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DEVELOPMENT OF OSMOTICALLY CONTROLLED RELEASE TABLET OF CANDESARTAN CILEXETIL

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Keywords:

Candesartan Cilexetil, Controlled release, Elementary Osmotic tablet, Semipermeable Membrane, PEG 400

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ABSTRACT

Candesartan Cilexetil is one of the antihypertensive drug used to control the high blood pressure .Osmotically Controlled release tablet of Candesartan Cilexetil was performed for reducing dosing frequency and patient compliance. Elementary osmotic tablets of Candesartan Cilexetil 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 (X1) and MCC (X2) on 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(CA) in acetone and PEG 400(15%) used as Plasticizer. Coated Elementary osmotic tablets were drilled for delivery orifice using standard micro drill of diameter size 0.8mm .Drug release rate was increased as the increase in the concentration of sodium chloride and release rate decreased on increasing the concentration of MCC. Drug release rate was directly proportional to delivery orifice size .SEM Study carried out for detection of diameter size of delivery orifice. The FTIR studies demonstrate that there was no interaction between polymer and drug. The optimized formulation was stable for 3 months of accelerated stability study.

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 [1]. Rate controlled dosage form and less or not at all, a property of the drug molecules inherent kinetic properties [2]. Thus design of controlled release systems necessities a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug Candesartan Cilexetil. 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 9 hours. The dosing regimen is two or three times a day. 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 [3, 4]. Treatment of hypertension may require continuous supply of drug to the heart Single dose from that provides particular plasma profile of Candesartan Cilexetil is desirable. Conventional formulations may require high dosing frequency to maintain the drug within the therapeutic concentration hence it is necessary to formulate Osmotically controlled release tablet of Candesartan Cilexetil.

In elementary osmotic pump tablet (EOP) the delivery of a drug is in the form of a solution that release the active material at controlled 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 1.5 mm. Candesartan Cilexetil 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 osmotically controlled release tablet of Candesartan Cilexetil 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 0.8mm using mechanical driller.

MATERIALS AND METHODS

Candesartan Cilexetil was obtained as a gift sample from Mylan laboratories, Nashik. Cellulose acetate, Sodium chloride, Sodium Lauryl sulphate, Lactose, PVP – K30, PRG400, Acetone, Isopropyl alcohol, 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 (1:1 w/w) were derived from an IR Affinity-1, FT-IR, Shimadzu, Japan.

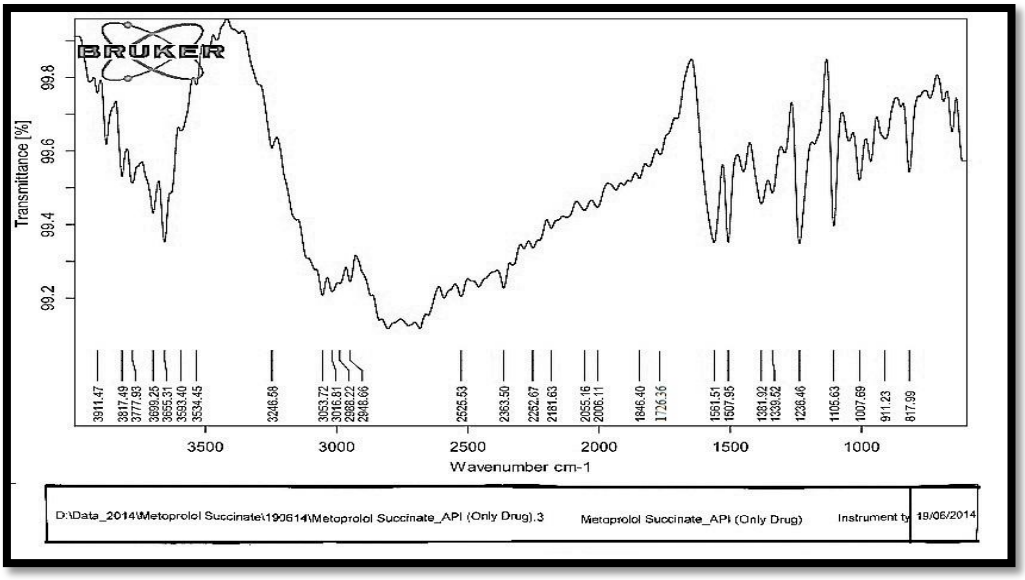

Figure 1: FTIR Spectral of Candesartan Cilexetil

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

Compatibility study between drug and polymer:

Fourier Transform Infrared Spectroscopy:

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 all drug- polymer mixture.

Compatibility study between drug and osmogent

FTIR spectrum of drug with Sodium Chloride is shown in (Figure 2)

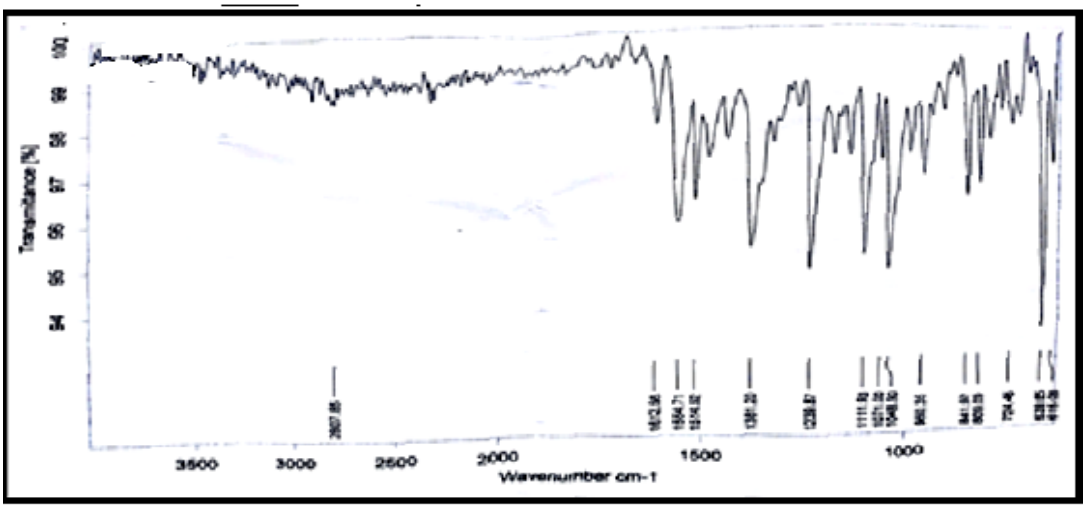

Figure2: FTIR spectrum of drug with Sodium Chloride

Compatibility study between drug and Microcrystalline Cellulose

FTIR spectrum of drug with Microcrystalline Cellulose is shown in (Figure 3)

