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FORMULATION AND EVALUATION OF MONOLITHIC OSMOTIC TABLET OF VALSARTAN

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ABSTRACT

Valsartan is an orally active and specific angiotensin II antagonist acting on the AT1 receptor subtype and belongs to the class of antihypertensive agents. Monolithic Osmotic Tablet of Valsartan were developed using Sodium chloride as a key ingredient which gives osmogent property which provides driving force inside the core tablet and which leads to release of drug. Microcrystalline cellulose used as a release retardant material in the present work. Different formulations were prepared by varying the concentrations using 3^2 factorial design. It was applied to see the effect of variables Sodium chloride and MCCon the response percentage drug release as a dependent variable. These formulations were evaluated for, Hardness, Flow property, Thickness, Friability, Drug content and In-vitro drug release. Tablets were coated with a semipermeable membrane using 5% w/v cellulose acetate in acetone and PEG 400(15%) used as Plasticizer. Coated Monolithic osmotic tablets were drilled for delivery orifice using standard micro drill of diameter size 0.6 mm on both side of tablet. Drug release rate was increased as the increase in the concentration of sodium chloride and release rate decreased on increasing the concentration of MCC. SEM Study carried out for detection of diameter size of delivery orifices. The FTIR studies demonstrate that there was no interaction between polymer and drug. The optimized formulation was stable for 6 months of accelerated stability study.

KEYWORDS: Valsartan, MCC, NaCl, Monolithic Osmotic Tablet.

INTRODUCTION

The development of improved method of drug delivery has received a lot of attention in the last two decades. The basic rational for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems and pharmacological parameters inherent in the selected route of administration. Rate controlled dosage form and less or not at all, a property of the drug molecules inherent kinetic properties. It has been employed as pharmaceutically active agent for the treatment of hypertension. It shows high solubility in gastric pH and falls rapidly in intestinal pH .The biological half-life is 7.5 hours. Hypertension is an abnormal condition of heart in which level of blood pressure is determine by the amount of blood heart pumps and the amount of resistance to blood flow in the arteries. Treatment of hypertension may require continuous supply of drug to the heart Single dose from that provides particular plasma profile of Valsartan is desirable. Conventional formulations may require high dosing frequency to maintain the drug within the therapeutic concentration hence it is necessary to formulate Osmotically tablet of Valsartan.

In Monolithic Osmotic Tablet the delivery of a drug is in the form of a solution that release the active material at sustained rates. These systems work with the principle of osmosis; osmotic pressure is produced by active material in .itself and/or an accompanying osmotic agent. Preparation consists of the core that contains the active material and a semipermeable membrane that coats the core, having an orifice size 0.5 to 0.9 mm. valsartan is gastric irritant in nature. To overcome this problem cellulose acetate coating is applied to the core tablet. The aim of this study was to develop Monolithic Osmotic Tablet of Valsartan by using 3^2 full factorial design. Sodium chloride is a key ingredient which gives osmagent property which provides driving force inside the core tablet which leads to release of drug and microcrystalline cellulose used as a release retardant material. Core tablet was coated by cellulose acetate 10% and PEG400 5% used as a plasticizer. Tablets were drilled 0.5mm on both side using mechanical driller.

MATERIAL AND METHODS

Valsartan was obtained as a gift sample from Aarti drugs, Mumbai. Cellulose acetate, Sodium chloride, Lactose, Starch, PEG 400, Acetone was procured from Research – Lab Fine chem. industry, Mumbai. All other chemicals used in study were of analytical grade.

Drug-Excipients Interactions

The physicochemical compatibilities of the drug and excipients were tested by FT-IR spectrometry. FT-IR spectra of the drug alone and drug-excipients physical mixtures.

