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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLET OF VALSARTAN

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Keywords:

Hypertension, Valsartan, Solubility, Surfactant, Immediate Release, Direct Compression.

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ABSTRACT: The immediate release tablet of antihypertensive drug Valsartan were prepared and evaluated to increase solubility and bioavailability of low soluble drug. The tablets were prepared by direct compression method using Surfactants such as Poloxamer 188, Sodium stearate, Sodium Lauryl Sulfate and Superdisintegrant such as Cross carmellose sodium were used in tablet formulation. The formulation were evaluated for various physical parameters, dissolution study and drug release profile. From all formulations the formulations F-C of batch B 3 i.e SLS-3 showed 98.04% drug release within 30 minutes, which was highest drug release than other batches. The optimized immediate release tablet of batch B 3i.e SLS-3 of formulation F-C showed no change in physical appearance, drug content or in dissolution pattern storage at 40± 2^0 C / 75 ± 5 % for 90 days. Finally it was concluded that batch B-3 containing formulation F-C i.e. SLS-3 shows highest drug release.

INTRODUCTION: Oral route is most common route of administration of drug because of its systemic effect, patient compliance, less expensive to manufacture. Tablet provides high precision dosing. In most of the cases immediate on set of action is required as compare to conventional therapy. To achieve the rapid onset of action and eliminate the drawbacks of conventional therapy immediate release dosage form is now a days popular oral dosage form. Basic approach used in development is the use of superdisintegrants which provide rapid disintegration of tablet after administration [1]. This research work is concerned with the formulation and evaluation of immediate release tablet of Valsartan in order to provide immediate relief from hypertension.

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A solubility and dissolution are the key parameters for the therapeutic effect of a drug. Solubility is one of the important parameter to achieve desire concentration of drug in systemic circulation for pharmacological response [2]. More than 92% of the drug listed in U.S. pharmacopoeia which are having low solubility. It is commonly recognized in the pharmaceutical industry that on average more than 40% of newly discovered drug candidates are having poor solubility. Micronization, Nanonization, salt formation, use of surfactants, solid dispersion are the several methods for enhancement of solubility of the drugs [3, 4, 5].

Surfactant acts as an absorption enhancer and hence increases both dissolution and permeability of the drug [6]. Further enhancement of dissolution can be done by using super disintegrants. Super disintegrants, disintegrate the tablet rapidly which enhances the dissolution rate of the drug [7].

Immediate release drug delivery is desirable for drugs having long biological half -life, high

bioavailability, lower clearance and lower elimination half -life. But main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug [8]. Valsartan is a new potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists Valsartan has much greater affinity (about 20000 fold) for the angiotensin II type 1 (AT1) receptor than for the angiotensin II type 2 (AT2) receptor, thereby relaxing blood vessels and causing them to widen, which lowers blood pressure and improves blood flow [9].

Valsartan is rapidly absorbed after oral administration. The bioavailability is 10-35 %. Food affects it's absorption by 40% and peak plasma concentration by about 50% .Valsartan has extensive Plasma protein bound i.e 94-97 % and hence limited distribution outside plasma compartment. Because of presence of carboxylic groups Valsartan is soluble in neutral pH range and is present in ionized form at physiologic pH. The volume of distribution at steady state is 17 L. Valsartan does not require any metabolism in the body to become active [10].

The recommended adult dose of Valsartan is 80 mg or 160 mg once daily [11]. Direct compression method was preferred to prepare the tablet as it was proved to be most convenient one over other manufacturing process to formulate immediate release drug using disintegrating agent [12]. The basic aim of present study was to Formulate and Evaluate Immediate Release tablet of Valsartan to achieve maximum solubility by using Surfactants such as Poloxamer 188, Sodium Lauryl Sulfate, Sodium Stearate and to decrease Disintegration time by using Superdisintegrants Cross Carmellose Sodium. Thus ultimately it helps to enhance the bioavailability of poorly soluble Valsartan.