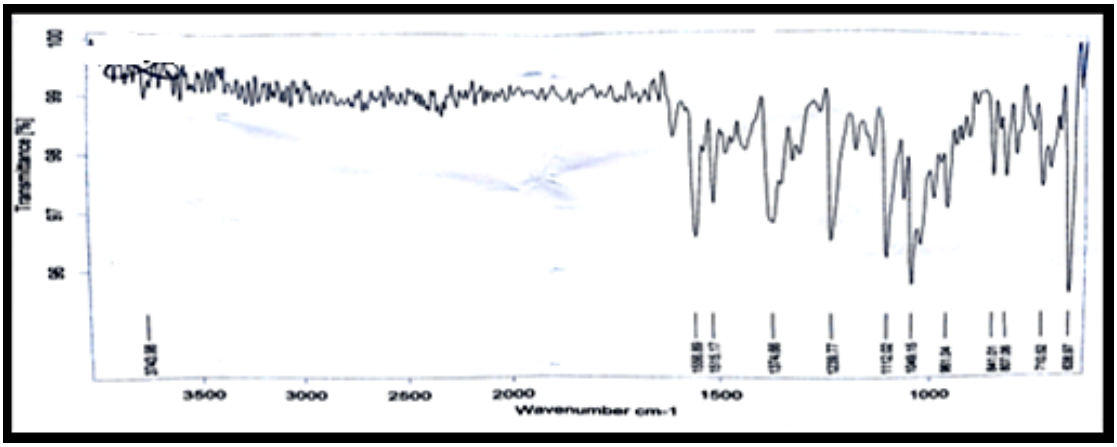

Figure 3: FTIR spectrum of drug with Microcrystalline Cellulose

Compatibility study between drug and lactose

FTIR spectrum of drug with Lactose is shown in (Figure 4)

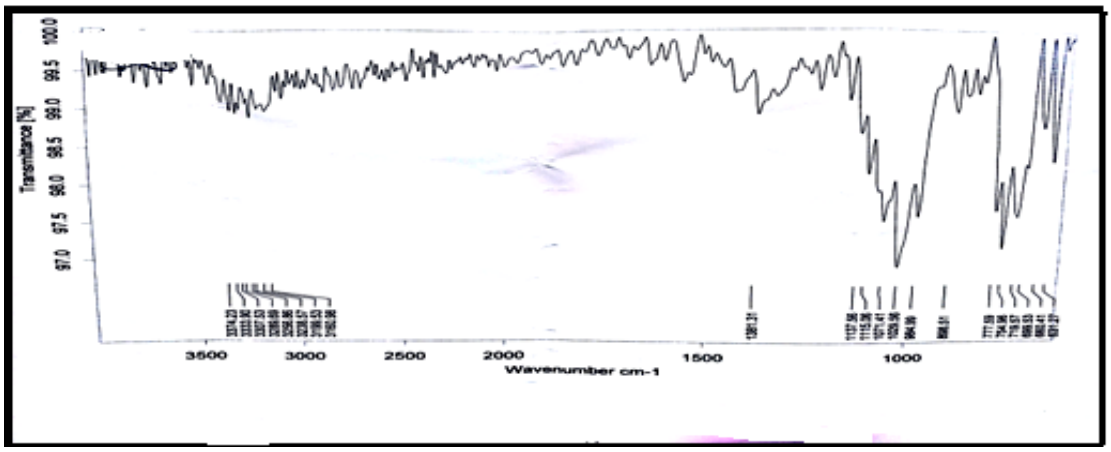

Figure 4: FTIR spectrum of drug with Lactose

Compatibility study between drug and Sodium Lauryl Sulphate

FTIR spectrum of drug with Sodium Lauryl Sulphate is shown in (Figure 5)

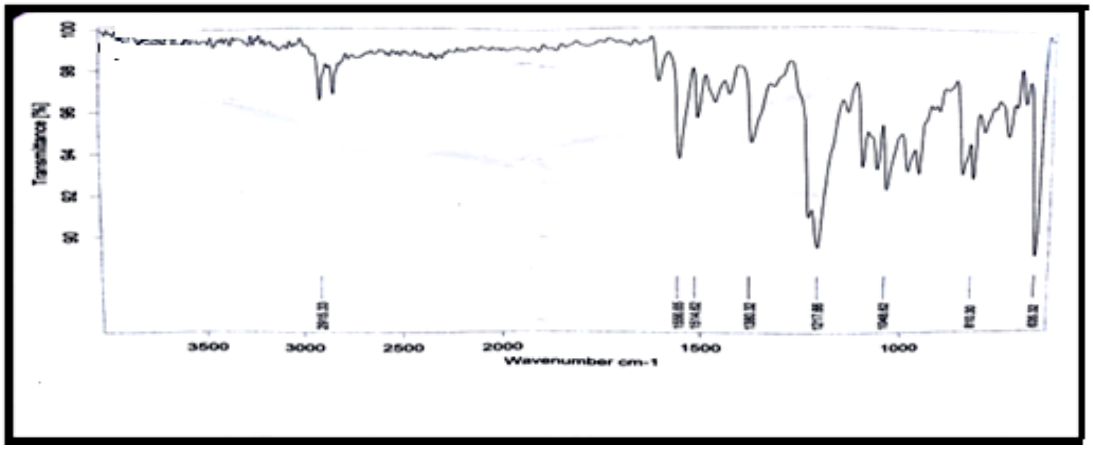

Figure 5: FTIR spectrum of drug with Sodium Lauryl Sulphate

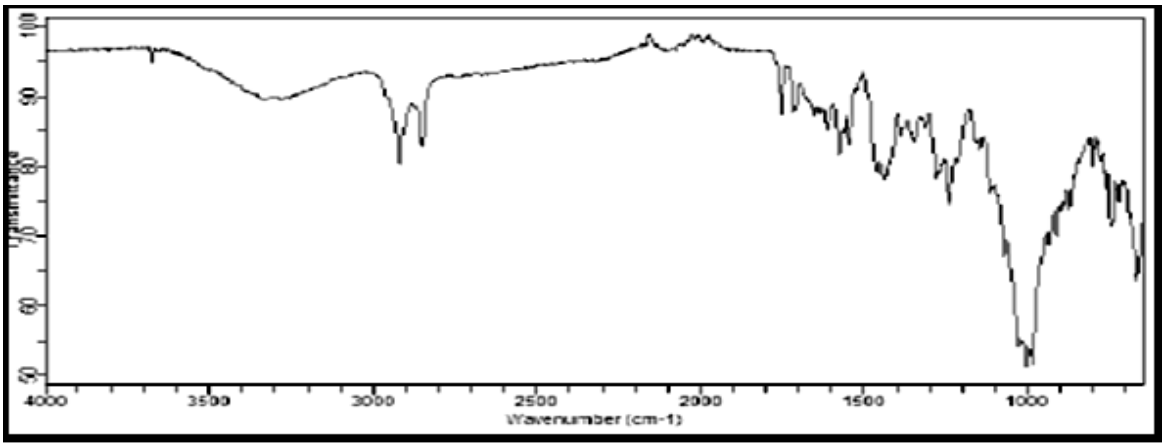

Figure 6: FTIR Spectral graph of formulation

METHODS:

Formulation development of Osmotic Tablet:

Core tablets of Candesartan cilexetil was prepared by wet granulation method. The compositions of core tablets are given in table no (1). Candesartan cilexetil was mixed with Sodium chloride, Lactose, Sodium Lauryl Sulphate and Microcrystalline cellulose these powder blend was knead in the mortar and pestle for 15-20 min .The blend was granulated using PVP K30 as a binder in IPA. 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 and talc. 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 225 mg.

Ingredients	Formulation code								
Quantity(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Candesartan cilexetil	08	08	08	08	08	08	08	08	08
Sodium chloride	10	30	50	10	30	50	10	30	50
Microcrystalline cellulose	125	75	100	75	100	125	100	125	75
PVP K30	15	15	15	15	15	15	15	15	15
Lactose	47	77	32	97	52	57	72	27	57
Sodium Lauryl Sulphate	15	15	15	15	15	15	15	15	15
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Total	225	225	225	225	225	225	225	225	225

Table 1: Composition of Elementary osmotic pump tablet as per 3^2 full Factorial Design

(All values are expressed in mg)

Evaluation of Granules [5, 6]

Bulk Density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. bulk density (BD) of powder blends was determined using the following formula.

$$\text{Bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of powder}}$$

Tapped density (TD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The tapped densities (TD) of powder blends were determined using the following formula.

$$\text{Tapped density} = \frac{\text{Total weight of powder}}{\text{Total volume of tapped powder}}$$

Angle of repose (θ)

Angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles. The angle of repose (θ) for powder was determined by placing the powder in a funnel.

$$\tan \theta = h/r$$

Where, θ=Angle of repose, h= height of the pile of powder (h=1), r= radius of the base of cone.

Hausner's Ratio

The Hausner's ratio is an indication of the compressibility of a powder .It is calculated by the formula.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Compressibility Index

It is a simple index that can be determined on small quantities of powder. In theory, the less compressible a material the more flowable it is. The compressibility indices of the powder blends was determined using following formula,

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Formulation code	Angle of repose(θ) (n = 3)	Bulk density (gm/cm^3) (n = 3)	Tapped density (gm/cm^3) (n = 3)	Compressibility index (%) (n = 3)	Hausner's ratio (n = 3)
F1	27.96±0.026	0.3968±0.006	0.4587±0.07	10.56±0.016	1.18±0.046
F2	27.29±0.026	0.3968±0.006	0.4363±0.06	12.69±0.017	1.14±0.036
F3	28.90±0.013	0.3902±0.098	0.4545±0.033	14.05±0.059	1.18±0.046
F4	29.30±0.027	0.3968±0.199	0.4347±0.106	12.69±0.017	1.21±0.047
F5	26.72±0.025	0.3906±0.006	0.4545±0.032	8.71±0.147	1.14±0.046
F6	28.20±0.026	0.4207±0.102	0.4454±0.106	14.74±0.019	1.18±0.046
F7	27.16±0.006	0.3875±0.098	0.4636±0.033	8.71±0.147	1.19±0.014
F8	26.87±0.025	0.3950±0.198	0.4347±0.032	10.56±0.016	1.18±0.046
F9	27.78±0.001	0.3968±0.0006	0.4454±0.031	9.25±0.048	0.91±0.047

Table 2: Evaluation of powder blend

Evaluation of uncoated Tablet:

Before coating was performed the uncoated tablets were evaluated for Hardness, Friability Weight uniformity, Content uniformity and Thickness. Data is given in (Table 3)

Friability [7]

In this test 20 tablets were weighed and placed in a Roche Friabilator test apparatus, and then the tablets were subjected to rolling ad replaced shocks, resulting from free falls within the apparatus from the height of 6 inches. After 100 revolutions the tablets were removed, de-dusted and weighed again .The friability was determined as the percentage loss in weight of the tablets,

$$\%\text{Friability} = \frac{\text{Initial weight of Tablet} - \text{Final weight of Tablets}}{\text{Final weight of tablet}} \times 100$$

Weight uniformity [8]

Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits (±7.5%). The percent deviation was calculated using the following formula

% Deviation= (Individual weight - Average Weight /Average weight) x 100

Uniformity of Content [9]

Twenty tablets were weighed individually and powdered in pestle mortar, and an amount equivalent to 8 mg of Candesartan Cilexetil was extracted with 100 mL of phosphate buffer 6.8.The solution was filtered through whatman filter, and the content of Candesartan Cilexetil in the solution was determined by measuring absorbance on double beam UV spectrophotometer (Jasco V-630) at 256 nm after suitable dilution.

Hardness [8]

Tablets require a certain amount of strength, or hardness, to withstand the mechanical shocks of handling in manufacturing, packaging as well as in shipping. The hardness of the tablets here was measured using Monsanto hardness tester (Cadmech). In this, was tablet is placed between the plungers, and was tightened from one end, and pressure required to break tablet diametrically was measured. The hardness was measured in terms of kg/cm^2.

Uniformity of thickness

The uniformity of thickness was measured using Digital vernier calliper (Absolute Digimatic, Mitutoyo Corp., Japan). The average diameter and thickness of the tablet was calculated.