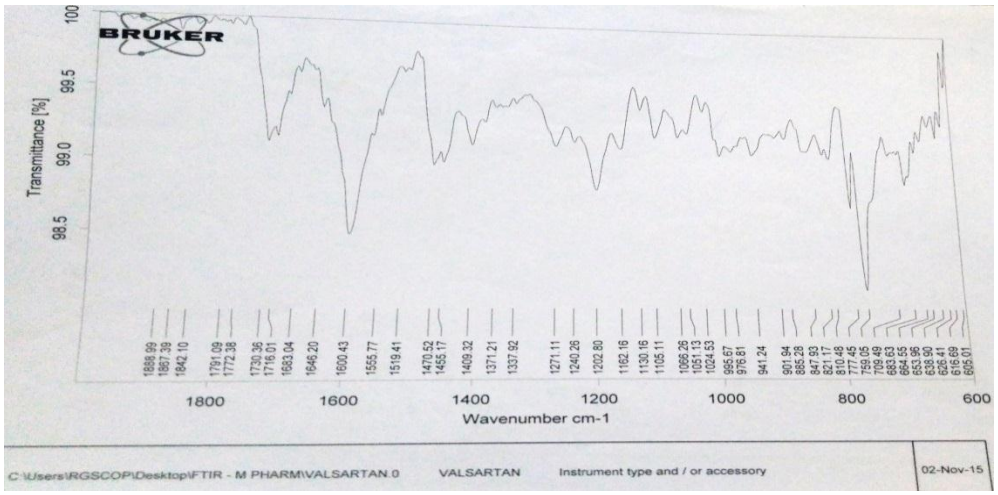

Fig 1: FT-IR Spectra of Valsartan.

The FTIR spectra of pure Valsartan showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug.

Infra-red spectra of drug and polymer mixture showed matching peaks with the drug spectra. The characteristic peak of drug was also seen in the spectra of physical Mixture.

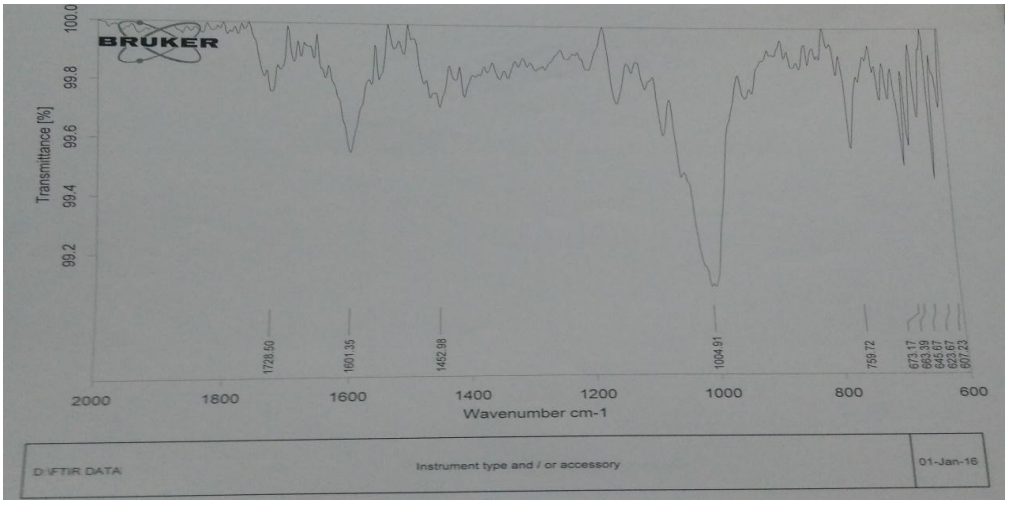

Fig 2: FT-IR Spectra of Physical Mixture.

Factorial Design

The application of mathematical optimization in the pharmaceutical field was first reported by Fonner et al (1970), using the Lagrangian method as a constrained optimization technique.

A factorial design is used to evaluate two or more factors simultaneously. The treatments are the combinations of levels of the factors. The advantages of factorial design over one factor at a time experiment are that they are more efficient and they allow interactions to be detected. Intervention studies with 2 or more categorical explanatory variables leading to a numerical outcome variable are called as" Factorial design ". A factor is simply a categorical variable with 2 or more values referred to as levels. A study in which there are 2 factors with 3 levels is called as 3^2 Factorial designs. For present work 3^2 Factorial designs was selected.

In this design, 2s factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations as reflected.