MATERIALS: Valsartan was received as a gift sample from Lupin Pharma Ltd, Aurangabad India. Poloxamer 188, Sodium Stearate, Sodium Lauryl Sulfate, Lactose, Cross Carmellose Sodium, avicel, Talc, Vanilla were received as a gift sample from Chempure Lab, Mumbai, India.

Method: Valsartan immediate release tablet were prepared by direct compression method. Sift the lactose, cross carmellose sodium, avicel (pH-102), talc through #30 mesh, mixed and triturate with different surfactant such as poloxamer188, sodium Stearate, sodium Lauryl sulfate. Again it all blended with Valsartan. Finally this material pass through #30 mesh.

The powder blends were evaluated for the properties such as Bulk density, Tapped density, Carr's Index, Hausner's ratio, Angle of repose. Finally the blends from each formulation were compressed by using 10 mm punch in 8 station single rotary compression machine and tablets were prepared. The composition of different formulations of immediate release tablet is shown in **Table 1**.

TABLE 1: COMPOSITION FOR PREPARATION OF IMMEDIATE RELEASE TABLET OF VALSARTAN

Ingredients	Batch 1			Batch 2			Batch 3		
	P1 (F-A)	SS1 (F-B)	SLS1 (F-C)	P2 (F-A)	SS2 (F-B)	SLS2 (F-C)	P3 (F-A)	SS3 (F-B)	SLS3 (F-C)
Valsartan	160	160	160	160	160	160	160	160	160
Poloxamer188	1.5	-	-	3.0	-	-	6.0	-	-
Sodium stearate	-	1.5	-	-	3.0	-	-	6.0	-
Sodium lauryl sulfate	-	-	1.5	-	-	3.0	-	-	6.0
Lactose	47.75	47.75	47.75	46.25	46.25	46.25	43.25	43.25	43.25
Cross carmellose sodium	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0	20.0
Avicel (pH102)	260.75	260.75	260.75	260.75	260.75	260.75	260.75	260.75	260.75
Talc	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Vanilla	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Total	500	500	500	500	500	500	500	500	500

P: Poloxamer, SS: Sodium stearate, SLS: Sodium lauryl sulphate
F-A: Formulation A, F-B: Formulation B, F-C: Formulation C

Evaluation of Valsartan Immediate release tablets: The tablets were subjected to evaluation for the following parameters.

a) Tablet hardness [13]:
Tablet hardness is also known as tablet crushing strength. Monsanto Hardness tester was used. It applies force to the tablet diametrically with the help of an in built spring.The hardness of the tablet is measured by using conventional hardness testers like Monsanto hardness tester. The prepared tablets were subjected to hardness test. It was carried out by using hardness tester and expressed in Kg/cm2.

b) Friability test[14]:
Friability test was performed by taking 20 tablets. Pre weight of the individual tablet was taken before subjecting to friability test. Weighed tablet samples are transformed into friabilator and subjected to combined effects of abrasion and shock by revolving at 25rpm for 4min for 100revolutions. Samples are withdrawn after set time completions and loose dust powder was removed from the tablet and final weight is noted and substituted in the formulae.

% friability= Initial weight-Final weight / Initial weight x 100

c) Thickness:
The thickness of tablets was determined using Digital Vernier Caliper. It is expressed in mm.

d) *In - vitro* Disintegration time [14]: The disintegration test was performed using Electrolab disintegrating apparatus. Placed one tablet in each of the six tubes of the basket and operate the apparatus using 0.1N HCl maintained at 37±0.5ºC as the immersion fluid. Then noted down the time to complete disintegration of tablets.

e) Content Uniformity:
The Valsartan content in tablets was determined by powdering 10 tablets in each batch. Powder equivalent to 100 mg of Valsartan was dissolved in Methanol. 1 ml of filtrate wasfurther diluted to 100 ml with 0.1 N HCL and it was determined by spectroscopy at 250 nm.

f) Weight variation test [14]:
20 tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was calculated. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more than 10%.

g) *In - vitro* release profile of formulated Valsartan tablet[14]:
Drug release studies were done by using USP type II apparatus (paddle type).For that 900ml of dissolution medium (0.1N HCl) was transferred into round bottomed beaker and the temperature was maintained at $37^0c \pm 2^0c$ and Speed of Paddlewas 50rpm. At regular time interval (5min.) 5ml sample was withdrawn and replaced with fresh dissolution medium. Removed sampled was diluted and observed in UV spectrophotometer at 250 nm.

