FORMULATION AND EVALUATION OF SOLID SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM

Ph.D. Synopsis

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By

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1. ABSTRACT

Candesartan cilexetil is an orally administered ACE inhibitor for the treatment of hypertension and cardiac failure, but its solubility, stability and oral bioavailability are poor. The objective of our investigation was to formulate a self microemulsifying drug delivery system (SMEDDS) of candesartan cilexetil using minimum surfactant concentration that could improve its solubility, stability and oral bioavailability. The composition of optimized formulation [C7IIB] consist of Capryol 90 as oil, Labrasol as surfactant and Captex 500 as cosurfactant , containing 32 mg of candesartan cilexetil showing drug release for liquid SMEDDS formulation (99.91%), droplet size (9.15 nm), Zeta potential (-23.2), viscosity (0. 8824 cP) and infinite dilution capability. *In-vitro* drug release of the C7IIB was highly significant ($p < 0.05$) as compared to marketed conventional tablet (M). The C7IIB was further used for the preparation of various Solid SMEDDS(S-SMEDDS) formulations (Tablet). These tablets were prepared via adsorption to solid carrier technique, using optimized liquid SMEDDS formulation [C7IIB] whereas Aeropearl 300 pharma as optimized adsorbents .The resulting S-SMEDDS tablet exhibited particle size (78.3 nm) whereas the liquid SMEDDS showed (9.15 nm). The *in vitro* release was almost similar for the S-SMEDDS as well liquid i.e. 78.32% and 84.6% respectively within 5 min. Also, one of the main objectives to enhance the oral bioavailability of drug (15%) which was enhanced to 1.78 folds. In conclusion, our studies illustrated that adsorption to solid carrier technique could be a useful method to prepare the solid SMEDDS tablets from liquid SMEDDS, which can improve oral absorption of candesartan cilexetil, nearly equivalent to the liquid SMEDDS, but better in the formulation stability, drugs leakage and precipitation, etc.

2. BRIEF DESCRIPTION ON THE STATE OF THE ART OF THE RESEARCH TOPIC

In recent years, increasing attention has been focused on solid self-microemulsifying formulations (S-SMEDDS) which were prepared by incorporating a liquid self-microemulsifying formulation (SMEDDS) into a solid dosage form, combining the advantages of SMEDDS with those of a solid dosage form and overcoming the shortcomings of liquid formulations. However, traditional preparations of SMEDDS are usually prepared in the liquid state. So the liquid SMEDDS are generally enclosed by soft or hard capsules to facilitate oral administration but it produce some disadvantages, such as high production

costs, low drug incompatibility and stability, drugs leakage and precipitation, capsule ageing. Then incorporation of liquid SMEDDS into a solid dosage form is compelling and desirable, and some S-SMEDDS dosage forms have been initially explored, such as SE tablet and pellets.

In the recent study an attempt was made to enhance the solubility, *in-vitro* dissolution and bioavailablity of candesartan cilexetil by formulating it as SMEDDS and thereby converting it as S-SMEDDS tablet dosage form. Candesartan cilexetil is an esterified prodrug of candesartan, a nonpeptide angiotensin II type 1(AT_1) receptor antagonist used in the treatment of hypertension. Based on its solubility across physiological relevant pH conditions and absorption characteristic, candesartan cilexetil is classified in the Biopharmaceutical classification system as a class II dug. Low solubility of candesartan cilexetil across the physiological pH range is reported to result in incomplete absorption from the GI tract and hence is reported to have an oral bioavailability of about 15%.candesartan cilexetil is a highly lipophilic compound and has good solubility in tri and diglyceride oils. These factors, may contribute toward absorption via the lymphatic route. The formulation was characterized for its ability to form microemulsion by various parameters.

3. DEFINITION OF THE PROBLEM

- By developing the SMEDDS formulation for candesartan cilexetil which is poorly water soluble drug, its solubility, *in-vitro* dissolution and bioavailablity can be enhanced.
- The stability can be achieved more by developing a solid dosage by converting the liquid SMEDDS to solid dosage form (Tablet) i.e. S-SMEDDS formulation.

4. OBJECTIVE AND SCOPE OF WORK

The main objective of this work is to prepare S-SMEDDS for oral bioavailability enhancement of poorly water soluble drugs

- To formulate a stable liquid SMEDDS formulation using suitable excipients and study the factors affecting it.
- To enhance the solubility, dissolution rate and bioavailability of drugs using suitable vehicles and excipients.