Table No. 1 Composition of Monolithic Osmotic Pump Tablet as per Factorial Design (All values are expressed in mg)

Ingredients	**Formulation code**								
Quantity(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Valsartan	40	40	40	40	40	40	40	40	40
Sodium chloride	5	7	9	5	7	9	5	7	9
Microcrystalline cellulose	125	125	125	150	150	150	175	175	175
Starch	75	73	71	50	48	46	25	23	21
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Total Weight (mg.)	250	250	250	250	250	250	250	250	250

Method of preparation of Core tablet of Valsartan:

Core tablets of Valsartan was prepared by wet granulation method. The compositions of core tablets are given in table 1. Valsartan was mixed with Sodium chloride, starch and Microcrystalline cellulose these powder blend was knead in the mortar and pestle for 15-20 min .The blend was granulated using starch as a binder in water. Wet mass was formed; resulting wet mass was passed through sieve # 22. Granules were dried in oven at 50°C for 2 hrs. Dried granules were lubricated with magnesium stearate. Lubricated blend was evaluated for powder characteristics and flow properties like bulk density, tapped density, Carr index, Angle of repose, and Hausner's ratio. Then desired amount of blend was compressed in to the tablet using Rimek tablet punch machine equipped with 8 mm punch, Weight of the tablet was kept to 250 mg.

Coating of Osmotic Tablet

The core tablets of Valsartan were coated with 10% w/v Solution of Cellulose acetate in Acetone was used as a semipermeable membrane provider. PEG 400 5% v/v was used as

plasticizer .The tablets were warmed to 40±2°c before applying coating solution .The composition of coating solution used for coating of core tablets is given in (Table 2).

Dip coating technique was used for the coating of osmotic tablet. Coating was continued until desired weight gain (10%) was obtained and tablets were dried at 50°C for 10 h. before further evaluation.

Table No. 2: Coating composition.

Ingredients	Quantity for 100 ml
Cellulose Acetate	10%
Polyethylene glycol 400	5%
Acetone	100 ml

Drilling

For the coated tablets, a small orifice were drilled through both side of each coated tablet by standard mechanical drilling technique using 0.5 mm needle. Orifice size was 0.5 mm.

RESULTS

1. Evaluation of Powder Bulk

Many different types of angular properties have been employed to assess flow ability, of these; angle of repose is the most relevant. Repose angle of the powder was investigated. The value of Angle of repose (°θ) decreased after the addition of lubricant. Angle of repose (°θ) is an indicative parameter of powder flow ability from hopper to die cavity. The angles of repose of all the formulations were within the range of 40°–53° indicative of excellent and good flow ability. Bulk density may influence compressibility, tablet porosity, dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. The bulk density of powder was found to be between 0.37-0.39 gm/cm^3. The value indicates good packing capacity of granules. The tap density of the granules of factorial design batches were found in the range of 0.42-0.48gm/cm^3. The bulk density and tap density was used to calculate the percent compressibility of the powder.

The compressibility index of the Powder was observed in range of 11 to 22, indicating good compressibility of the granules. The values of the Hausner's ratio were found to be in the range of 1.12 to 1.27 indicating good and fair flow ability. Data is summarized in (Table No. 3).

Table No. 3: Evaluation of Powder.

Formulation code	Angle of repose(θ) Mean± S.D	Bulk density (gm/cm^3) Mean± S.D	Tapped density (gm/cm^3) Mean± S.D	Compressibility index (%) Mean± S.D	Hausner's ratio Mean± S.D
F1	42.03 ± 0.04	0.391± 0.0045	0.48± 0.0068	18.78±2.122	1.23±0.031
F2	40.55 ± 0.52	0.386± 0.0034	0.43± 0.0438	10.81±1.469	1.12±0.018
F3	45.37 ± 0.88	0.388± 0.0034	0.44± 0.0045	11.91 ±1.674	1.13±0.021
F4	48.90 ± 0.71	0.375± 0.0032	0.42± 0.0040	11.00±0.010	1.12±0.018
F5	47.68 ± 1.06	0.376± 0.0032	0.43± 0.0043	13.55 ±1.412	1.15±0.011
F6	52.74 ± 0.37	0.380± 0.0033	0.45± 0.0046	15.72 ±0.813	1.18±0.786
F7	48.55 ± 0.69	0.371± 0.0031	0.47±0.0052	21.79 ±0.012	1.27±0.786
F8	46.39 ± 1.39	0.382± 0.0033	0.46± 0.0049	16.83± 1.405	1.20±0.020
F9	46.77 ± 1.17	0.388± 0.0034	0.46± 0.0149	15.54± 1.439	1.18±0.020

