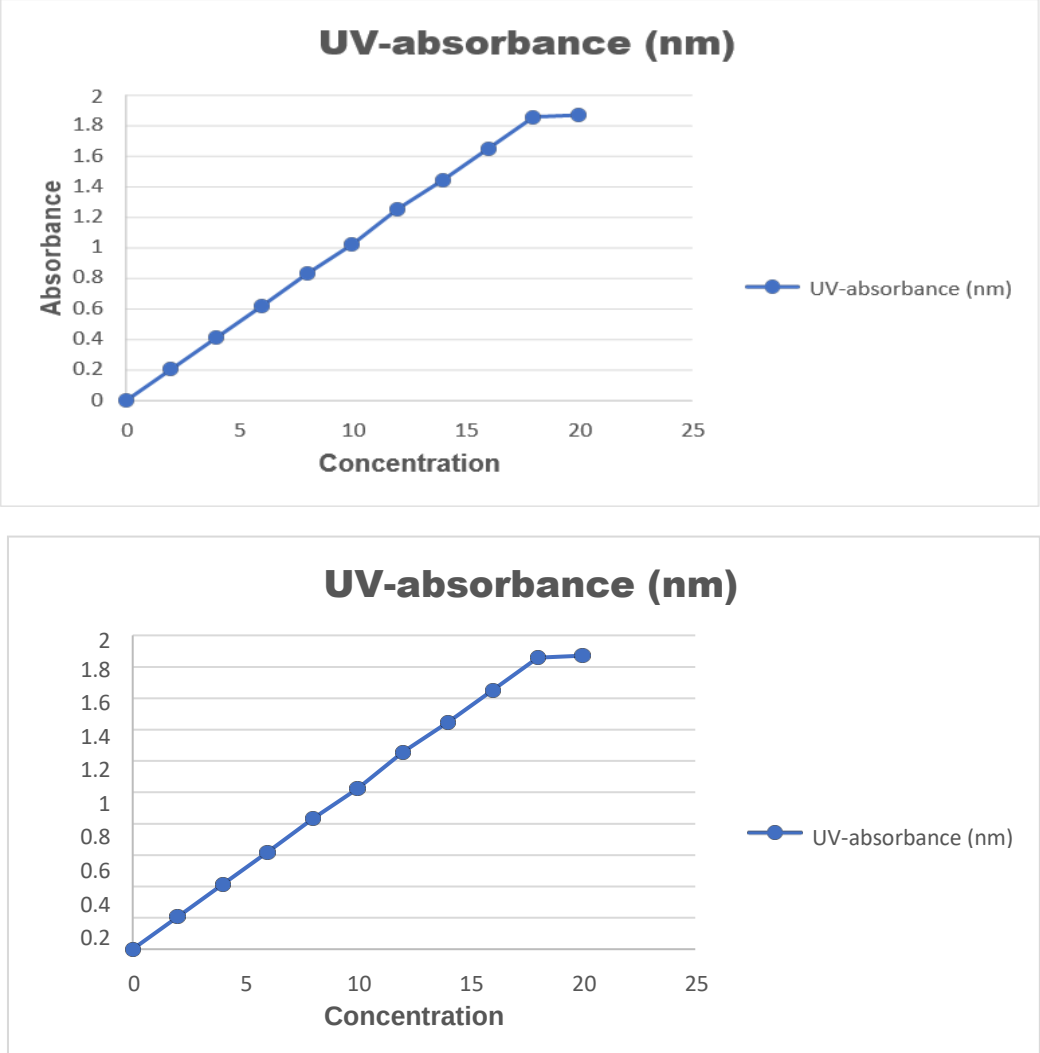

Fig. 3 Calibration Curve of Valsartan

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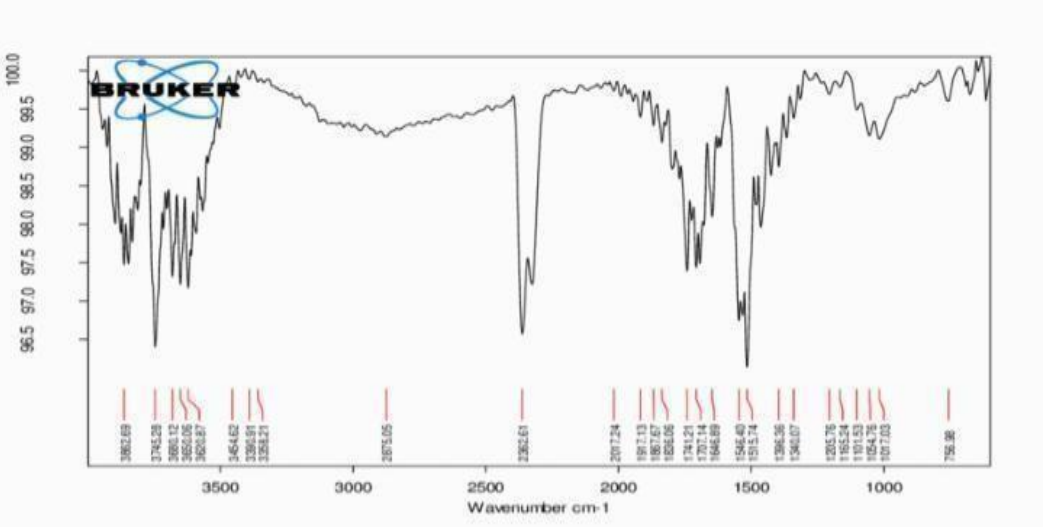

Fig. 4 FTIR spectra of pure Valsartan drug

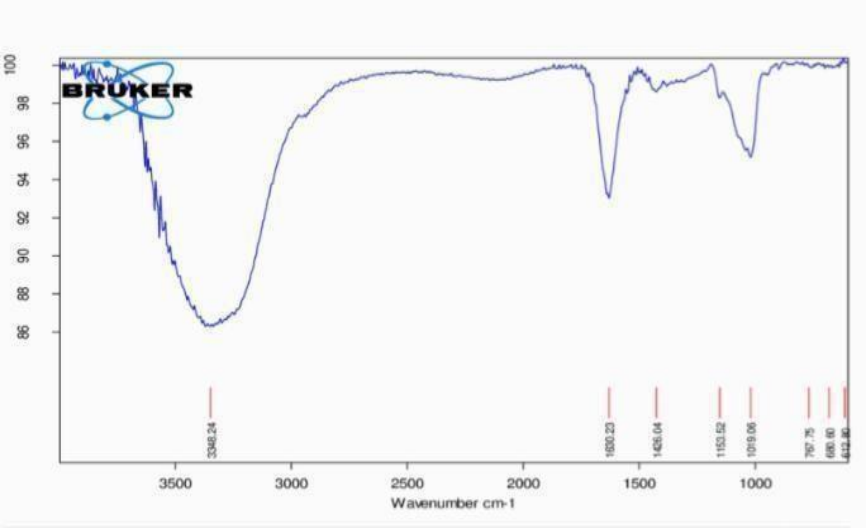

Fig. 5 FTIR spectra of Valsartan + All ingredients

Pre-compression Parameters:

Before preparing the batches of tablets, several pre-compression parameters were evaluated for the granules used in the formulation of tablets. Some of the precompression parameters evaluated were the angle of repose, bulk density, tapped density, Hausner's ratio show in table no.4

Table no. 4: Pre-compression permanents of tablet

S.No.	Parameters	Formulation Code					
		F1	F2	F3	F4	F5	F6
1	Bulk density	0.41±0.05	0.42±0.04	0.44±0.02	0.40±0.05	0.42±0.09	0.44±0.07
2	Tapped density	0.47±0.02	0.49±0.01	0.51±0.04	0.45±0.02	0.49±0.05	0.52±0.05
3	Hausner's Ratio	1.16±0.01	1.26±0.02	1.20±0.03	1.27±0.01	1.33±0.02	1.46±0.02
4	Angel of repose	27.32±0.02	25.86±0.02	30.30±0.01	29.20±0.20	29.39±0.05	30.38±0.06
5	Compressibility index	15.047±0.64	15.67±0.26	16.83±0.20	13.42±0.24	11.64±0.01	10.64±0.01

Post-compression permanents:

The floating tablet of Acebutolol were evaluated for thickness, hardness, friability, weight variation, % of drug content, floating lag time, and floating time shown in table no.5