- To perform the stability study of liquid and solid optimized SMEDDS formulation as well as marketed formulation as per ICH guidelines and to find out shelf life of the developed S-SMEDDS.
- To perform the bioavailability assessment of optimized S-SMEDDS formulation.

5. ORIGINAL CONTRIBUTION BY THE THESIS

The entire work in this synopsis, as well as thesis is the original work, with research papers as the back bone. The details of the associated papers are as follows:

List of Publications Accepted for Publication:

1. Jill B. Shukla and Dr. Girish K Jani. Formulation and evaluation of oral self microemulsifying drug delivery system of candesartan cilexetil. International Journal of Pharmacy and Pharmaceutical Sciences. ISSN- 0975 – 1491. [10794]
2. Jill B. Shukla and Dr. Girish K Jani. Formulation and evaluation of Solid self microemulsifying drug delivery system of candesartan cilexetil. International Journal of Pharma and Bio Sciences. ISSN 0975-6299[M.S.No: 7683]

6. METHODOLOGY OF RESEARCH, RESULTS / COMPARISONS

6.1 Methodology of research

6.1.1 Screening of components

The most important criterion for the screening of components for SMEDDS is the solubility of poorly soluble drug in oils, surfactants and co-surfactants. In this study excess amount of drug was added to 2mL of each vehicle separately in screw capped glass vial and mixture was heated to 60˚C in water bath under continuous stirring using a vortex mixture to facilitate drug solubilization. The vials were then kept at 25±1.0˚C in an isothermal shaker for 72 h to reach equilibrium. The equilibrated samples were removed from shaker and centrifuged at 2000 rpm for 10 min. The supernatant was taken, filtered and diluted with methanol. The concentration of candesartan cilexetil was determined for various vehicles using HPLC technique.

6.1.2 Preparation of Candesartan cilexetil SMEDDS

A series of SMEDDS formulations were prepared using various oils, Surfactants and Co-surfactants as shown in Table 1. In all the formulations, the level of Candesartan cilexetil was kept constant (i.e. 32 mg). Candesartan cilexetil was added in the oil phase and solubilized. Then the mixture of surfactant and co-surfactant (Smix) was added in oil phase, mixed by gentle stirring, vortex mixing and heating at 37±0.5˚CTotal 96 liquid formulations were prepared using various surfactants and cosurfactant concentrations.

Table 1: Various Formulations of Candesartan cilexetil SMEDDS

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8
Candesartan cilexetil	√	√	√	√	√	√	√	√
Capryol 90	√	√	√	√	√	√	√	√
Labrasol				√	√		√	√
Peceol	√							
Plurol Oleique	√							
Transcutol P		√	√					
Tween 80						√		
Lauroglycol		√	√					
Capmul MCM (C8)				√				
Capmul MCM (EP)					√			
Acconon cc-6						√		√
Captex 500							√	

Code	Amount of oil (%)	Code	Ratio of S/CoS
I	5	A	1:1
II	10	B	2:1
III	15	C	1:2
		D	3:1

6.1.3 Pseudoternary phase diagram

The existence of microemulsions regions were determined by using pseudo-ternary phase diagrams. SMEDDS were diluted under agitation conditions using water titration method. The mixture of oil and Smix at certain weight ratios were diluted with water in a dropwise manner. Phase diagrams were constructed in presence of drug to obtain the optimum concentrations of oil, surfactant and co-surfactant. SMEDDS form fine oil-water emulsion upon addition to an aqueous media under gentle agitation. Distill water was used as an aqueous phase for the construction of phase diagrams. The concentration of water at which turbidity-to-transparency and transparency-to-turbidity transitions occurred was derived from the weight measurements. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils, as well as the Smix ratio.

6.1.4 Thermodynamic stability and Dispersibility test

The Heating cooling cycle, Centrifugation and Freeze thaw cycle were performed for liquid SMEDDS formulation. The dispersibility test was performed to find the efficiency of self-emulsification of formulation. The results are visually assessed to find its clarity.