2. Evaluation of Tablets

A) Pre coating evaluation

All formulated coated osmotic tablet batches were evaluated for weight variation, hardness, thickness, friability and drug content. Weight variation, hardness, thickness, friability and drug content of uncoated tablet were found within the range.

All f9ormulated osmotic core tablet batches were shiny white with smooth surface, with good texture. The Average weight of the tablets was found to be 250 mg. Thickness of the tablet was found to be 3.4 mm, Hardness of the tablet was found 4.15-4.9 $kg/cm^{2,}$ Friability of the tablets was found to be 0.27-0.39% and Drug content of the tablet was found to be 97-98%. Due to constant tablet press setting across all batches irrespective of weight variation. This ensured good mechanical strength (Table 4).

Table No. 4: Pre coating evaluation parameters of osmotic tablet.

Formulation Code	Average Weight (mg) Mean ± S.D	Hardness ($kg/cm^{2)}$ Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean± S.D	Drug content (%) Mean± S.D
F1	250.2±2.5298	4.6±0.21082	3.445±0.0085	0.35±0.003	97.13
F2	250.1±1.6633	4.85±0.24152	3.438±0.00919	0.31±0.002	97.65
F3	250.1±2.3309	4.35±0.24152	3.439±0.00994	0.35±0.002	98.13
F4	250.5±1.90029	4.9±0.21082	3.436±0.00843	0.31±0.001	97.94
F5	251.9±2.3309	4.15±0.24152	3.442±0.00919	0.27±0.004	98.03
F6	251.3±2.2632	4.6±0.31623	3.439±0.00994	0.31±0.002	97.70
F7	249.4±3.0983	4.3±0.3496	3.439±0.01792	0.31±0.003	97.89
F8	248.4±3.06232	4.4±0.39441	3.438±0.00422	0.39±0.002	97.91
F9	251.3±1.82878	4.7±0.2582	3.44±0.00919	0.31±0.001	97.99

B) Post coating evaluation

All formulated coated osmotic tablet batches were evaluated for Weight variation, thickness and Film thickness. After coating of the tablets average weight of tablets was found to be 256.2 mg., thickness of coated tablet was found to be 3.78-3.80 mm and thickness of film was found to be 0.36 mm. Due to uniform coating weight variation and thickness of coated tablet was found within the range. Evaluated data is shown in (Table 5).

Table No. 5: Post coating evaluation parameters of Osmotic Tablet.

Formulation Code.	Average Weight (mg) Mean	Thickness of coated tablet Mean	Thickness of film(mm) Mean
F1	254.4	3.805	0.358
F2	255.4	3.803	0.365
F3	256.1	3.796	0.356
F4	255.2	3.788	0.352
F5	253.7	3.799	0.357
F6	256.4	3.801	0.362
F7	255.8	3.789	0.355
F8	256.6	3.785	0.344
F9	256.7	3.785	0.350

From above evaluated data of coated osmotic tablet it was confirmed that weight variation and thickness of film was found within the range.

C) Diameter of delivery orifice

Evaluation of diameter size of delivery orifices were measured by Scanning Electron Microscope and were found to be 528um (Upper) and 583um (Lower) SEM data give in fig 3.