RESULT AND DISCUSSION:

Precompression parameters:
The Precompression parameters were the primary requirements to determine whether the specific material was suitable for the targeted formulation or not. The aim was to formulate the tablet formulation with direct compression method, so it was mandatory to known the bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose as those were the official requirement while choosing any material for its dosage form formulation. **Table 2** shows the results evaluated parameters of Bulk Density, Tapped Density, Carr's index, Hausner's ratio, Angle of Repose for various tablet formulation. The result of evaluation parameters clearly indicates its suitability to be the material of choice for formulation.

Post compression parameter:
All the prepared batches were evaluated systematically. The obtained results of the evaluated post compression parameters were represented in the bellow table i.e. on **Table 3**. The results of all the trial batches were compared and found satisfactory, as per the reported specification. Finally the comparison parameters were keenly observed to finalize for selection of the optimized batch and formula. Hardness of tablets was found to be in the range of 3.4 to 3.8 kg/cm^2 given in

Table 4. The friability of all tablets was found to be in the range of 0.16 to 0.56 which is less than 1% that showed good mechanical strength. Thus finally formulation F-C i.e. SLS-3 of batch B 3 shows disintegration time 140 seconds and drug release 98.28% which is higher than other tablets formulations.

TABLE 2: EVALUATION OF PRECOMPRESSION PARAMETER

Batch	Formulation	Bulk density	Tapped density	Carr's Index	Hausner's ratio	Angle of repose
Batch 1	P1(F-A)	0.571	0.723	21.02	1.26	29.49
	SS1(F-B)	0.555	0.740	25.00	1.33	28.84
	SLS1(F-C)	0.567	0.680	13.88	1.19	24.76
Batch 2	P2(F-A)	0.569	0.720	20.97	1.15	27.78
	SS2(F-B)	0.561	0.735	23.67	1.31	26.68
	SLS2(F-C)	0.448	0.540	17.03	1.20	28.30
Batch 3	P3(F-A)	0.493	0.625	18.02	1.26	27.57
	SS3(F-B)	0.543	0.731	25.71	1.34	22.45
	SLS3(F-C)	0.537	0.564	16.50	1.05	25.73

P: Poloxamer, SS: Sodium stearate, SLS: Sodium lauryl sulfate
F-A: Formulation A, F-B: Formulation B, F-C: Formulation C

TABLE 3: EVALUATION OF POST COMPRESSION PARAMETER

Batch	Formulation	Hardness (kg/cm^2)	Thickness (mm)	% Friability	Weight variation (mg)	Drug content %	Disintegration time (second)
Batch 1	P1(F-A)	3.6	3.29	0.43	500	96.65	146
	SS1(F-B)	3.8	3.23	0.40	501	97.21	143
	SLS1(F-C)	3.7	3.45	0.33	498	96.23	141
Batch 2	P2(F-A)	3.7	3.27	0.16	500	95.08	146
	SS2(F-B)	3.5	3.33	0.50	500	96.13	141
	SLS2(F-C)	3.4	3.41	0.20	499	96.65	139
Batch 3	P3(F-A)	3.7	3.32	0.53	501	95.08	145
	SS3(F-B)	3.7	3.33	0.56	501	94.56	142
	SLS3(F-C)	3.5	3.37	0.20	500	**98.28**	**140**

P: Poloxamer, SS: Sodium stearate, SLS: Sodium lauryl sulfate
F-A: Formulation A, F-B: Formulation B, F-C: Formulation C

Drug Excipient Compatibility Study:

Drug excipient compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). The IR Spectrum of pure Valsartanwas compared with the IR spectrum of drug-polymer mixturesuch as Valsartan + Poloxamer188, Valsartan + Sodium Stearate and Valsartan + Sodium Lauryl Sulfate. There was no appearance or disappearance of any characteristics peaks. This showed that there was no significant interaction between Valsartan and polymers such as Poloxamer188, Sodium Stearate and Sodium Lauryl Sulfate which were used in the tablets.

