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Reserach Article

FORMULATION AND EVALUATION OF SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM OF CANDESARTAN CILEXETIL

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A B S T R A C T

The aim of our investigation was to formulate a liquid self microemulsifying drug delivery system (SMEDDS) of candesartan cilexetil that could help to improve its solubility, stability, and oral bioavailability. The SMEDDS was prepared by using mixture of drug, oil, surfactant and cosurfactant. The liquid formulation was evaluated for various tests like solubility, Drug-surfactant compatibility, particle size, zeta potential, in vitro dissolution, etc. The optimized formulation S1 showed drug release (99.91%), drug content (97.42%), droplet size (62 nm), Zeta potential (-24.2), PDI (0.228), viscosity (0. 8269 cP) etc. In vitro drug release of the S1 was highly significant 97.96% as compared with marketed preparation (M) 66.73%.
The present investigation shows that SMEDDS of Candesartan cilexetil can be formulated as a unit dosage form. The S1 can be further used for preparation of different solid dosage forms.

INTRODUCTION

Novel drug delivery system has been introduced to overcome the drawback of fluctuating drug levels associated with conventional dosage forms [1]. Current research is aimed at development of drug delivery system (DDS) with maximum therapeutic benefits.

SMEDDS or Self-Microemulsifying Drug Delivery System is defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents and co-solvents/surfactants [4]**.** Upon mild agitation followed by dilution in aqueous media, such as gastrointestinal (GI) fluids, these systems can form fine oil-in-water (o/w) emulsions or microemulsions or selfmicroemulsifying drug delivery system (SMEDDS). Fine oil droplets would pass rapidly from the stomach and promote wide distribution of the drug throughout the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substances and the gut wall. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. An additional advantage of SMEDDS over simple oily solutions is that they provide a large interfacial area for partitioning of the drug between oil and water [1, 2].

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Apart from solubilisation, the presence of lipid in the formulation helps to improve bioavailability by affecting the drug absorption [1].

Candesartan cilexetil is an esterified prodrug of candesartan, a nonpeptide angiotensin II type 1(AT1) 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 drug. 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. Thus, a novel oral formulation of candesartan cilexetil can be developed which increases its solubility and enhances permeability across the biological membrane to overcome its poor bioavailability.

Selection of a suitable self-emulsifying formulation depends upon the assessment of

1. The solubility of the drug in various components,
2. The area of the self-emulsifying region as obtained in the phase diagram, and
3. The droplet size distribution of the resultant emulsion following self-emulsification [6].

The objective of this study was to develop and characterize liquid SMEDDS of candesartan cilexetil for increasing

solubility and permeability across the biological membrane to improve the bioavailability, dosing frequency, in vitro dissolution as well as enhance patient compliance.

MATERIALS AND METHODS

Materials for component selection

Candesartan cilexetil was obtained as a gift sample from Alembic Pharmaceuticals, Gujarat. Oleic acid, Olive oil, Castor oil, Cotton seed oil, Isopropyl myristate, Labrafac PG, Tween 80, Tween 20, Span 80, Span 20, Propylene glycol& Polyethylene Glycol 400 were kindly gifted by Lobachemie, Mumbai. The other chemicals used were of the analytical grades. Double-distilled water was used throughout the study.

Screening of components

The solubility of drug in oils, surfactants and co-surfactants is the most important criterion for the screening of components for SMEDDS. As the aim of this study is to develop an oral formulation, hence, solubility of drug in oils is more important because the ability of SMEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oil phase. The solubility of candesartan cilexetil in various oils and distilled water was determined by adding an excess amount of drug in 2mL of selected oils (oleic acid, capryol 90, isopropyl myristate, castor oil, olive oil) and distilled water separately in 5mL capacity stopper vials, and mixed using a vortex mixer. The mixture vials were then kept at 25±1.0 o C in an isothermal shaker for 72 h to reach equilibrium. The equilibrated samples were removed from shaker and centrifuged at 3000 rpm for 15 min. The supernatant was taken and filtered through a 0.45 µm membrane filter. The concentration of candesartan cilexetil was determined in oils and water using UV spectrophotometer at 254 nm. [2]

Drug and surfactant compatibility study

Physical compatibility of the water-insoluble drug with surfactants should be used in surfactant selection procedure. Physical compatibility may include precipitation/ crystallization, phase separation and color change in the drug – surfactant solution during course study. Chemical compatibility is primarily regarded as the chemical stability of the drug in a surfactant solution. A surfactant was considered for further development only if it was physically and chemically compatible with drug[2].