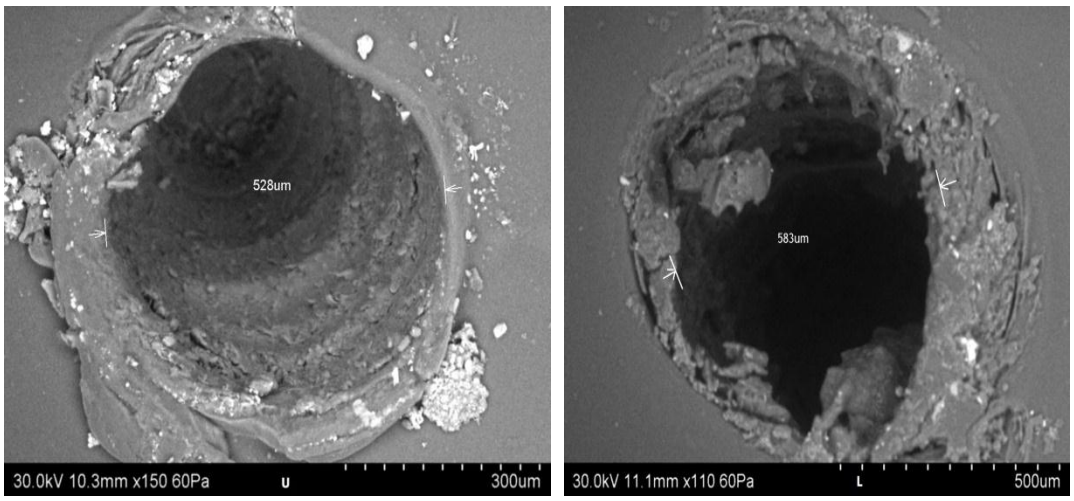

Fig 3: Scanning Electron Microscopy (SEM) of delivery orifice.

3. In *Vitro* Dissolution study of Formulations (F1-F9)

Osmotic tablets were subjected to *In-vitro* drug release studies in simulated gastric and intestinal fluid. Dissolution study was performed in 0.1 N HCl for 2 hrs and for remaining 22 hrs. in Phosphate buffer pH 6.8, obtained result summarized in (Table No. 6).

Table No.6: Cumulative Drug Release of Formulations (F1-F9)

Time (hr)	Cumulative Drug Release (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	3.319	2.723	2.920	2.738	1.465	2.343	1.885	3.553	2.427
2	5.508	5.725	5.634	5.345	4.940	5.560	5.267	5.735	5.390
3	10.662	11.111	10.731	10.514	10.102	10.282	9.252	10.514	10.475
4	13.962	13.600	14.177	13.888	14.517	13.699	13.733	14.034	13.600
5	18.424	18.187	18.589	18.303	18.438	18.187	18.542	18.658	18.345
6	22.806	21.150	21.554	21.054	23.105	20.763	23.055	22.905	20.642
7	26.025	25.017	26.816	26.296	27.129	25.858	26.395	26.417	25.781
8	30.541	30.652	31.768	30.942	31.161	30.117	30.824	30.992	30.696
10	40.030	35.101	40.262	40.516	40.369	40.094	38.741	40.466	39.954
12	47.284	46.626	52.667	48.065	48.183	51.294	46.683	48.682	49.924
16	56.552	61.888	67.619	60.202	56.183	65.985	51.844	58.142	64.010
24	76.633	88.449	94.909	84.471	73.612	91.813	71.666	80.335	89.304