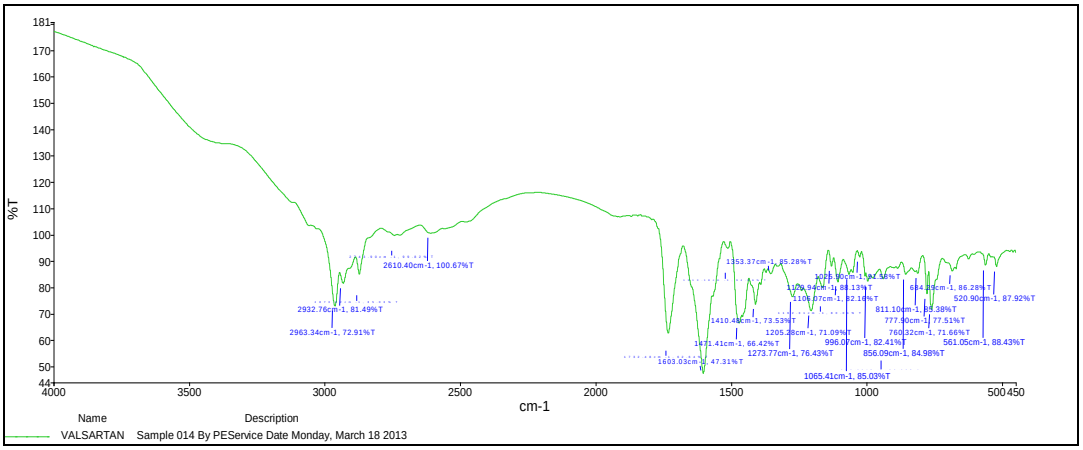

FIG 1: FTIR SPECTRUM OF VALSARTAN

Finally drug and polymer compatibility studies were performed by FTIR. FTIR absorption spectra of Valsartan and combination of Valsartan, Sodium Lauryl Sulfate, Lactose, Cross Carmellose Sodium, Avicel (pH102) were shows no significant interaction between Valsartan and Polymers (**Figure 2** and **Figure 3**).