Construction of 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 surfactant/cosurfactant at certain weight ratios were diluted with water in a dropwise manner. Distilled water was used as an aqueous phase for the construction of phase diagrams. Oil, surfactants and co surfactants were grouped in four different combinations for phase studies. Surfactant and cosurfactant (Smix) in each group were mixed in different weight ratios (1:1, 2:1, 1:2, 2:1, 3:1). These Smix ratios were chosen in increasing concentration of surfactant with respect to cosurfactant and increasing concentration of cosurfactant with respect to surfactant for detailed study of the phase diagrams for formulation of SMEDDS. For each phase diagram, oil and specific Smix ratio was mixed thoroughly in different weight ratios from 1:1 to 3:1 in different glass vials. Twelve different combinations of oil and Smix were made so that maximum ratios were covered for the study to delineate the boundaries of phases precisely formed in the phase diagrams. Pseudo-ternary phase diagrams were developed using aqueous titration method.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 S/CoS mixing ratio[6]. On the basis of the solubility studies of drug, Oleic acid was selected as the oil phase. The physical state of the SMEDDS was marked on a pseudo-three-component phase diagram aqueous phase,the other representing oil and the third representing mixture of surfactant and cosurfactant at fixed weight ratios (Smix ratio)[1].

Preparation of Liquid Microemulsion:

A series of SMEDDS formulations were prepared using oleic acid as oil, Tween80 as surfactant and Propylene glycol as co-surfactant. Accurately weighed amount of Candesartan Cilexetil was dissolved in oleic acid and then mixture of Smix (2:1) added in a glass vial. The mixture was mixed by gentle stirring by using vortex mixture. The mixture was placed on magnetic stirrer at 50rpm for 15min.The mixture was stored at room temperature until further use. Briefly, for microemulsion Smix ratio(2:1) was selected from pseudo ternary phase diagram. The conditions for preparation of microemulsion were maintained throughout the preparation 50rpm and temp. at 25^0c the material was mixed slowly for getting well result[3].

Table no 1 Liquid batches of Self microemulsifying drug delivery system

Sr.No.	Formulation Code	Candesartan Cilexetil(mg)	Percentage Of Oil (%)	Percentage of Smix(2:1)(%)
1	S1	10	5	95
2	S2	10	7.5	92.5
3	S3	10	10	90
4	S4	10	12.5	87.5
5	S5	10	15	85

Evaluation of Liquid SMEDDS Formulation [1,4,8]:

pH

The pH microemulsion was measured using a systronic digital pH meter at 25 ±1 ºC. The pH meter was calibrated before use and pH value of all formulations were determined in triplicate. The pH of SMEDDS was determined after diluting 1 ml of the formulation with 9 ml of water. The results are given in Table no.2.

Viscosity measurement

The viscosity was determined by using Brookfield Rheometer r/s plus on different rpm and same rpm with different time. Sample was placed on plate and spindle no. C25/2 was adjusted on it and readings were taken with RH-3000 software. The result was shown in table no.2.

Thermodynamic stability

Heating cooling cycle: Six cycles between refrigerator temperature 4˚C and 45˚C with storage at each temperature of not less than 48h was studied. Those formulations, which were stable at these temperatures, were subjected to centrifugation test.

Centrifugation: Passed formulations were centrifuged at 3500 rpm for 30min. Those formulations that did not show any phase separation were taken for the freeze thaw stress test.