6.2 CHARACTERIZATION OF SMEDDS OF CANDESARTAN CILEXETIL

The various properties that were characterized for liquid SMEDDS were;

- Viscosity and pH
- Globule size and ζ-potential analysis
- % Transmittance
- Polydispersibility Index
- *In-vitro* diffusion study

7. PREPARATION OF SOLID SELF MICROEMULSIFYING DELIVERY SYSTEM (S-SMEDDS) OF CANDESARTAN CILEXETIL

7.1. Adsorption to solid carrier: Adsorbent Selection for Optimized Liquid SMEDDS Formulation (C7IIB)

The optimized liquid SMEDDS formulation (C7IIB) was converted into free flowing powder by adsorption of liquid onto solid carriers that provided a high surface area with good disintegration characteristic The soild carriers used includes Aerosil 200 pharma (A1), Aeropearl 300 Pharma (A2) and Fujicalin SG (F1). The conversion process involved addition of liquid formulation on solid carriers under continuous mixing. 0.2 ml optimized liquid SMEDDS i.e. C7IIB (containing drug 32 mg) was used to convert into solid SMEDDS. The combination of adsorbent and Liquid SMEDDS which showed the best result was used for developing final tablet formulation. Various evaluation parameters were also performed on the optimized adsorbent as; Bulk density, Tapped density, Carr's index, Hausner's ratio and *In-vitro* dissolution.

7.1.1 Morphological analysis of solid SMEDDS

The outer macroscopic structure of solid SMEDDS was characterized by Scanning electron microscope (JSM-5610, JEOL, Japan). Some amount of optimized formulations was mounted on the stub. This specimen was then sputter coated with gold particles and observed with a SEM (JSM-5610, JEOL, Japan) at an accelerating voltage of 10 kV. Surfaces of powder were photographed.

7.2 Formulation Development Of Solid Self Micro Emulsifying Drug Delivery System (S-SMEDDS)

The 3^2 Full factorial design was applied for the tablet SMEDDS formulation of candesartan cilexetil. The composition is as shown below in Table 2. The Prepared tablets were evaluated for various tests like, Weight variation, Thickness, Hardness, Friability and *In-vitro* dissolution study.

Table 2: 3^2 Full factorial design for S-SMEDDS

Ingredients(mg)	T1	T2	T3	T4	T5	T6	T7	T8	T9
S-SMEDDS	120	120	120	120	120	120	120	120	120
Lactose monohydrate	74			69			64		
Mannitol		74			69			64	
Microcrystalline cellulose-102			74			69			64
Pre-gelatinized starch	5	5	5	10	10	10	15	15	15
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total(mg)	200	200	200	200	200	200	200	200	200

7.2.1 Tablet Evaluation

Prepared tablets were evaluated by following tests;

- Weight variation
- Thickness
- Hardness
- Friability
- *In -Vitro* Dissolution Testing
- Assay of Candesartan cilexetil Tablet

- **Comparison of *In-vitro* dissolution of prepared tablet with marketed formulation**

Here *in-vitro* dissolution of prepared tablet is compared with the marketed tablet formulation (Atacand Tablet).

- **Stability Study:**

The stability study was carried out for selected formulation as per ICH guidelines. An accelerated stability study was performed at 40^0C ± 2^0C and 75% ± 5% RH and real time stability study was performed at 25 ±0.5˚C / 60 ± 5 % RH for a period of three months.

7.3 *In Vivo* Studies

7.3.1 Measurement of systolic blood pressure

The studies were performed for optimized batch of solid SMEDDS formulation i.e. T4. A pharmacodynamic method was applied to determine enhancement in bioavailability to S-SMEDDS (T4) of drug as compared to plain drug suspension. DOCA [deoxycorticosterone acetate] salt model was applied to induce hypertension in rats. After induction of hypertension, treatment was started with plain drug suspension and S-SMEDDS and blood pressure was measured by tail-cuff method using LE 5002 Storage Pressure Meter [Letica Scientific Instruments]. The animal experiments are conducted in full compliance with Institutional Animal Ethical Committee [IAEC] regulations, as per CPCSEA guidelines. The registration number of our institute is 282/14/a/CPCSEA.

- **Measurement of systolic blood pressure**

Systolic blood pressure was measured once a week before drug administration for first two weeks [using tail-cuff method]. During treatment, systolic blood pressure was measured daily for all subgroups of DOCA salt rats except DC0, 2–3 hours after administration. In UNX rats and DC0 rats, blood pressure was measured once a week throughout the experiment.