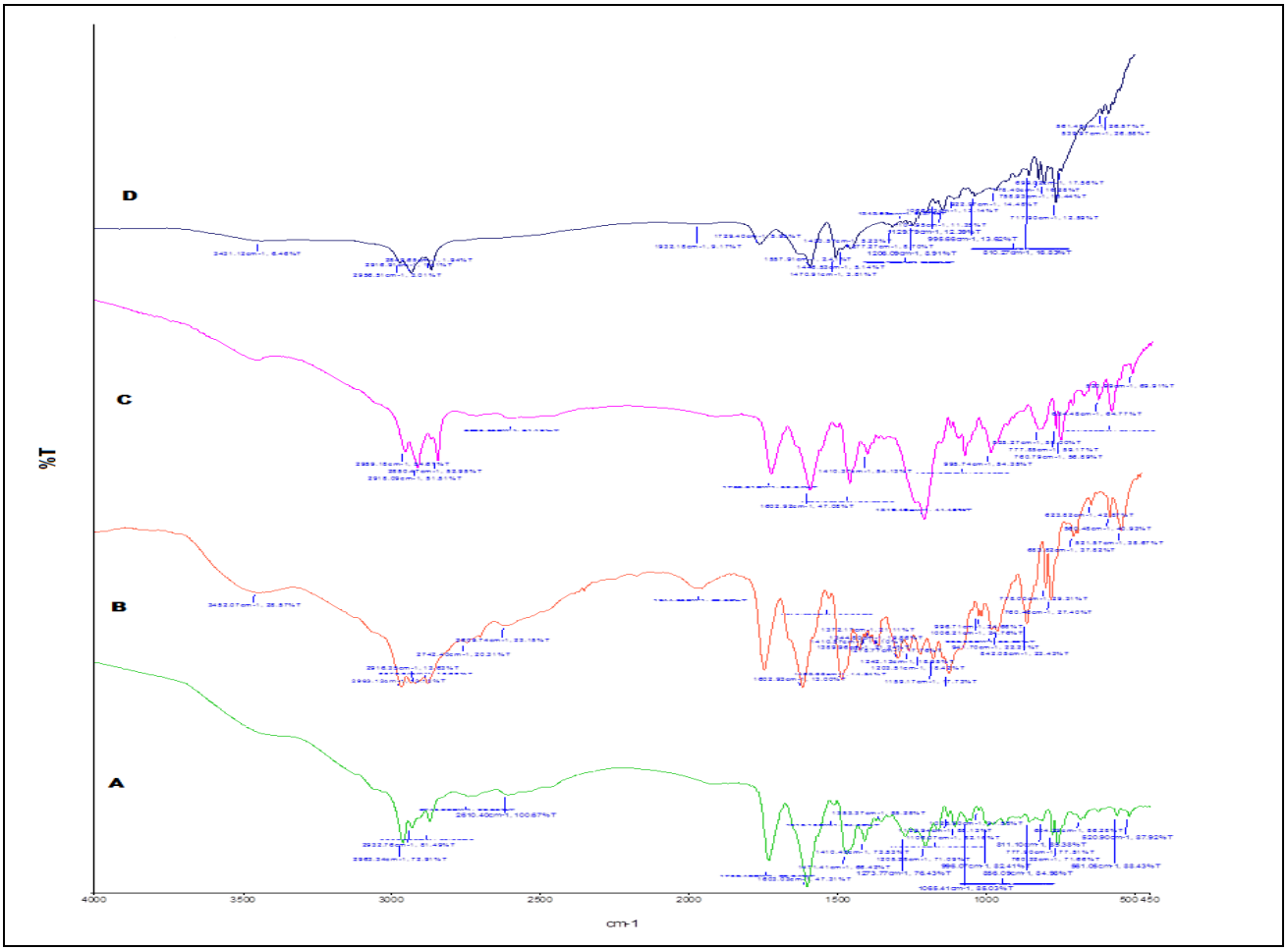

FIG. 2: COMPATIBILITY STUDY OF DRUG AND EXCIPIENT BY FTIR (A) VALSARTAN (B) VALSARTAN + POLOXAMER 188 (C) VALSARTAN + SODIUM STEARATE (D) VALSARTAN + SODIUM LAURYL SULFATE