Freeze thaw cycle: Three freeze thaw cycles between 4˚C and +25 ˚C with storage at each temperature for not less than 48hrs was done for the formulations. Those formulations, which passed these thermodynamic stress tests, were further taken for the dispersibility test for assessing the efficiency of self-emulsification. The formulations were observed visually for any phase separation or color change.

Dispersibiity test

The efficiency of self-emulsification of SMEDDS was assessed using a standard USP XXII dissolution apparatus. One ml of each formulation was added to 500 ml of water at 37±0.5 ˚C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in-vitroperformance of the formulations was visually assessed using the following grading system:

Table No.2 Grades of Dispersibiity Test

Sr.No.	Observations	Grades
1	Rapidly forming (within 1 min) microemulsion, having a clear or bluish appearance.	A
2	Rapidly forming, slightly less clear bluish emulsion.	B
3	Fine milky emulsion that formed within 2min.	C
4	Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2min).	D
5	Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.	E

Grade A and B formulation will remain as microemulsion when dispersed in GIT.

% Transmittance Measurement

The percent transmittance of various formulations was measured at 254 nm using UV spectrophotometer keeping water as a blank.

Drug content determination

The drug content of SMEDDS formulation was determined by dissolving 1 ml (equivalent to 10 mg of drug) of the formulation in 50 ml methanol and mixed it well with shaking or inverting in volumetric flask for two to three times. After that 0.1 ml of this solution was diluted with fresh methanol and drug content was determined using UV spectrophotometer at 254nm.

Particle size distribution (PSD) and zeta-potential analysis:
SMEDDS formulation was diluted 100 times with distilled water at 37 ± 0.5˚C. The resultant emulsions were prepared by gentle agitation for 10 min using a magnetic stirrer. PSD and zeta-potential of the final microemulsion were determined using, Malvern zetasizer.

Polydispersibility Index

The procedure is same as in for particle size determination and described in section vii. Polydispersivity which determines size range of particles in the system is measured by No. of particles having size greater than 100nm divided by No. of particles having size less than 100nm.It is expressed in terms of polydispersivity index (PDI).

Cloud Point Determination

Dilute the formulation containing 10mg Candesartan cilexetil with 50ml of distilled water in beaker and placed on water bath with gradually increasing the temperature until the diluted formulation turned to cloudy. It gives the information about the stability of the microemulsion at body temperature.

In-vitroDrug release study

In 0.1 N HCl

Liquid SMEDDS containing 10mg Candesartan cilexetil was filled in hard gelatin capsule shell and placed in 900ml of 0.1N HCl as a dissolution medium. Dissolution study was carried out using USP type II apparatus (paddle) at 50 rpm at 37^0c. 5ml of aliquot was withdrawn after 5,10,15,20,30,45,60 min. The amount of drug release was determined using UV spectrophotometer at 254nm. All experiments were repeated in triplicate. Same procedure was applied for API.

In pH 6.8 phosphate buffer

Liquid SMEDDS containing 10mg Candesartan cilexetil was filled in hard gelatin capsule shell and placed in 900ml of 0.1N HCl as a dissolution medium. Dissolution study was carried out using USP type II apparatus (paddle) at 50 rpm at 37^0c. 5ml of aliquot was withdrawn after 5,10,15,20,30,45,60 min. The amount of drug release was determined using UV spectrophotometer at 254nm. All experiments were repeated in triplicate. Same procedure was applied for API.

RESULT & DISCUSSION

One important consideration when formulating a self-micro emulsifying formulation is avoiding precipitation of the drug on dilution in the gut lumen in vivo. Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion. Results from solubility studies are reported in table 3. The solubility of candesartan cilexetil was found to be highest in Oleic acid (85.80±0.81 mg/ml) as compared to other oils while in water it was 0.09±0.01 mg/ml. This may be attributed to the polarity of the poorly water soluble drugs that favor their solubilization in small/medium molecular volume oils such as medium chain triglyceride or mono or diglyceride. Hence, oleic acid is selected as a oil for preparation of SMEDDS.