7.3.2 Bioavailability Assessment Of S-SMEDDS Of Candesartan Cilexetil Tablet

Bioavailability of candesartan cilexetil S-SMEDDS formulation (T4) was compared with suspension of marketed (M) Atacand tablet 32 mg (AstraZeneca). T4 suspension was prepared as mentioned above and diluted to a definite volume using the same vehicle afterwards. Six rats (200–250 g) were allocated at random to two treatment groups and administered T4 and M suspension in a crossover design. The washout period between the two treatments was 7 days. Female rats (weighing approximately (200–250 g) were fasted for 12 h prior to the experiment and water was available *ad lib*. After oral administration of drug dose (5.6 mg/1.5 kg body weight), about 2 mL of blood sample was collected through retro-orbital plexus into heparinized tubes at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 h. Blood samples were centrifuged at

5,000 rpm for 10 min using a high-speed centrifuging machine, and plasma samples were withdrawn and stored at −18°C.

8. RESULT AND DISCUSSION

8.1 Screening of components

The solubility of candesartan cilexetil was found to be highest in Capryol 90 (80.12±4.04mg/mL) as compared to other oils while in water it was 0.09±0.01mg/mL. Thus, Capryol 90 was selected as the oil phase for the development of the formulation.

Table 3: Solubility study of Candesartan cilexetil in various vehicles (oils, surfactants, Co surfactants and distill water) at 25˚C

Solvent	Solubility
Transcutol P	253.1±0.27
Plurol oleique	169.21±2.19
Labrasol	159.7±3.53
Capryol 90	80.12±4.04
Labrafil 1944 CS	49.76±1.13
Captex 200	5.67±0.68
Captex 200 P	7.29±0.94
Captex 355	10.31±1.02
Capmul MCM	35.02±1.32
Tween 80	261.09±2.85
PEG 400	108.13±3.22
IPM	22.54±0.29
Lauroglycol FCC	177.05±1.54
Capmul MCM (C8)	198.70±2.13
Acconon CC-6	181±1.76
Captex 500	191.35±2.78
Capmul MCM EP	173.64±1.19
Distill water	0.09±0.01

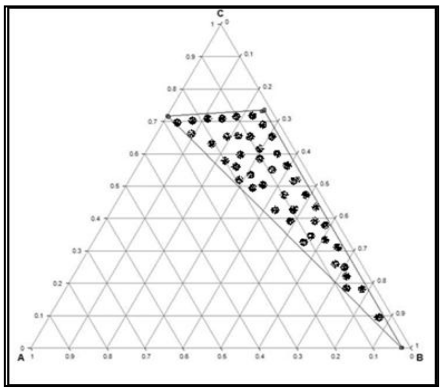
***Mean±SD, n=3**

8.2 Drug and surfactant compatibility study

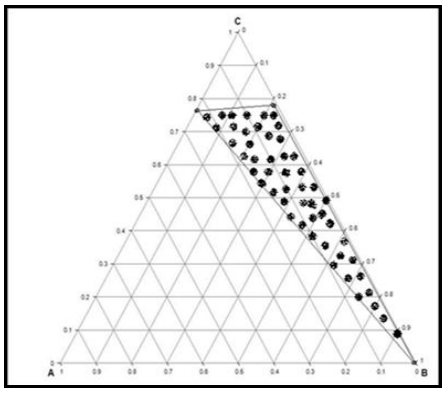
All the formulations passed the physical as well as chemical compatibility tests. The formulations did not show any changes during the compatibility studies and were found to be stable. Further studies were carried out using these formulations.

8.3 Pseudoternary phase diagram

Self-microemulsifying systems form fine oil-water emulsions with only gentle agitation, upon their introduction into aqueous media. As seen from the ternary plot C7IIB gave a wider microemulsion region at all S/CoS ratios. The microemulsion area increased as the S/Cos ratios increased. However, it was observed that increasing the surfactant ratio resulted in a loss of flowability. Thus, an S/CoS ratio 10% 2:1 was selected for the formulation study.



C7IIB



C7IIIB

Fig 1: Phase diagrams for various liquid SMEDDS formulations

8.4 Dispersibility and Thermodynamic stability

In the present study, we used distilled water as a dispersion medium. Keeping the criteria of increasing oil concentration and minimum amount of surfactant used for its solubilization, one formulation for each percent of oil (5%, 10% and 15%) was selected irrespective of the Smix ratio used for that percent of oil. The results for the dispersibility test are as shown in Table 4.