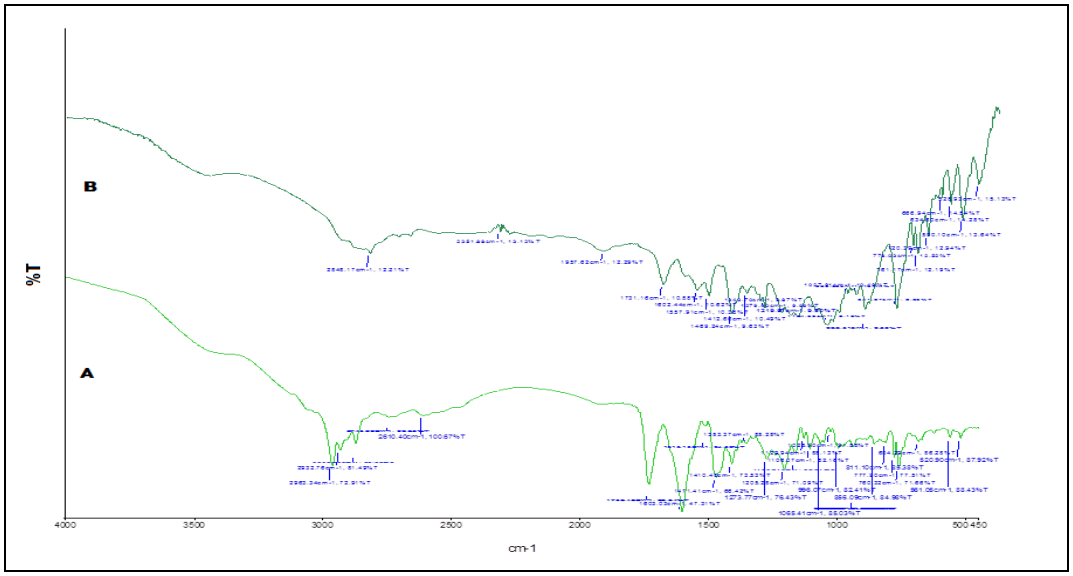

FIG. 3: FTIR OF OPTIMIZED TRIAL FORMULATION F-C OF BATCH B 3 I.E SLS-3
A: FTIR SPECTRUM OF VALSARTAN
B: FTIR SPECTRUM OF OPTIMIZED BATCH B 3 (FORMULATION F-C i.e.SLS-3)

In-Vitro Drug Release Study:

In-vitro drug release studies of the prepared formulations were carried out by using 900 ml of 0.1N HCl standard dissolution medium. The % drug release were calculated by with-drawing the samples from the experimental medium and recording the absorbance from UV-Spectrophotometer at definite time interval such as after 5, 10, 15, 20, 25 and 30 minutes interval. The observed result were reported below in the **Table 4**. Systematically for comparisons of % drug release and it was observed after 30 minutes all the batches shows good release profile as per the reported specification. As formulation F-C i.e. SLS-3 of batch B 3 shows highest release % after 30 minutes so it may be considered as an important criteria to be chosen it as optimized batch if other parameters shows encouraging results like *in-vitro* drug release. *In- vitro* release data was applied to various kinetic models to predict the drug release kinetic mechanism **(Table 5)**. The kinetic models used were zero order, first order, Higuchi and Peppas. The results of mathematical model fitting of data obtained indicated that, the best fit model in all the cases the release was found to be by zero order kinetic for optimized formulation F-C i.e. SLS-3 of batch B 3. Thus the release of the drug from the dosage form was found to be zero order kinetic release containing formulation F-C i.e. SLS-3 of batch B 3.

TABLE 4: RESULTS FOR *IN-VITRO* DRUG RELEASE OF IMMEDIATE RELEASE TABLET OF VALSARTAN

Time(min)	P1	SS1	SLS1	P2	SS2	SLS2	P3	SS3	SLS3
0	0	0	0	0	0	0	0	0	0
5	59.93	70.82	37.56	38.97	67.6	67.6	54.49	58.52	73.04
10	63.77	74.85	47.84	45.42	74.65	73.65	58.52	64.57	79.89
15	70.02	80.9	54.49	56.1	77.27	78.27	64.57	74.65	80.9
20	73.24	85.94	69.41	67.39	81.31	83.31	74.65	80.7	87.35
25	79.69	87.35	81.31	77.07	85.34	88.34	82.72	88.77	93.81
30	82.92	90.18	94.41	81.31	88.97	97.03	86.75	92.8	**98.04**