Table No 3 Results of Solubility

Sr.No.	Name of Oils	Solubility)(mg/ml) Mean ±SD
1	Oleic acid	85.80 ± 0.81
2	Olive oil	81.18 ± 0.27
3	Castor oil	76.66 ± 0.05
4	Isopropyl myristate	69.32 ± 0.12
5	Labrafac PG	54.24±0.145

*Mean ±SD, n=3.

Drug and surfactant compatibility study

Physical and chemical compatibility of the water-insoluble drug candesartan cilexetil with various surfactants and co-surfactants was carried out to check the physical as well as chemical compatibility. As shown in table 4, 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 with this formulations.

Table No 4 Drug surfactant compatibility study.

Ratio (1:1)	Precipitation	Crystallization	Phase separation	Color change
Drug+Tween8o	√	√	√	√
Drug+Tween20	√	√	√	√
Drug+Span8o	√	√	√	√
Drug+Span20	√	√	√	√
Drug+Propylene glycol	√	√	√	√
Drug+Polyethylene glycol 400	√	√	√	√

√-Passed and ×-Failed

Construction of pseudo ternary phase diagram

The pseudo ternary phase diagram for SMEDDS was constructed by using water titration method. Based on solubility study, the Oleic acid selected as oil, Tween80 selected as surfactant and Propylene glycol as co-surfactant. For construction of pseudo ternary phase diagram the surfactant and co-surfactant are mixed in different weight ratios (1:1, 2:1, 3:1). For each phase diagram oleic acid and mixture of tween80 and propylene glycol are mixed thoroughly in different weight ratios from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) in different beakers. Each mixture was titrated with double distilled water and mixed uniformly by magnetic stirrer at room temperature. The mixture was visually examined for transparency. Clear and isotropic mixture indicates the presence of microemulsion region. The phase diagrams are presented below-