The selected formulations were subjected to different thermodynamic stability by using heating cooling cycle, centrifugation and freeze thaw cycle stress tests. Those formulations, which survived thermodynamic stability tests, were taken for dispersibility test.

Table 4: Thermodynamic stability and dispersibility test of different formulations

Formulation code	A	B	C	D
C7I	+	+	+	+
C7II	+	+	+	+
C7III	+	+	+	+

Where; I-5%; II-10% and III- 15% oil concentration. Also, Whitish-XX; Slightly whitish-X and clear-+ is visual appearance.

8.5 Globule size and ζ-potential analysis

The globule size of the emulsion is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as drug absorption. Also, it has been reported that the smaller globule size of the emulsion droplets may lead to more rapid absorption and improve the bioavailability. The optimal batch was C7IIB with mean globule size 9.15 nm in water.

The optimal batch C7IIB has the least zeta potential i.e. -23.2 mV which highest zeta potential towards negative side. The zeta potential governs the stability of microemulsion, it is important to measure its value for stability of samples. A negative force means a negative potential between the droplets.

Table 5: Particle size and zeta potential of the optimized batch C7IIB of Candesartan cilexetil SMEDDS

Formulation code	Avg. Particle size (nm)		Zeta potential
	Water	HCL	
C7II B	9.15	24.5	-23.2

8.6 *In- vitro* diffusion study

The dissolution profile for formulations C2II B, C4II B, C7II B and C8II B is as shown in the figure 2. The formulation C7IIB showed highest release rate among all the liquid SMEDDS formulations i.e. 92.01% in 10 min which is highest among all batches. The results indicate that candesartan cilexetil SMEDDS can be diluted previously with aqueous phase before performing the *in-vitro* release test in dialysis bag. Thus, *in-vitro* study concludes that release of candesartan cilexetil was greatly enhanced by SMEDDS formulation. The batch C7IIB was thus taken for further studies and comparison.

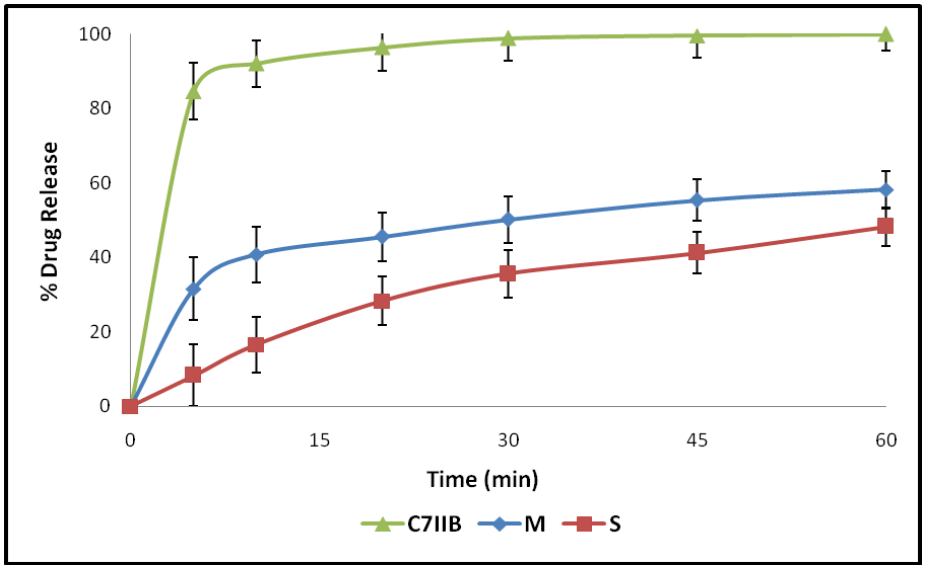


Fig. 2 :*In-vitro* diffusion study of C7IIB, M and S

TABLE 6: Various result of C7IIB

PARAMETERS	RESULTS
Particle size distribution (PSD)	9.15 nm
Zeta potential	-23.2 mV
Polydispersibility Index(PDI)	0.221
Viscosity	0.8824
pH	5.14
In-vitro drug release (10 min)	92.01%