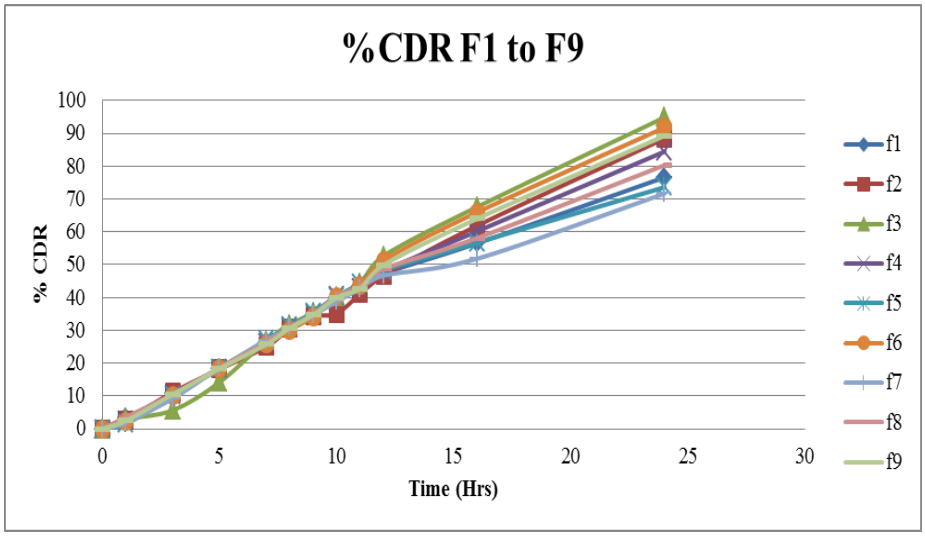

Figure 4: Dissolution Profile of Formulation Batches (F1-F9)

4. Optimization

Statistics are apply to the results obtained from General Factorial Design in which Two independent Variables varied namely Sodium chloride (NaCl) (X1) and Microcrystalline cellulose MCC (X2) and their effect is recorded on dependent Variable namely % drug release (Y1).

Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings. (Table No. 7) shows ANOVA for the dependent variable % drug release. The values of X_1 and X_2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of both the variables on the selected responses. Decreasing the concentration of the Sodium chloride (NaCl) and microcrystalline cellulose (MCC) resulted in the decrease in the release of quetiapine. Variable caused significant change in the responses. From this data optimum concentration of NaCl 09 mg and MCC 125 mg was found.

A) Drug release

Table No. 7: ANOVA for % drug release (Y1)

Source	Sum of Squares	Degree of Freedom	Mean Square	F value	P-value	Inference
Model	504.075	2	252.37	10.94	0.0100	Significant
A-NaCl	387.53	1	387.53	16.80	0.0064	
B-MCC	117.22	1	117.22	5.08	0.0651	

Standard deviation = 4.80

R-Squared = 0.7848

The Model F-value of 10.94 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > P" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms.

The Variance Inflation Factor (VIF) measured how much the variance of that model coefficient was inflated by the lack of orthogonality in the design and was calculated for % drug release. It was found to be near one indicating good estimation of the coefficient. Similarly Ri-squared was near to zero which led to good model. The values of Prob > F were less than 0.05, which indicated model terms were significant.

The quadratic model obtained from the regression analysis used to build a 3-D graph's in which the responses were represented by curvature surface as a function of independent

variables. The relationship between the response and independent variables can be directly visualized from the response surface plots.

The response surface plot was generated using Design Expert 8.0.4 software presented in (Fig 5). To observe the effects of independent variables on the response studied % drug release. From response surface 3 level factorial design was choosen using quadratic design mode.

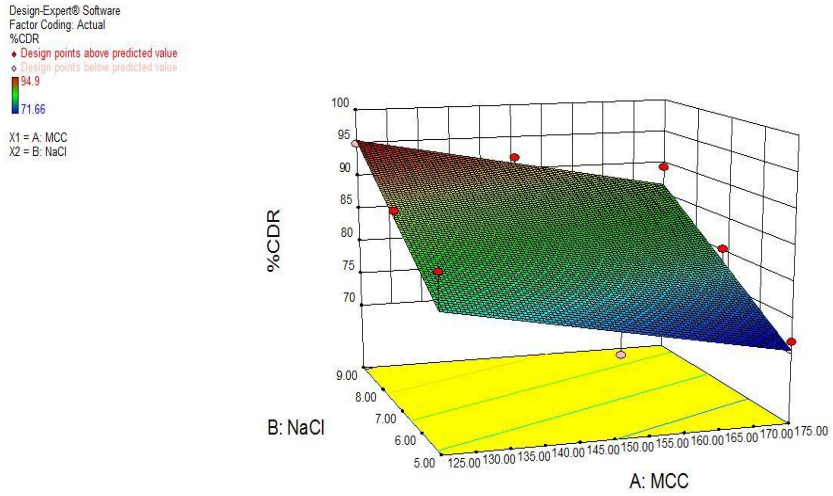

Fig 5: Surface response plot showing effect of Sodium Chloride and Microcrystalline Cellulose on release.