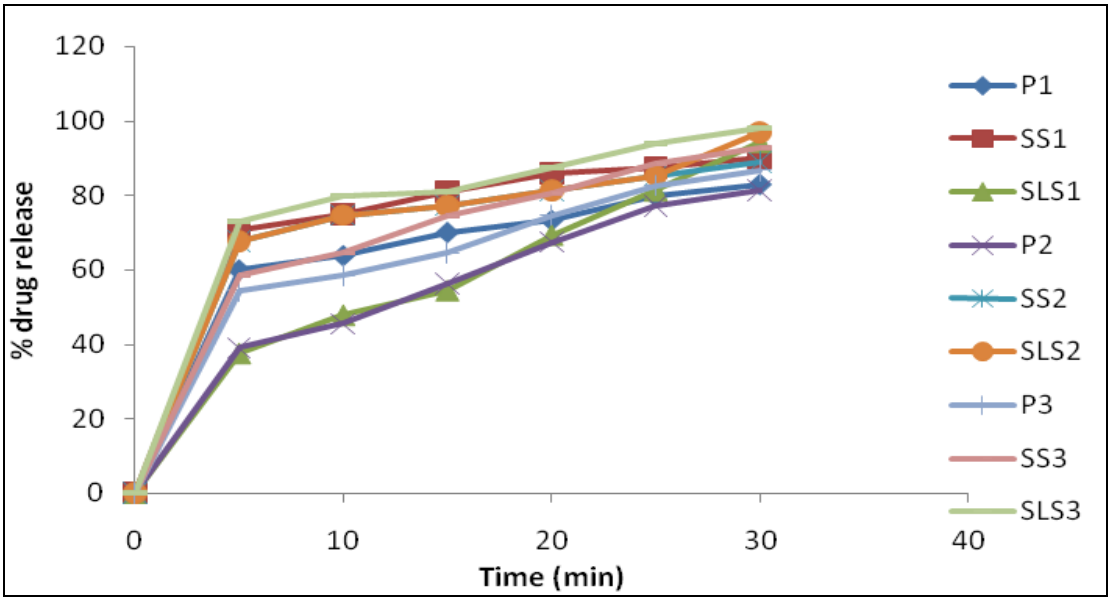

FIG 4: *IN-VITRO* DRUG RELEASE PROFILE

TABLE 5: DATA OF VARIOUS PARAMETERS OF MODEL FITTING FOR OPTIMIZED FORMULATIONSF-C I.E. SLS-3 OF BATCH B 3.

Formulation	Zero order		First order		Higuchi		Peppas		Parameter for Peppas equation	Best fit model
	R^2	K	R^2	K	R^2	K	R^2	K	N	
SLS3 (F-C)	0.964	0.980	0.892	-0.029	0.940	7.03	0.914	1.75	0.1427	**Zero order**

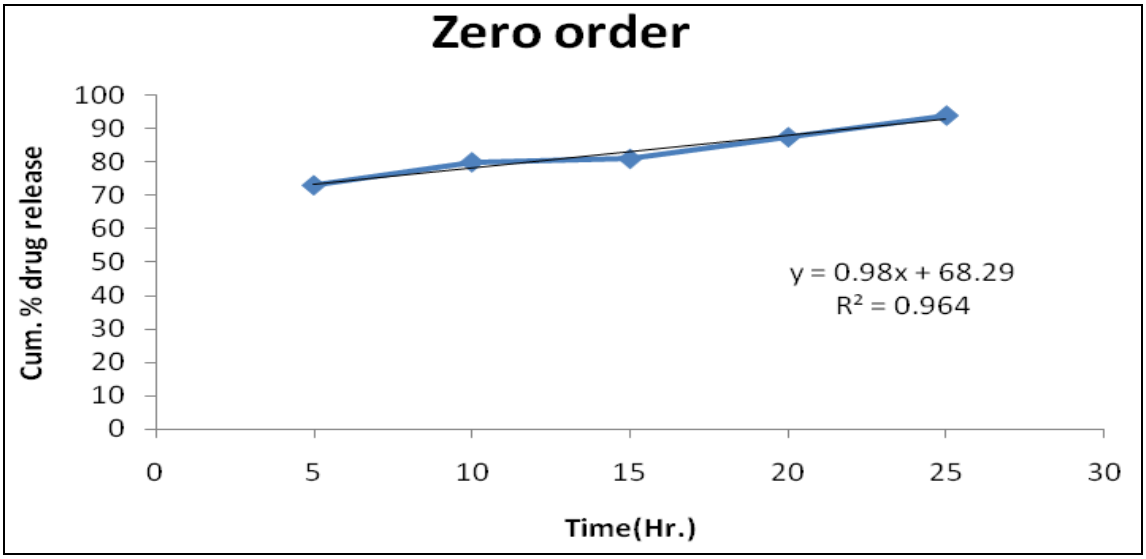

FIGURE 5: PLOT SHOWING ZERO ORDER RELEASE KINETICS OF FORMULATIONS F-C I.E. SLS-3 OF BATCH B 3.