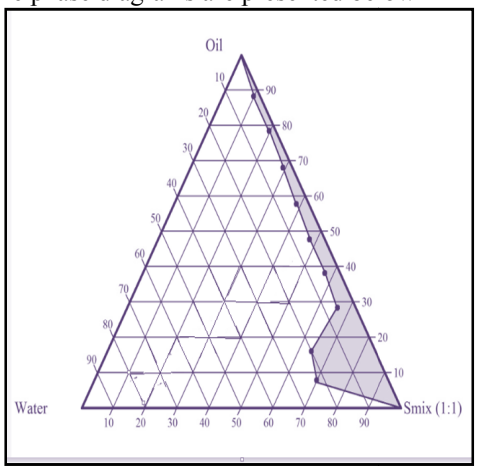

Fig No.1 Phase Diagram of Ratio 1:1

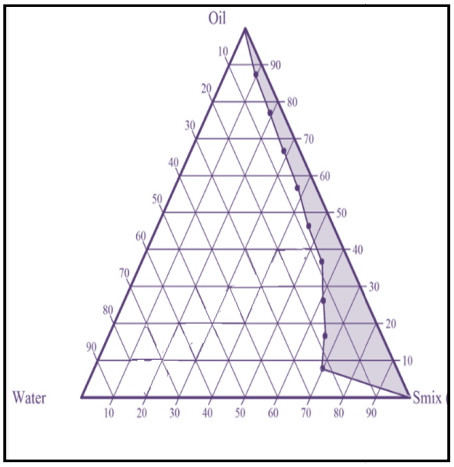

Fig No 2 Phase Diagram of Ratio 2:1

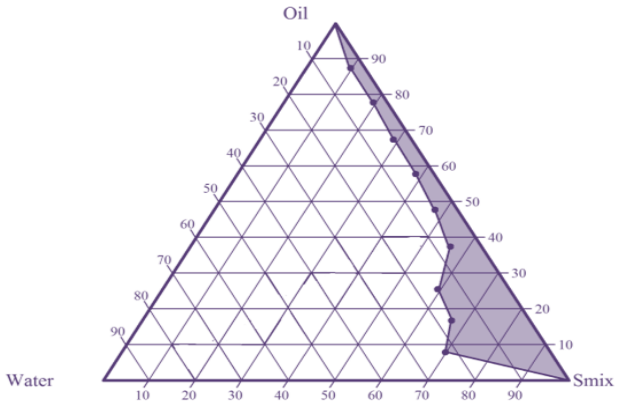

Fig No 3 Phase Diagram of Ratio 3:1

Viscosity & pH

The viscosity of microemulsion systems can be monitored by standard rheological techniques. All the formulation has viscosity which is highly similar to that of water i.e.1.0. Thus, it shows that SMEDDS forms o/w microemulsion and water remains as external phase. The results of viscosity are as shown in Table No. 5.

The excipients used in the formulation decide the pH of the final preparation. The change in the pH may affect the zeta potential of the formulation which in turn can affect the stability of preparation. All the formulations showed similar pH values in the range of 5.1 to 6.0. Thus pH is not affecting stability. Therefore it can be assumed that drug is not diffusing in the external phase and remains in the oil phase. Since, water is the external phase entire system showed pH of water. Candesartan cilexetil is unstable in alkaline pH. Here the formulations show acidic to neutral pH which is suitable for stability of Candesartan cilexetil.

Table No 5 Result of Viscosity & pH

Sr.No.	Formulation Code	pH	Viscosity(cp)
1	S1	5.53	0.8269
2	S2	5.42	0.8858
3	S3	5.89	0.8858
4	S4	5.21	0.8858
5	S5	5.14	0.8858

Thermodynamic stability

SMEDDS are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking. It is the thermostability which differentiates nano-or microemulsion from emulsions that have kinetic stability and will eventually phase separate[92].Thus, 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. The results are as shown in Table No.6.

Table No. 6 Thermodynamic stability test of different formulations

Sr.No.	Formulation Code	Centrifugation	Freeze Thaw Cycle	Inference
1	S1	√	√	Passed
2	S2	√	√	Passed
3	S3	√	√	Passed
4	S4	√	√	Passed
5	S5	√	√	Passed

Determination of Cloud Point

The cloud point is the temperature above which an aqueous solution of water soluble surfactant, especially non-ionic, becomes turbid**.** Hence the cloud point of formulation is greater than 37^0C to avoid irreversible phase separation. The following table shows the cloud point of all formulation. The data of cloud point reveals that all formulations are having cloud point greater than 37^0C. The higher cloud point value is 79^0C obtained from batch S1 and least value is 61^0C is of batch S5.

Table No 7 Result of Cloud Point measurement

Sr.No.	Formulation Code	Cloud point(^{0}C)
1	S1	79
2	S2	75
3	S3	71
4	S4	66
5	S5	61

Determination of Self emulsification Time

The self-emulsification time was measured for all formulations. The following data shows the self emulsification time of all formulations. From the data obtained it is revealed that when the concentration of oil increases then the self emulsification time also increases. If the concentration of Smix increases then the self emulsification time also decreases. The least self-emulsification time is obtained from batchS1 is 32 Sec. and higher self emulsification time obtained from batch S5is 2.04min. The results shown in Table No.8

Table No 8 Result of Self-emulsification Time

Sr.No.	Formulation Code	Self-emulsification time(min.)
1	S1	32
2	S2	43
3	S3	1.12
4	S4	1.45
5	S5	2.04

Dispersibiity Test

From the above data of dispersibility study the formulation S1 belongs into the grade A that emulsified in less than 1min. that is 32 sec. Batch S2 belongs to grade A which also emulsified rapidly. S3 and S4 formulations are emulsified within less than 2min. S5 formulation emulsified within more than 2min.The results are as shown in Table No.9.