B) Contour plot

The contour plot showing effect of Sodium chloride and Microcrystalline cellulose on release is shown in (Fig 6).

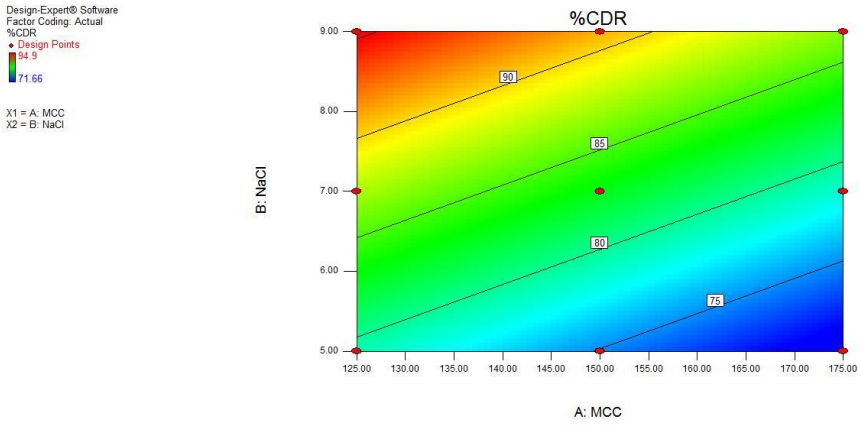

Fig 6: Contour plot showing effect of Sodium chloride and Microcrystalline cellulose on drug release.

C) Design summary and Response summary

Design summary is shown in (Table No. 8).

Table No. 8: Design Summary.

Factor	Name	Units	Type	Minimum	Maximum	-1 Actual	+1 Actual	Mean
A	NaCl	Mg	Numeric	05.00	09.00	05	09	07
B	MCC	Mg	Numeric	125	175	125	175	150

D) Perturbation plot

The perturbation plot is shown in (Fig 7).

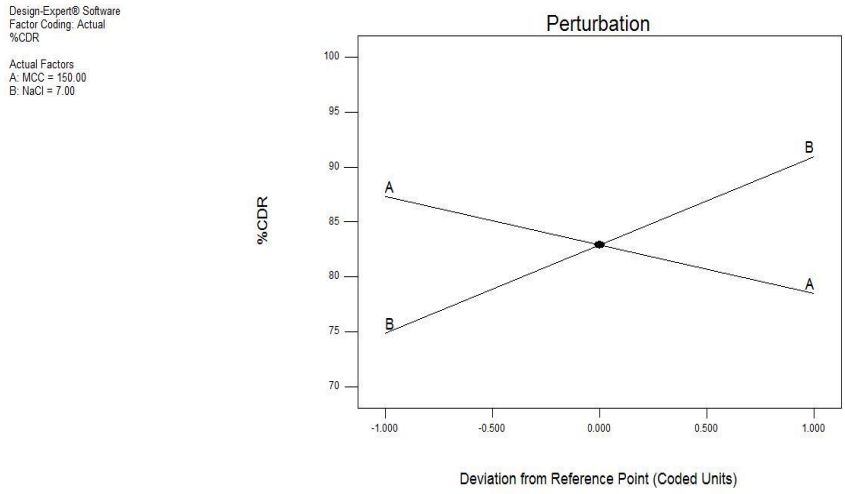

Fig 7: Perturbation.

5. Dissolution Kinetics

In present study dissolution were analyzed by PCP Disso Version 3 software to study the dissolution kinetics is given in (Table 9).

Table No. 9: Kinetic treatment of prepared Valsartan osmotic tablet formulations.