8.7 Results Of Solid Self Micro Emulsifying System Of Candesartan Cilexetil

8.7.1 Adsorbent selection

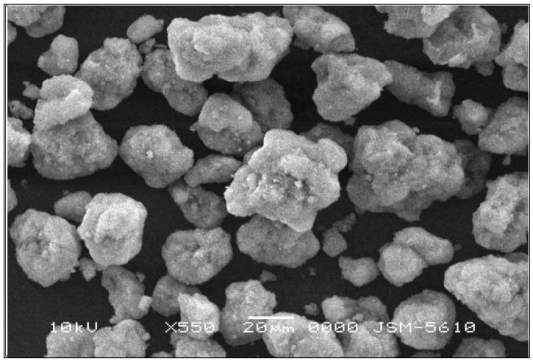
Three different adsorbent (Aerosil 200 pharma, Aeroperl 300 pharma and Fujicalin SG) were used to convert liquid SMEDDS into free flow powder. Among this adsorbents Aeroperl 300 pharma require only 60 mg to convert liquid SMEDDS (0.2 ml containing 32 mg drug) into free

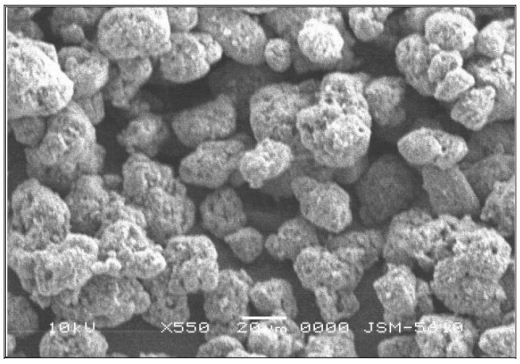
flow powder. Various powder characteristics were also performed for all adsorbents and it was observed that A2 showed best result.

Free flow powder of all three different adsorbent containing 32 mg of drug was filled into capsule and *in-vitro* dissolution was performed. Aeroperl 300 pharma based free flow powder gives 63 % drug release within 5 min and 90% drug release within 15 min which was faster drug release as compare to two other adsorbents based on free flow granules of liquid SMEDDS.

8.7.2 Morphological analysis of solid SMEDDS

SEM of Aeroperl 300 pharma and solid SMEDDS was shown in fig. 3. Surface of Aeroperl 300 pharma was rough before and after adsorption of liquid SMEDDS a smooth surface was observed which indicate that liquid smedds was adsorbed on the surface of Aeroperl 300 pharma.





(A) **(B)**

Fig.3: (A) SEM of aeroperl 300 pharma (B) SEM of aeroperl 300 pharma after adsorption

8.8 Evaluation Paramters Of S-SMEDDS Tablets Of Candesartan Cilexetil

The various evaluation parameters like Weight variation, Hardness, Thickness, Friability and Disintegration time were performed for all the batches T1 to T9 and all the results were found to be satisfactory and within the limits. Among all the Batch T4 showed the best result.

Table 7: Evaluation parameters for T4

Batch	Evaluation Parameters				
	Weight variation (mg)	**Hardness (kg/cm^2)**	**Thickness (mm)**	**Friability (%)**	**Disintegration time (sec)**
T4	201±1.3	2.0– 3.0	3.12 – 3.26	0.15	30