Table No.9 Results of Dispersibiity Test

Sr.No.	Formulation Code	Grades	Observation
1	S1	A	Rapidly forming (within 1 min) microemulsion, having a clear or bluish appearance.
2	S2	A	Rapidly forming, slightly less clear bluish emulsion.
3	S3	B	Fine milky emulsion that formed within 2min.
4	S4	B	Fine milky emulsion that formed within 2min.
5	S5	D	Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2min).

Droplet size analysis

Droplet size measurement was performed by using Malvern Metasizer the instrument is based on the principle Dynamic light scattering and Brownion motion of droplets. The results obtained are presented below in Table no.10.

Table No. 10 Results of Droplet Size

Sr.No.	Formulation Code	Droplet Size (nm)
1	S1	**62**
2	S2	105
3	S3	189.9
4	S4	413.7
5	S5	682.1

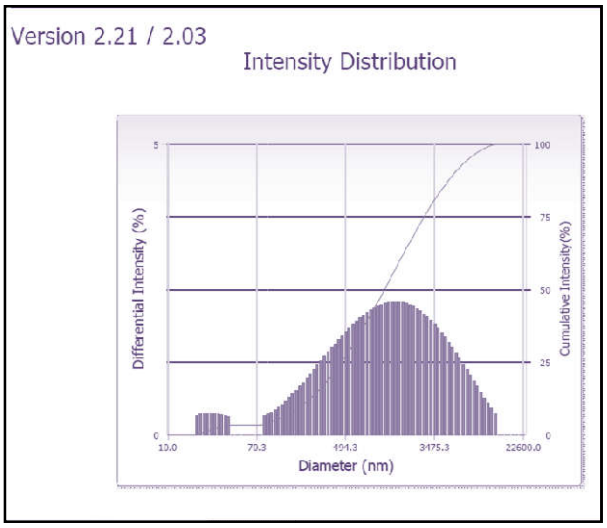

Fig No 4 Graphical Droplet size distribution of batch S1

From the above data it is revealed that the smaller droplet size is of Batch S1. It is found to be 62nm and larger droplet size was obtained of batch S5, 682.1 nm. This result revealed that when concentration of oil increase then the droplet size also increases but similarly if we increases concentration of Smix the droplet size decreases.

Zeta potential Measurement

Zeta potential was measured by using zetasizer (Horiba SZ100Z). The zeta potential analysis was performed for all batches. The zeta potential of Batch S1 was found to be -24.2, which is good. The zeta potential value is negative due to charge on droplets is negative. The zeta potential for various Candesartan cilexetil SMEDDS formulations are as shown in table no.11.

Determination of Polydispersibility Index (P.I.)

Ploydispersibility index was determined by using Nano particle analyzer SZ100Z (HORIBA). Following table shows results of P.I. batches. All formulation batches have P.I. **less** than1. From the above results it is concluded that the droplets are having uniform size range and having uniform distribution throughout in formulation.

Table No 12 Results of Polydispersibility Index

Sr.No.	Formulation Code	Polydispersibility Index
1	S1	0.228
2	S2	0.307
3	S3	0.328
4	S4	0.332
5	S5	0.397

Determination of % Transmittance

The clarity of Microemulsions &SMEDDSs was checked by transparency, measured in terms of Transmittance (%T). SMEDDS forms o/w microemulsions upon dilution since water is external phase. In case of systems having %T values less than 98% suggest less clarity of microemulsions. This may be due to greater droplet size of the formulation. Due to higher droplet size, oil globules may reduce the transparency of microemulsions and thereby values of % T, so such batches were eliminated from the further study.

Table No 13 % Transmittance of various formulations of SMEDDS (S1 to S5)

Sr.No.	Formulation Code	Appearance after 100 times dilution	%Transmittance (Mean ±SD)
1	S1	Clear	99.91 ± 0.17
2	S2	Clear	99.41 ± 0.16
3	S3	Clear	98.22 ± 0.15
4	S4	Clear	98.17 ± 0.26
5	S5	Clear	97.11 ± 0.02

Drug content determination

% Drug content of SMEDDS formulations are determined. The data is given in following table. The data revealed that highest drug content is found to be of batch S1 97.42±0.39 because it contain high surfactant concentration which can solubilise 10mg dose of Candesartan cilexetil.