Formulation code	Average Weight (mg) (n = 20)	Hardness ($kg/cm^{2)}$ (n = 5)	Thickness (mm) (n = 3)	Friability (%) (n = 20)	Drug content (%) (n = 3)
F1	224.8±0.0012	3.33±0.163	3.21±0.035	0.37±0.016	97.82±0.614
F2	224.63±0.0014	3.39±0.166	3.24±0.032	0.42±0.012	98.57±0.782
F3	219.21±0.0013	3.40±0.163	3.27±0.026	0.36±0.012	98.74±0.974
F4	224.67±0.0012	4.1±0.163	3.26±0.033	0.38±0.016	98.57±1.17
F5	224.67±0.0012	4.2±0.166	3.22±0.034	0.41±0.020	98.2±0.538
F6	224.66±0.0013	4.4±0.163	3.27±0.023	0.42±0.016	98.65±0.815
F7	213.19±0.0014	4.0±0.163	3.24±0.016	0.34±0.012	99.12±0.678
F8	224.89±0.0014	3.9±0.163	3.23±0.027	0.40±0.012	98.05±0.763
F9	224.72±0.0011	4.1±0.164	3.29±0.021	0.38±0.008	97.88±0.517

Table 3: Precoating evaluation parameters of osmotic tablet

Coating of Osmotic Tablet [10,11]

The core tablets of Candesartan Cilexetil were coated with 5% w/v Solution of Cellulose acetate in Acetone was used as a semipermeable membrane provider. PEG 400 15% 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 are given in (Table:4) 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

Ingredients	**Quantity for 100 ml**
Cellulose Acetate	5 %
Polyethylene glycol 400	15 %
Acetone	100 ml

Table 4: Coating composition

Drilling:

The formulated coated tablets, a small orifice were drilled through one side of each coated tablet by standard mechanical drilling technique using 0.8mm needle. Orifice size was 0.8 mm.

Evaluation of Osmotic Tablets [12]

After coating osmotic tablets were evaluated for Thickness of tablet, Thickness of film, weight uniformity, Diameter of delivery orifice, dissolution test of prepared formulations.

Thickness of tablet:

All tablets were initially subjected for thickness measurement by using digital venire caliper after coating to assess thickness of coat. All the measurements were made in triplicate.

Thickness of film:

The tablet after dissolution was taken of to the bowl and washed with water and air dried for 6 hr. The part of the tablet coat was cut and thickness was measured by digital venire caliper (Mituyoyo, Japan)

Weight Uniformity:

Weight variation was calculated as per method described in Indian pharmacopoeia.20 tablets were weighed individually and the average weight is calculated.

Formulation Code.	Average Weight (mg) (n = 20)	Thickness of coated tablet (n = 3)	Thickness of film(mm) (n = 3)
F1	235.9±0.0008	4.10±0.035	0.2822±0.002
F2	236.2±0.0008	4.11±0.032	0.2902±0.001
F3	237.5±0.0007	4.19±0.026	0.2189±0.004
F4	237.7±0.0005	3.98±0.033	0.2122±0.002
F5	238.1±0.0007	4.09±0.034	0.2110±0.003
F6	236.8±0.0009	4.09±0.023	0.2010±0.001
F7	239.9±0.0005	4.11±0.016	0.2100±0.002
F8	235.5±0.0006	4.07±0.027	0.1900±0.004
F9	237.7±0.0005	4.17±0.021	0.2800±0.002

Table 5: Post coating evaluation parameters of osmotic tablet

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

Diameter of delivery orifice:

The size of the delivery orifice was determined using scanning electron microscopy (SEM).Tablet before and after dissolution was taken and scanned under (SEM, JEOL5400, Japan) data is shown in (Figure:7)

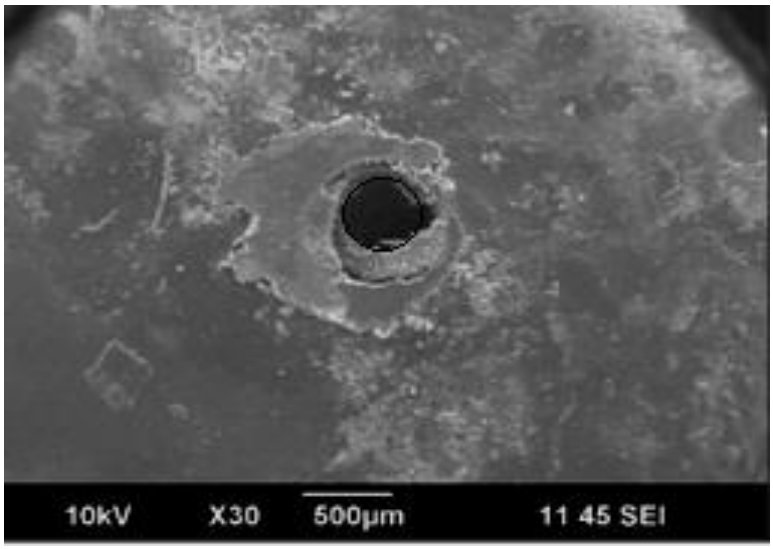

Figure 7: Scanning Electron Microscopy (SEM) of delivery orifice

From above interpretation of SEM data it was confirmed that the diameter of delivery orifice is 0.8mm

Dissolution Test [13, 14]

The test is designed to determine compliance with the dissolution requirement for solid dosage forms administered orally. As the tablet was enteric coated hence the dissolution was

performed in both acid stage as well as in buffer stage. Dissolution test was performed in dissolution Test (apparatus I-IP) (Electrolab TDT 08L)

Apparatus: IP TYPE 1(Paddle)

RPM: 50

Temperature: 37^0c.

Acid stage: Tablet was placed in jar containing 900ml of 0.1M hydrochloric acid for two hours and 10 ml of aliquots were removed at different time interval (1,2 hr.) and filtered through whatmann filter paper no.52,from which was further diluted to 10ml and analyzed by UV-Visible spectroscopy (Jasco V 630) at 256 nm using 0.1M hydrochloric acid as blank. After 2 hours of the test in acid medium, the tablet was immediately subjected to buffer stage.

Buffer stage: Then the tablets were subjected to phosphate buffer pH 6.8 and dissolution was carried for 24 hrs in the time interval of (3, 4, 5, 6, 7, 8, 12, 16, 20, 24 hr.) 10ml sample was withdrawn and filtered through whatmann filter paper no. 52, and filtrate was further diluted to 10ml and resulting solution was analyzed by UV-Visible spectroscopy (Jasco V 630) at 256 nm using Phosphate buffer pH 6.8 as blank. % Cumulative drug release was calculated.