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Table no. 5: Post-compression permanents of tablet

S.No.	Parameters	Formulation Code					
		F1	F2	F3	F4	F5	F6
1	Weight variations (mg)	200.03±0.21	199.78±0.02	200±0.012	199.99±0.31	198.32±0.5	199.4±0.15
2	Thickness(mm)	2.75±0.05	2.12±0.017	3.10±0.025	2.7±0.04	2.76±0.25	2.07±0.05
3	Hardness (kg/cm2)	4.00±0.04	3.21±0.08	3.30±0.05	4.20±0.04	4.30±0.05	3.25±0.01
4	Friability (%)	0.46±0.04	0.80±0.08	0.52±0.7	0.56±0.6	0.48±0.04	0.54±0.7
5	Drug content (%)	98.5±0.1	97.2±0.2	98.1±0.6	97.5±0.5	98.3±0.1	98.4±0.7

Table no. 6: *In-vitro* dissolution study

Time (minutes)	F1	F2	F3	F4	F5	F6	Innovator
0	0	0	0	0	0	0	0
5	25.31	31.43	38.91	33.13	42.53	39.47	45.69
10	40.64	47.50	45.32	60.41	55.97	57.35	60.07
15	61.25	67.32	59.25	69.42	69.51	79.29	79.24
20	73.53	78.36	75.24	83.84	89.54	93.25	90.06
25	84.25	83.54	89.54	90.78	94.52	96.69	95.63
30	89.90	95.56	95.90	95.97	96.50	99.5	95.87

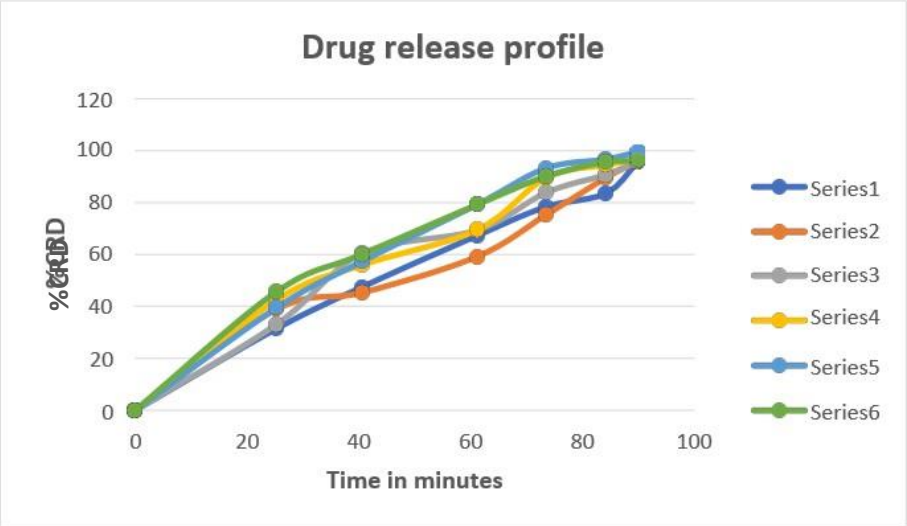

Fig. 6 Comparative *in-vitro* Drug Release Profiles of F1, F2, F3, F4, F5, F6

CONCLUSIONS

The present study was aimed at developing immediate release tablet of valsartan by using combination of Superdisintegrant such as Crospovidone, Sodium stearate, Cross carmellose sodium and other polymer such as lactose, sodium starch glycolate, talc, magnesium Stearate by using direct compression technique.

Pre compression parameters and post compression of the formulations were found to be within the range. Post compression studies, for tablets like thickness, hardness, friability, disintegration, drug content uniformity was done. All tablets conformed to the requirement of drug content, hardness, friability and thickness. The optimized formulation was checked for compatibility of drug with the other excipients. This indicates that there were no interaction between drug and excipients. The *In-vitro* drug release study were found that optimized formulation F6 show immediate drug release within 30 minutes up to 99.5%. It showed excellent release during the period of study, when compared to otherformulations.

Thus, formulation F-6 was found to be the most promising formulation on the basis of acceptable tablet properties and *In-vitro* drug release. Suitable combination and concentrations of ingredients provided reasonably good immediate release tablet.

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