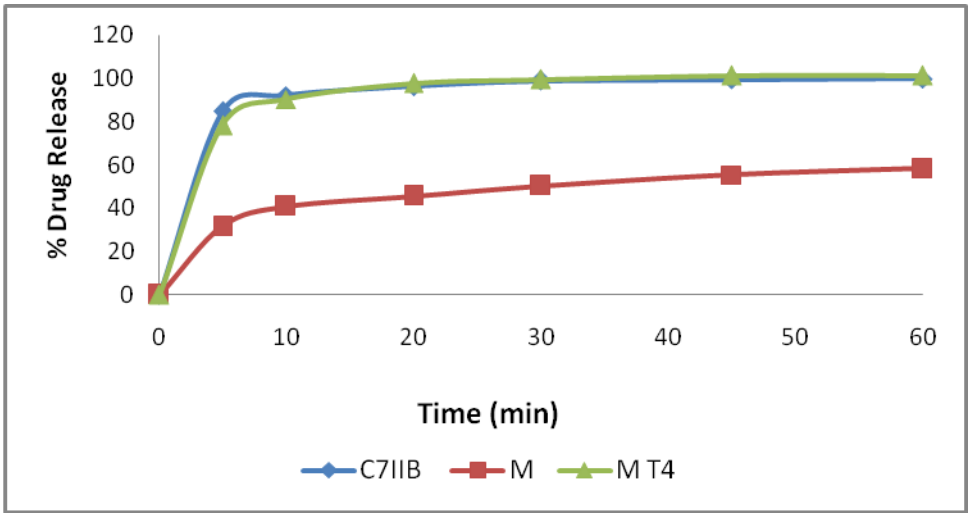


Fig .4 *In-vitro* dissolution comparison of M, T4 and C7IIB

- The result of Particle size and zeta potential of the optimized batch C7IIB and M are as shown below;

Table 8: Particle size and zeta potential of the optimized batch C7IIB of Candesartan cilexetil SMEDDS

Formulation code	Avg. Particle size in water (nm)	Zeta potential
C7II B	9.15	-23.2
T4	78.3	-17.4

8.9 3^2 Full factorial design

The effect of various diluents (Lactose monohydrate, Mannitol and MCC) and the concentration of pre gelatinized starch were kept as independent variables X1 and X2 respectively. The data clearly indicate that the DT, T70 and T90 values are strongly dependent on the selected independent variables. The fitted equations (full and reduced) relating the responses DT (sec), T70(min) and T90(min) to the transformed factors are shown in Table 9. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative)

Table 9: Various data for full factorial design

3^2 FULL FACTORIAL DESIGN					
Batch no.	**Variables levels in coded form**		**DT (sec)**	**T_{70} (min)**	**T_{90} (min)**
	X_1	**X_2**			
T1	**-1**	**-1**	**50**	**5**	**15**
T2	**-1**	**0**	**70**	**10**	**30**
T3	**-1**	**+1**	**78**	**10**	**15**
T4	**0**	**-1**	**30**	**5**	**10**
T5	**0**	**0**	**60**	**10**	**30**
T6	**0**	**+1**	**66**	**10**	**30**
T7	**+1**	**-1**	**42**	**5**	**10**
T8	**+1**	**0**	**56**	**10**	**15**
T9	**+1**	**+1**	**58**	**10**	**15**

TRANSLATION OF CODED LEVELS IN ACTUAL UNITS			
Variables level	Low (-1)	Medium (0)	High (+1)
Pre-gelatinized starch conc. (X_1)	5	10	15
Effect of Diluents (X2)	Lactose monohydrate	Mannitol	Microcrystalline cellulose 102

8.10 Stability Study

Accelerated stability study (40^0C ± 2^0C /75% ± 5% RH) and real time stability study (25^0C ± 2^0C /60% ± 5% RH) was performed on batch T4 for a period of three months. No significant changes were observed in appearance, average weight, hardness, thickness and friability of the tablets for both the condition. Assay was decreased to 84.76 % in the sample stored at accelerated condition after three months which indicate that formulation were not stable at higher

temperature. So other evaluation parameters like particle size, zeta potential and *in-vitro* dissolution was not performed on the sample store at accelerated condition. After three months storage of batch T4 at real time condition assay value was fond to be 98.83% which indicate formulation were stable at this condition. *In vitro* dissolution study was found to be satisfactory for batch T4 after three month storage at real time condition. Results were shown in table 9. Initial value for particle size of the batch T4 was 78.3 nm and after stability it was found to be 79.2 nm. Zeta potential value after stability was found to be -17.1 mv and the initial value was -17.4 mv so data indicate that formulation was stable.

8.11 In *Vivo* Studies

8.11.1 Measurement of systolic Blood Pressure

The %decrease in systolic blood pressure after one week of treatment in comparison to that of after 14 days are as observed in figure below;