Finally from *in vitro* drug release studies of all formulations; formulation F-C i.e. SLS-3 of batch B 3 shows highest release i.e 98.04 % after 30 minutes so it may be considered as an optimized formulation. Thus formulation F-C i.e. SLS-3 was selected for comparative *in vitro* drug release study with marketed preparation. The result of dissolution study of optimized formulation with marketed preparation shows in following **Table 6** and **Figure 6**.

TABLE 6: COMPARISON OF DISSOLUTION PROFILE BETWEEN FORMULATED VALSARTAN TABLET AND MARKETED TABLET

Time (min)	% drug Release formulated Valsartan tablet	% drug release marketed tablet
0	0	0
5	73.04	66.47
10	79.89	77.16
15	80.9	83.11
20	87.35	88.09
25	93.81	96.52
30	98.04	98.87

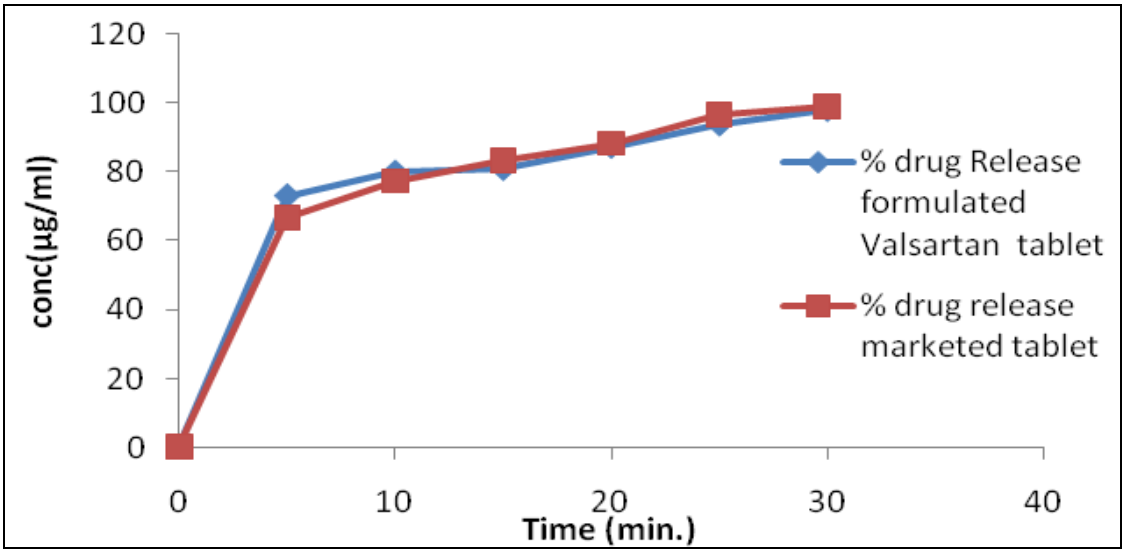

FIG. 6: COMPARISON OF DISSOLUTION PROFILE BETWEEN FORMULATED VALSARTAN TABLET AND MARKETED TABLET

From the above comparison study it is found that the evaluated parameters of prepared immediate release tablet of Valsartan is showing promising result as compared to the marketed formulation i.e. Diovan. Finally concluded that prepared immediate release tablet shows enhanced drug release i.e. 98.04 % which is nearer to drug release of marketed tablet i.e.98.87%.

CONCLUSION: The present study was aimed at developing immediate release tablet of valsartan by using combination of surfactants such as Poloxamer188, Sodium Lauryl Sulfate, Sodium stearate and other polymer such as Cross carmellose sodium, Avicel pH102, Lactose monohydrate, Talc by using direct compression technique. The immediate release tablets were evaluated for physicochemical parameter like thickness, hardness, weight variation, friability and *in-vitro* drug release. The *in-vitro* drug release study were found that optimized formulation F-C i.e.SLS-3 of batch B 3 show immediate drug release within 30 minutes up to 98.04%.

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