Time (Hrs.)	Cumulative Drug Release (%)(Mean± S.D)								
	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
30 min	3.568± 0.18	6.76± 0.31	13.29± 0.32	3.56± 0.15	6.2± 0.11	6.38± 0.19	3.00± 0.17	2.379± 0.24	15.54± 0.31
1	21.60± 0.37	8.777± 0.77	23.61± 0.27	20.88± 0.40	13.15± 0.55	10.21± 0.18	5.41± 0.35	5.73± 0.06	25.14± 0.26
2	24.88± 0.75	21.33± 0.34	29.61± 0.76	25.90± 0.35	26.60± 0.37	24.8± 0.43	9.85± 0.74	12.37± 0.82	32.75± 0.57
3	27.13± 0.03	26.33± 0.57	40.63± 0.65	27.51± 0.74	33.44± 0.36	24.9± 0.37	22.48± 0.65	19.3± 0.55	44.30± 0.33
4	28.61± 0.46	32.67± 0.36	44.73± 0.26	29.65± 0.52	37.56± 0.16	30.08± 0.62	24.73± 0.31	23.6± 0.07	51.11± 0.26
6	38.37± 0.57	38.15± 0.40	50.98± 0.47	37.67± 0.39	44.76± 0.65	36.36± 0.74	34.65± 0.66	25.3± 0.39	57.61± 0.44
8	49.21± 0.37	44.50± 0.48	54.73± 0.60	49.40± 0.61	47.65± 0.33	40.74± 0.62	43.52± 0.55	46.8± 0.24	65.03± 0.82
12	55.91± 0.35	57.60± 0.38	64.57± 0.16	56.33± 0.45	56.49± 0.32	51.87± 0.07	50.53± 0.43	57.1± 0.22	73.20± 0.35
16	63.49± 0.82	64.20± 0.30	66.59± 0.42	63.82± 0.37	64.07± 0.46	58.06± 0.46	57.30± 0.42	64.5± 0.37	80.93± 0.41
20	65.32± 0.40	73.25± 0.62	77.34± 0.91	66.78± 0.21	70.92± 0.47	75.21± 0.56	62.03± 0.35	72± 0.75	85.72± 0.44
24	72.56± 0.31	82.47± 0.26	88.19± 0.21	75.75± 0.36	81.15± 0.40	86.53± 0.18	69.28± 0.11	78.2± 0.29	91.97± 0.15

Table 6: Cumulative Drug Release of Formulations (F1-F9)

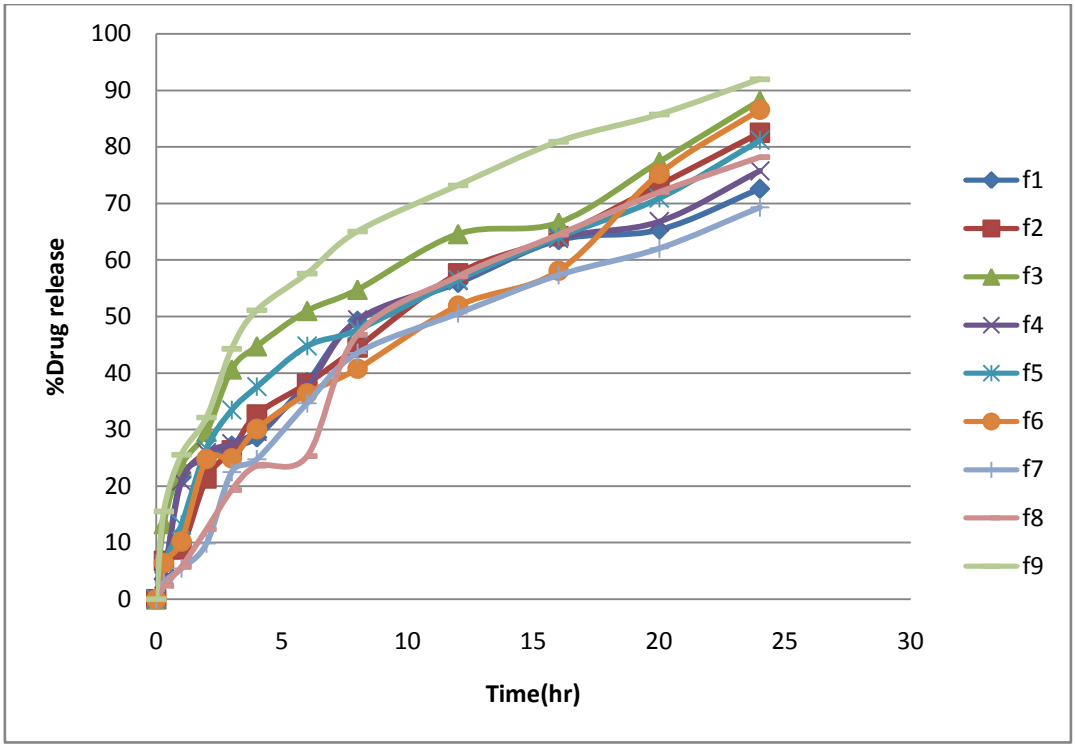

Figure 8: Dissolution Profile of Formulation Batches (F1-F9)

The result shows that with increase in concentration of Sodium chloride(NaCl) and Microcrystalline cellulose (MCC) the release rates were found to decrease gradually. The results showed that the osmotic tablet had the ability to extend the release of Candesartan Cilexetil for the duration of about 24 hr.

On the basis of Hardness, Friability, Weight variation, Thickness, percent drug content and In- vitro drug release profile the optimum formulation of Sodium chloride 50mg and Microcrystalline cellulose 75mg was selected. The **F9** batch was selected as optimized and subjected for stability study.

Dissolution of optimized (F9) batch

Effect of orifice size on the drug release from optimized formulations:

To study the effect of orifice size on the drug release from the optimized formulations, the in vitro analysis of the selected tablets formulations was carried out. Coated tablets were selected from the optimized batch F9 and orifices with varying sizes (0.6 mm, 0.8mm,) were drilled using a mechanical micro drill. The data for the cumulative % drug release with varying orifice size for the selected formulation F9 is as shown in the (Table7)

Time (Hrs.)	Cumulative Drug Release (%) F9 Batch (Mean ± S.D) through 0.8 mm delivery orifice	Cumulative Drug Release (%) F9 Batch (Mean± S.D) through 0.6 mm delivery orifice
0	0.00	0.00
30min	15.54±0.31	6.2±0.11
1	25.14±0.26	14.15±0.55
2	32.75±0.57	23.50±0.37
3	44.30±0.33	27.04±0.36
4	51.11±0.26	35.56±0.16
6	57.61±0.44	40.76±0.65
8	65.03±0.82	44.65±0.33
12	73.20±0.35	49.19±0.32
16	80.93±0.41	54.07±0.46
20	85.72±0.44	67.02±0.47
24	91.97±0.15	78.15±0.40