Formulation code	Coefficient of determination (R^2)				
	Zero order	First order	Higuchi square root	Hixon crowell	Korsemeyer plot
F1	0.9888	0.9845	0.9194	0.9957	0.9951
F2	0.9960	0.9229	0.8926	0.9650	0.9880
F3	0.9972	0.8844	0.8881	0.9499	0.9976
F4	0.9954	0.9582	0.9039	0.9849	0.9955
F5	0.9863	0.9898	0.9213	0.9969	0.9891
F6	0.9962	0.9146	0.8822	0.9986	0.9614
F7	0.9813	0.9921	0.9244	0.9963	0.9880
F8	0.9906	0.9756	0.9168	0.9928	0.9956
F9	0.9966	0.9251	0.8850	0.9666	0.9965

Different kinetic treatments (zero order, first order, Higuchi's square root equation and Korsmeyer treatment) were applied to interpret the release of Valsartan from different matrices The best formulation i.e. optimized formulation F3 follow Zero order kinetics r^2 = 0.9972 and n < 0.5 for all batches. So the drug release is of fickian releas.

6. Stability Studies

Table No. 10: Characteristics of optimized formulation F3 after 6 months storage.

Parameter	Initial sample of optimized formulation	After storage at 25±2°C / 60% RH, for 6 month
	F3	F3
Hardness	4.35 kg/cm^2	4.23 kg/cm^2
Drug content	97.70 %	97.40 %
% Drug Released (After 24 hrs.)	94.909 %	94.800 %

Table No. 11: In vitro drug release study of formulation F3 stored at 25°C / 60% RH for 6 months.

Time (Hrs.)	Cumulative Drug Release (%) F3 Batch (Mean± S.D)	Cumulative Drug Release (%) F3 Batch (Mean± S.D)
	Before 6 month	After 6 month
0	0.00	0.00
1	2.920	2.620
2	5.634	4.356
3	10.731	10.258
4	14.177	13.985
5	18.589	18.198
6	21.554	21.256
7	26.816	26.783
8	31.768	31.245
10	40.262	39.875
12	52.667	52.265
16	67.619	66.588
24	94.909	93.548

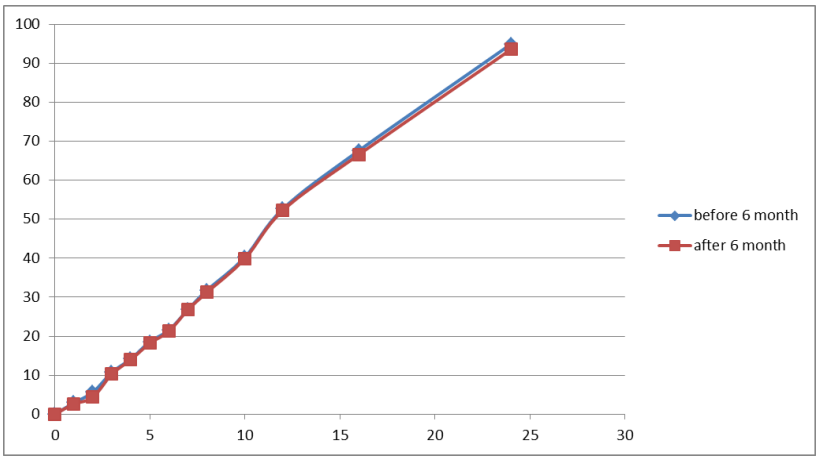

Fig 8 : Dissolution profile of optimize F3 formulation before and after 6 month.

The selected formulation were wrapped in aluminium foil and stored at 25±2ºC temperature for 6 months. After 6 months the formulation F3 were evaluated for the hardness, dug content and in vitro % drug release. It was observed that there was no significant variation in the physical appearance, average weight, hardness and loss of drying after placing the tablets at various temperature and humidity conditions for a period of 6 months. Also the cumulative % drug release data showed that each of the formulation released a drug amount, within the limits laid down as per the ICH guidelines for stability studies.

CONCLUSION

The results of experimental studies of Valsartan osmotic tablets proved that the granules of Valsartan showed good flow properties, tablet evaluation tests are within the acceptable limits, IR spectral analysis proved that there was no drug-excipients interaction, the kinetic studies revealed that optimized formulation followed zero order drug release kinetics and stability studies revealed that all the formulations were found to be stable after storing at temperature of $45^{o} \pm 2^{o}$, 75% ± 5% relative humidity for 6 months. Thus the results of the above study clearly indicated that Developed osmotically sustained release tablet of Valsartan provide release of drug at a predetermined rate and for a predetermined time in sustained manner.

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