Table No.14 % Drug content of various formulations of SMEDDS (S1 to S5)

Sr.No.	Formulation Code	%Drug Content Mean±SD
1	S1	97.42±0.39
2	S2	93.24±0.83
3	S3	91.65±0.09
4	S4	89.56±0.62
5	S5	87.57±0.08

In-vitro Dissolution Study

Dissolution study of API and liquid SMEDDS formulation batches S1 to S5 is carried out in different medium such as pH 6.8 phosphate buffer and 0. 1N HCl as per the procedure described in experimental work section.

Dissolution study in pH 6.8 phosphate buffer

When in-vitro dissolution study of pure drug Candesartan cilexetil, marketed preparation (M) of Candesartan cilexetil and liquid SMEDDS formulations were carried out in pH 6.8 phosphate buffer, it was found that the pure drugshows 43.91±1.03 release in 60min, marketed drug shows 66.73±0.77 while prepared liquid batch S1 shows higher release 97.96±1.58 in 60min.Lowest drug release was obtained from batch S5 is76.31±0.36. From the above data it is concluded that the rate of dissolution increases with decrease in droplet size. If droplet size decreases then the relative surface area increases for dissolution.

Dissolution study in 0.1N HCl

When in-vitro dissolution study of pure drug Candesartan cilexetil, marketed preparation of Candesartan cilexetil and liquid SMEDDS formulations were carried out in 0.1N HCl, it was found that the pure drug shows 41.77±0.41 release in 60min, marketed drug (M)shows 66.73±0.77 in 60 min. while prepared liquid batch S1 shows higher release 94.03±0.90in 60min.Lowest drug release was obtained from batch S5 is 71.15±1.08. From the above data it is concluded that the rate of dissolution increases with decrease in droplet size.

From the above data, it is revealed that the drug release of pure drug was increases in pH 6.8 phosphate buffer than in 0.1N HCl. It shows ph dependent release.

Optimization of Liquid SMEDDS formulation Batch

Microemulsions having least globule size are expected to have larger surface area andtherefore, may get absorbed or may transverse rapidly across the gastric mucosa. Moreover, literature citation revealed that SMEDDS which are negatively charged and having zeta potential -30 mV or less exhibits moderate to excellent physical stability. Therefore, both the selection criteria were used as a filter for further studies.

1. Microemulsions having mean droplet size below 100 nm; and
2. Zeta potential at least -5 mV.
3. The other criteria considered for the selection of the optimized formulation are;

Table No.15 Results of % Drug Release

Time (min)	% Drug Release in pH 6.8 phosphate buffer						
	API	M	S1	S2	S3	S4	S5
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	11.13±0.01	28.33±0.38	45.03±0.15	38.09±0.91	33.08±0.13	23.21±0.51	22.10±1.15
10	19.29±1,15	32.65±0.60	53.14±1.05	41.11±1.01	42.85±0.12	38.57±0.39	38.16±0.27
15	23.47±0.19	38.79±0.93	59.09±1.13	49.35±0.09	59.60±0.55	48.55±0.31	47.97±0.15
20	29.69±1.01	43.57±1.01	66.17±0.13	57.91±0.28	67.11±0.24	60.91±0.01	56.97±0.15
30	34.88±1.08	49.26±0.52	73.01±1.11	72.37±0.23	73.99±0.18	70.72±0.56	67.63±0.63
45	39.70±0.71	57.83±1.12	85.31±1.07	86.71±0.39	86.71±0.31	79.72±0.21	71.25±1.09
60	43.91±1.03	66.73±0.77	97.96±1.58	91.19±0.12	89.05±0.12	83.39±0.34	76.31±0.36

∗Mean±SD, n=3.