Table 7: Cumulative drug release through 0.8mm & 0.6 mm delivery orifice

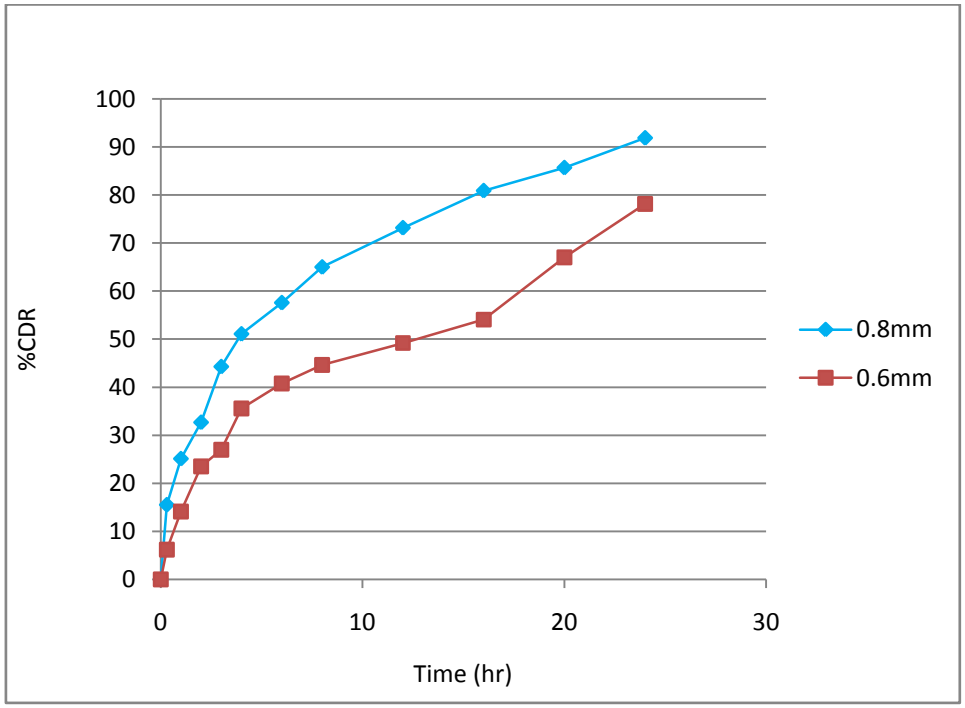

Figure 9:% cumulative release of optimized batch through 0.6mm & 0.8mm delivery orifice

Effect of variables on release profiles of optimized formulation:

The optimized formulations (F9) were subjected to various comparative tests to study the effect of variables on release profiles of the optimized formulations. The effect of concentration of release retardant material, Effect of osmogent, diameter and size of delivery orifice on drug release.

Effect of orifice size on the drug release from optimized formulations:

To study the effect of orifice size on the drug release from the optimized formulations, the in vitro analysis of the selected tablets formulations was carried out. Coated tablets were

selected from the optimized batch F9 and orifices with varying sizes (0.6 mm, 0.8mm,) were drilled using a mechanical micro drill. The data for the cumulative % drug release with varying orifice size for the selected formulation F9 is as shown in the (Table 7) As can be seen from the results of the above study of varying orifice sizes, it was observed that there was significant change in the drug release pattern with orifice size in the range of 0.6 mm to 0.8 mm. However, as can be seen from the above observations, it was found that a comparative higher release pattern and rapid release of drug was seen in tablets drilled with an orifice of 0.8mm and 0.6mm. It was found that almost 87.32% from 0.8mm and 78.22% from 0.6mm drug was released around the 24th hour

This may be due to the result of higher diffusion of fluids from the bigger orifice. Hence it was concluded that the release rates were dependent of the orifice size in the range of 0.6mm to 0.8mm. However, a higher orifice size (0.8mm) or a lower orifice size (0.6mm) had a significant influence on the release rate of drug from the osmotic drug delivery system.

The effect of Concentration of release retardant material on drug release from optimized formulations

In order to study the effect of concentration of release retardant material on the drug release .it was found that increase in concentration level of release retardant material in the formulation drug release rate was decreased .F9 formulation contains low level of the release retarding material drug release was found to be significant.

The effect of Concentration of osmogent on drug release from optimized formulations

Candesartan Cilexetil is moderately water soluble drug exerting low osmotic pressure, thus to increase its release, core needed to to have sufficient osmotic pressure to deliver the drug from the delivery orifice .Stronger osmotic agents would be expected to produce greater osmotic pressure in core .Sodium chloride best as an osmotic agent for moderately or poorly soluble drugs for the formulation of osmotic tablet. On increasing the concentration of sodium chloride shows increase in the drug release.

Dissolution Kinetics [15]

In present study dissolution were analyzed by PCP Disso Version 3software to study the dissolution kinetics is given in (Table 8)

	Coefficient of determination (R^2)				
Formulation code	**Zero order**	**First order**	**Higuchi square root**	**Korsmeyer plot**	**Korsmeyer plot 'n' (release exponent)**
F1	0.9415	0.9739	0.9878	0.8893	0.5698
F2	0.9406	0.9651	0.9710	0.8476	0.4023
F3	0.9453	0.7745	0.9753	0.7743	0.3727
F4	0.9483	0.9543	0.9763	0.7789	0.3833
F5	0.9453	0.9449	0.9667	0.7948	0.3741
F6	0.9501	0.9711	0.9762	0.8367	0.4097
F7	0.9872	0.9494	0.9941	0.7666	0.4655
F8	0.9496	0.9552	0.9735	0.7858	0.3822
F9	**0.9933**	0.9702	0.9795	0.6054	0.3634

Table 8: Kinetic treatment of prepared Candesartan Cilexetil osmotic tablet formulations

Different kinetic treatments (zero order, first order, Higuchi's square root equation and Korsmeyer treatment) were applied to interpret the release of Candesartan Cilexetil from different matrices The best formulation i.e. optimized formulation **F9** follow Zero order kinetics **r^2=0.9933**. So the drug release is of fickian release.

Optimization [16]

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.33) 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 Candesartan Cilexetil. Variable caused significant change in the responses. From this data optimum concentration of Nacl 50mg and MCC 75mg was found.