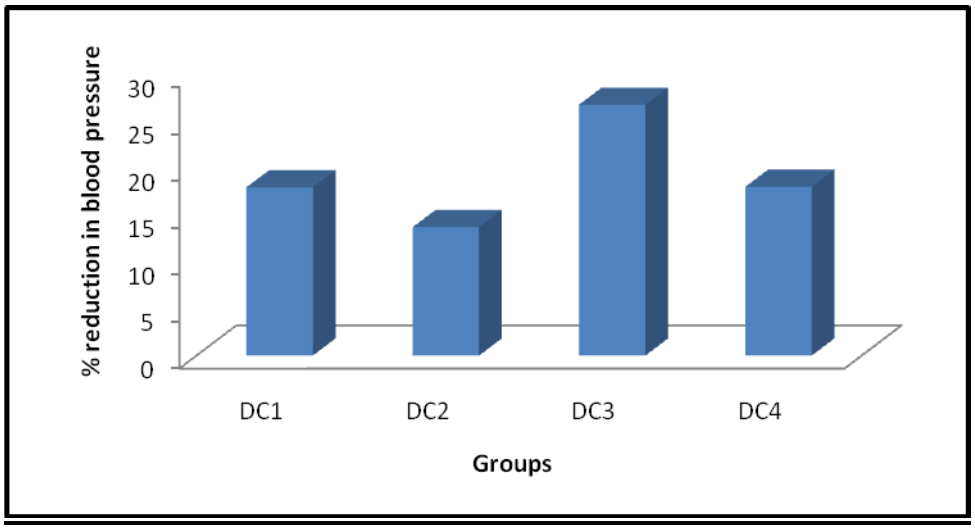


FIGURE. 5: % Decrease in systolic blood pressure after treatment in different groups.

8.11.2 Bioavailability Study

The non compartment model was used to evaluate pharmacokinetic paremeters of candesratan cilexetil absorption which is summarized in Table 10. The bioavailability was enhanced by 1.78 folds.

TABLE 10: Pharmacokinetic Parameters for T4 and M

Parameters	T4	M
t_{max} (h)	1 ± 0.37	1.36 ± 0.42
C_{max} (ng/mL)	115.51 ± 9.11	69.54 ± 3.87
$AUC_{0\rightarrow t}$ (ng h/mL)	606.93 ± 45.25	446.36 ± 72.32
$AUC_{0\rightarrow\infty}$ (ng h/mL)	1123.37 ± 79.66	893.72 ± 116.56
$AUMC_{0\rightarrow t}$ (ng h/mL)	4751.96 ± 103.70	3746.13 ± 265.20
$AUMC_{0\rightarrow\infty}$ (ng h/mL)	37936.75 ± 1702.08	33794.48 ± 1861.19
$MRT_{0\rightarrow\infty}$ (h)	34.73 ± 1.13	38.72 ± 1.40
Relative bioavailability (%)	178.75	–

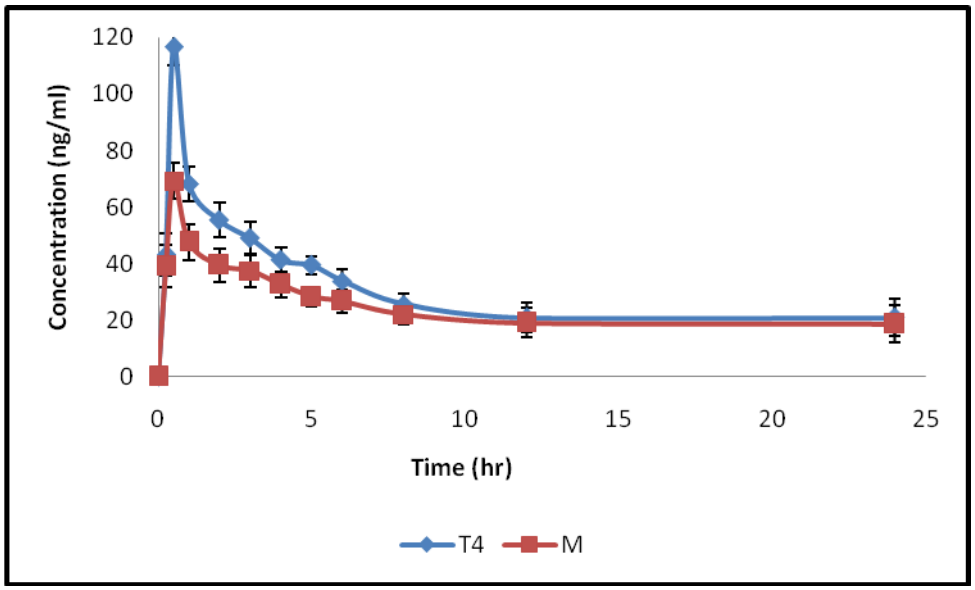


FIGURE.6 : Plasma concentration v/s time curve

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