Table No 15 Results of % Drug Release

Time (min)	% Drug Release in 0.1N HCl						
	API	M	S1	S2	S3	S4	S5
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	09.01±1.07	28.33±0.38	43.91±0.51	36.39±1.01	32.63±0.40	22.16±0.13	21.37±0.51
10	17.90±0.09	32.65±0.60	59.32±0.70	39.29±0.01	38.13±0.55	30.05±1.13	28.17±0.71
15	21.13±1.11	38.79±0.93	57.11±1.01	45.68±1.05	42.07±1.11	37.13±0.31	35.90±0.99
20	27.34±1.06	43.57±1.01	62.71±1.03	53.81±0.80	51.16±1.02	46.98±1.03	44.71±1.09
30	32.65±0.08	49.26±0.52	70.09±1.11	67.43±0.17	65.68±1.00	58.90±0.80	54.19±1.11
45	38.51±0.15	57.83±1.12	81.03±1.04	79.25±1.03	77.81±1.08	67.33±0.51	62.53±0.07
60	41.77±0.41	66.73±0.77	94.03±0.90	88.17±0.37	85.17±0.70	76.51±1.31	71.15±1.08

∗Mean±SD, n=3.

4. Polydispersity Index
5. % Drug release.

From all formulations of Candesartan cilexetil (S1 to S5), formulation S1 wasselected as final formulation due to lowest globule size (62 nm), higher negative zetapotential (-24.2 mV) and less PDI (0.228) compared to others which indicate thatsystem would remain stable compared to other formulations. The results of % Drug release in pH 6.8 phosphate buffer and 0.1N HCl supported the selection of S1 as the optimized formulation of Candesartan cilexetil SMEDDS. The optimized formulation S1 was further studied for FTIR.

FTIR Spectrum of Liquid SMEDDS (S1):

By using FTIR spectrophotometer, IR spectrum of optimized liquid SMEDDS (S1) prepared. Fig. No. shows FTIR of batch S1.Interpretation of IR is shown in table no.

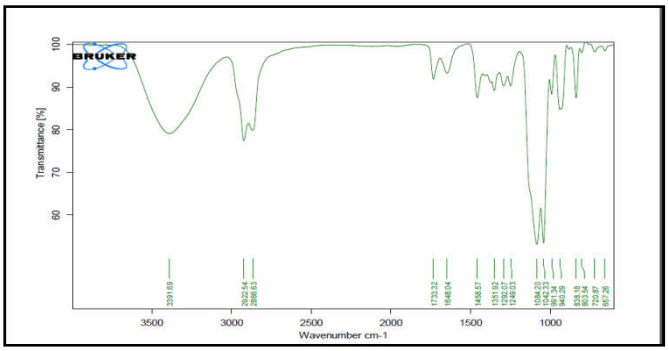

Fig No FTIR of liquid SMEDDS Batch S1

Table No IR interpretation of Liquid SMEDDS of Batch S1

Bond	Type of Compound	Wave number(cm^{-1})
C-H (stretching)	Alkene	838.18
C-N(stretching)	Amines	1038
C-H(stretching)	Aldehyde	2922.54
N-H (stretching)	Pri.& Sec. Amines	3391

DISCUSSION

The characteristic peaks at 838.18cm^{-1} (C-H Stretching) alkene, 1038cm^{-1}(C-N Stretching) amines, 2922.54^{-1} (C-H Stretching) aldehyde, and at 3391cm^{-1} (N-H stretching) pri. & sec. amines shown in fig.---. It shows all characteristics peak of drug and all excipients hence it reveals that there is no any chemical interaction takes place between drug and excipients.

CONCLUSION

Liquid SMEDDS are prepared using Oleic acid, Tween 80 & Propylene glycol. From the entire study it was found that the drug releases from liquid SMEDDS formulation was found to be significantly higher as compared with that of pure drug. Thus the solubility & dissolution rate of BCS Class-II drug Candesartan cilexetil was enhanced but in-vivo studies are needed to be conducted.

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