Design Summary for osmotic tablet

A) Drug release

Source	Sum of Squares	Degree of Freedom	Mean Square	F value	P-value	Inference
Model	407.18	2	203.59	27.40	0.0010	Significant
A-NaCl	404.59	1	404.59	54.45	0.003	
B-MCC	2.59	1	2.59	0.35	0.5767	

Table 9: ANOVA for % drug release (Y1)

Standard deviation = 2.73

R-Squared =0.9013

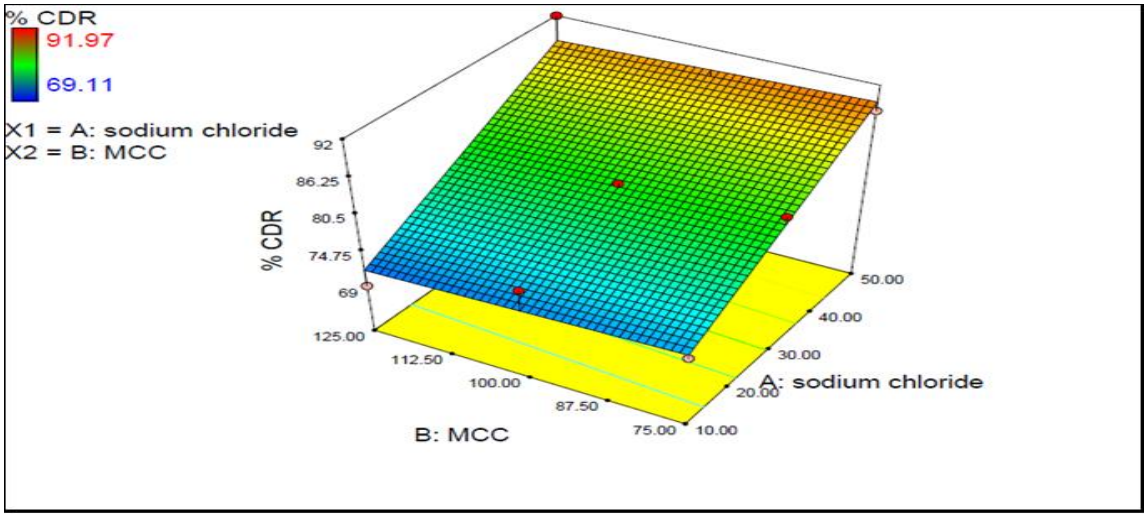

Figure 10: Surface Response plot showing effect of Sodium chloride and microcrystalline cellulose on release

B) Contour plot:

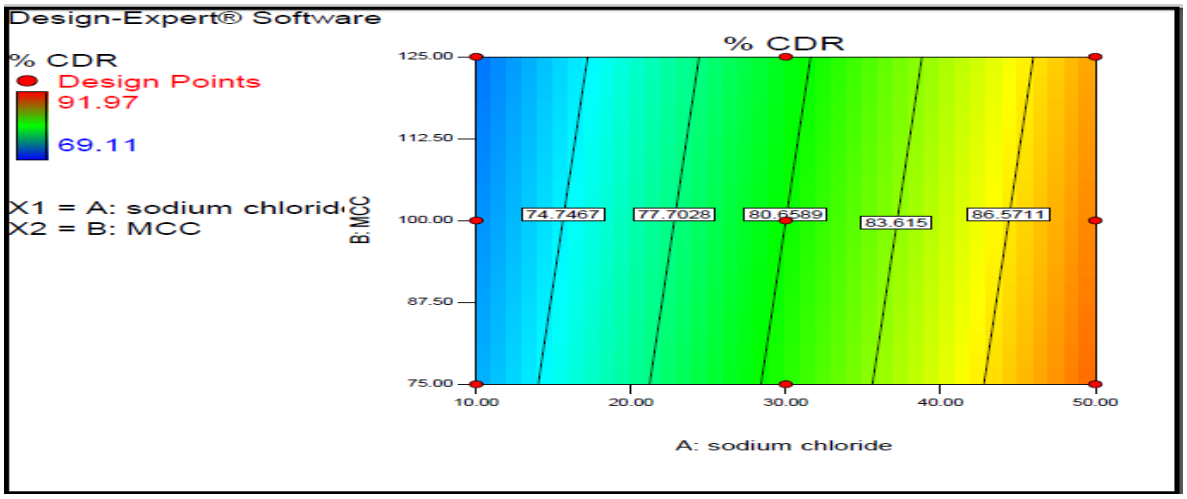

Figure 11: Contour plot showing effect of Sodium chloride and Microcrystalline cellulose on drug release.

C) Design summary:

Design summary and Response summary is shown in (Table 10)

Factor	Name	Units	Type	Minimum	Maximum	-1 Actual	+1 Actual	Mean	**Std. Dev.**
A	NaCl	%	Numeric	10	50	10	50	30	16.33
B	MCC	%	Numeric	75	125	75	125	100	20.41

Table10: Design Summary

C) **Perturbation plot:**

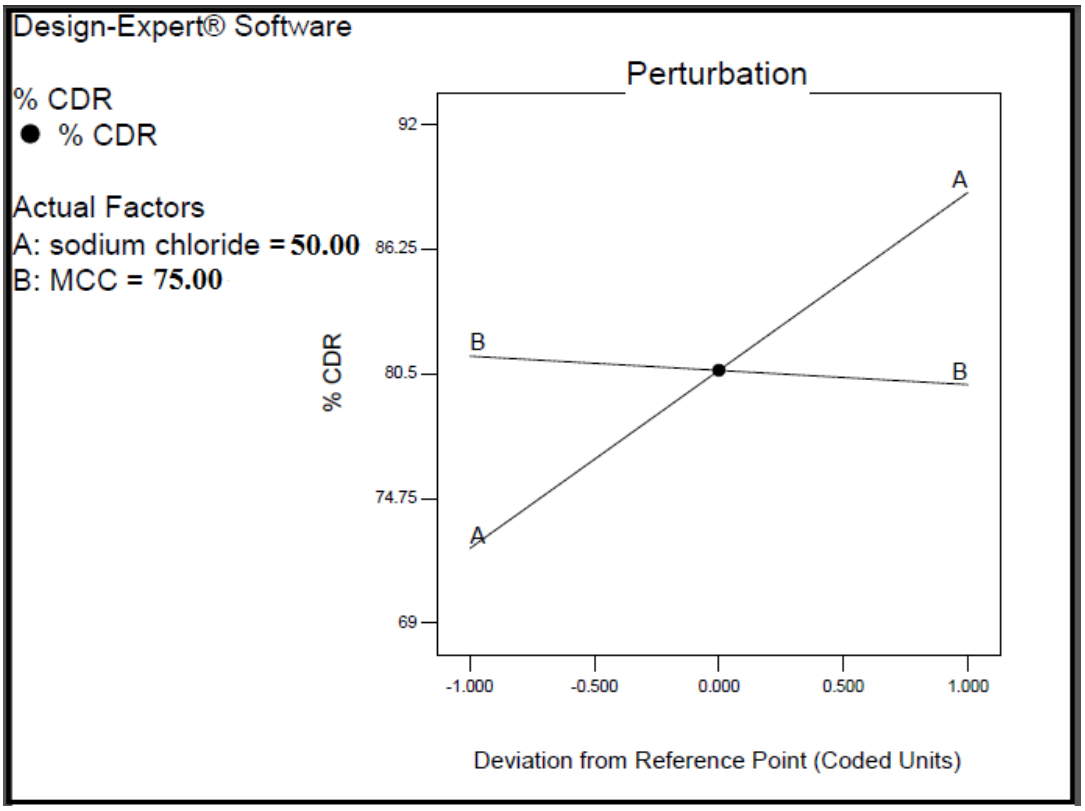

Figure 12: Perturbation plot

From design expert version 8.0.4 solutions were found in which optimum batch Sodium chloride (NaCl) 50 mg and microcrystalline cellulose (MCC) 75 mg with was found to be optimum. From this data F9 batch was selected as optimum formulation

Accelerated Stability Studies [17, 18]

During stability studies the product is exposed to normal conditions of temperature and humidity. However the studies will take a longer period of time and hence it would be convenient to carry out accelerated stability studies, where the product is stored under extreme condition of temperature and humidity. In the present work, stability studies were carried out on optimized formulation (F9) under the following conditions for period of 3

months as prescribed by ICH guidelines for accelerated study at $40^0 \pm 2^0$ and relative humidity of 75% ± 5%. The tablets were withdrawn after completion of 3 months and analyzed for visual appearance, hardness, weight variation, friability, drug content and in-vitro drug release studies.

Parameter	Initial sample of optimized formulation	After storage at 25±2°C / 60% RH, for 6 month
	F9	F9
Drug content	97.88%	97.10 %
% Drug Released (After 24 hrs.)	91.97%	90.74 %

Table 11: Characteristics of optimized formulation F9after 3 months storage

Time (Hrs.)	Cumulative Drug Release (%) F9 Batch (Mean± S.D)	Cumulative Drug Release (%) F9 Batch (Mean± S.D)
	Before 3 month	After 3 month
0	0	0
30 min	15.54±0.31	14.34±0.37
1	25.14±0.26	22.15±0.25
2	32.75±0.57	30.02±0.28
3	44.30±0.33	41.20±0.15
4	51.11±0.26	49.12±0.74
5	57.61±0.44	55.41±0.14
6	65.03±0.82	63.12±0.46
8	73.20±0.35	71.52±0.26
12	80.93±0.41	78.51±0.19
16	85.72±0.44	82.65±0.29
24	91.97±0.15	87.95±0.22

Table 12: In vitro drug release study of formulation F9 stored at 25ºC / 60% RH for 3 months

CONCLUSION

The results of experimental studies of Candesartan Cilexetil osmotic tablets proved that the granules of Candesartan Cilexetil 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 3 months. Thus the results of the above study clearly indicated that Developed osmotically controlled release tablet of Candesartan Cilexetil provide release of drug at a predetermined rate and for a predetermined time in controlled manner.

REFERENCES

1. Remington: The Science and Practice of Pharmacy, 21st edition, volume- I, Lippincott Williams and Wilkins, 939, 940.
2. Robinson Joseph R., Lee Vincent H. L.: Controlled drug delivery, fundamentals and application, 2nd edition, volume- 20, revised and expanded, Marcel Dekker Inc., 7, 8.
3. Tripathi K.D, Essentials of Medical Pharmacology, 5th Ed., Jaypee Brothers., New Delhi, 2003:390-404.
4. Rang.H.P,Dale.M,.Ritter.J.M,Moore.P.K,Pharmacology,5thEd.,Elsevier,publication,2006:525-535.
5. Aulton M.E.Aulton's Pharmaceutics:The design and manufacture of Medicines ,3rd ed.Churchill Livingstone:336-360.
6. Marcel K. Compression and consolidation of powdered solids .in:Liberman HA, Lachman L,Kaing JL ed.The theory and Practice of Industrial Pharmacy .3rd ed.New York ,Marcel Dekker ,Inc: 1981.
7. Khan Z.A,Tripathi R.,Mishra B.,Design and evaluation of enteric coated microporous osmotic pump tablet of quetiapine fumarate,Acta Poloniae Pharmaceutica –Drug research ,2010,69(6):1128.
8. Mulani T.H,Parmar I.,Shah J.N,Formulation and evaluation of sustained release drug delivery system of Quetiapine fumarate,International journal of Pharmaceutical innovations,2011,1(2):62.
9. Pattanayak Durga Prasad , Laxmi UnaKumar Alok, Design and evaluation of an extended release tablet doesage form of class 2 drug of quetiapine fumarate International research journal of pharmacy,2011 2(3):121-124
10. Leon Lachman and Herbert Libermann, The theory and practice of industrial pharmacy, CBS Publisher, Indian edition 2009: 372 .
11. Grahm Cole,John Hogan and Micheal Aulton ,Pharmaceutical Coating Technologgy ,Informa Healthcare special edition:152.
12. Thombre .A, Zentner. G, Himmelstein J, mechanism of water transport in controlled porosity osmotic devices, Journal of Membrane Science, 1989,40: 279-310.
13. Grahm Cole,John Hogan and Micheal Aulton ,Pharmaceutical Coating Technologgy ,Informa Healthcare special edition:152.
14. The Indian pharmacopoeia 2010, Government of India, Ministry of Health and Family Welfare.The controller of publications,New Delhi, vol 2: 2013-2014.
15. Costa p, Lobo J.Modeling and comparison of dissolution profile .European journal of pharmaceutical science .2001,13:123-133.
16. Gilbert S.Banker ,Modern Pharmaceutics ,drugs and pharmaceutical sciences 4th edition Marcel Dekker,Inc.New York :607.
17. Fung H..L, Drug Stability: Principles & Practice, Drug and Pharmaceutical Sciences, Marcel Dekker, New York, Vol. 43:235
18. George M.G, Robinson, J.R., In., Modern Pharmaceutics, (Banker, G.S., Rhodes H. Eds.), 2nd Ed., , Marcel Dekker Inc., New York, 1990: 770.