WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 13, 1633-1642. Research Article ISSN 2277– 7105

SOLUBILITY ENHANCEMENT OF POORY SOLUBLE DRUG CINACALCET HYDROCHLORIDE BY FORMULATING INTO SELF EMULSIFYING DRUG DELIVERY SYSTEM

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Article Received on
06 August 2022,

Revised on 27 August 2022,
Accepted on 17 Sept. 2022

DOI: 10.20959/wjpr202213-25647

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ABSTRACT

The present study is aimed to formulate and develop self emulsifying drug delivery system (SEDDS) of Cinacalcet for enhancement of bioavailability. Drug substance having poor water solubility are observed with low absorption and permeation through the GI tract which leads to the lower bioavailability. The self emulsifying drug delivery system (SEDDS) enhances the solubility of drug, The SEDDS formulation of Cinacalcet was optimized with combination of oil, surfactant, co-surfactant taken in different proportion having different HLB value to prepare a stable and effective formulation of nano sized globule. Glyceryl Caprylate Oil (Capmul MCM), surfactant (gelucire 44/14) and co surfactant (PEG 400) were selected, pseudo ternary phase diagram was plotted in titration method by taking in different combination of Smix with oil, surfactant and co-surfactant. The efficiency of emulsification was good when the surfactant/co-surfactant concentration was more than 50% of SEDDS formulation. The combination was evaluated with cinacalcet, the optimized formulation with the ratio of drug: oil: surfactant: co-surfactant at 3:20:15:15 respectively showed better performance with respect to emulsification time, dissolution study, assay of drug, Diffusion study revealed a significant improvement in dissolution rate.

KEYWORDS: SEDDS (Self emulsifying drug delivery system), Cinacalcet HCl, Surfactant, Co-surfactant, Phase diagram.

INTRODUCTION

The oral route is most preferred for chronic drug therapy in human beings. Around 50% of the drug compounds are facing problems because of the poor solubility and low permeability of the drug itself. For such compounds, the absorption rate from the gastrointestinal (GI) lumen is controlled by dissolution.[1,2]

Modification of the physicochemical properties, such as salt formation and particle size reduction of the compound may be one approach to improve the dissolution rate of the drug. Lipid-based formulations were first developed for delivering fat-soluble vitamins. However, some innovative formulations containing lipid excipients, such as SEDDS (Self-Emulsifying Drug Delivery Systems) SMEDDS (Self- Micro emulsifying Drug Delivery Systems), have recently emerged for enhancing oral drug delivery. This improvement is probably due to drug being administered in a pre-dissolved state, which reduces the energy associated with the solid- to-liquid phase transition process, and to the fact that the solubilization of the drug is enhanced in the colloidal structures as the result of interactions between the formulation and its digestionproducts and endogenous biliary amphiphiles such as bile salts, and dietary lipids. The lipolysisof lipid excipients by digestive lipases might also be an important factor involved in the drug absorption step.[3,4,5,6]

Self-emulsifying system (SES) is one of the oily based most popular and commerciallyviable approaches for the delivery of such solubility problem drugs that exhibit dissolution- rate-limited absorption. SES is ideally an isotropic mixture of oils and surfactants and sometimes co-solvents, which emulsifies spontaneously to produce fine oil-in-water (water-in- oil) emulsion when introduced into aqueous phase under gentle agitation. Upon peroral administration, these systems form fine (micro or nano) emulsions in the gastrointestinal tract (GIT) with mild agitation provided by gastric mobility.[7,8]

SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SEDDS requires the use of a co- surfactant to generate a micro emulsion. SEDDS formulations are characterized by in vitro lipid droplet sizes of 200 nm– 5 mm and the dispersion has a turbid appearance. Self- emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing co-solvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation4-8,. Recently, SEDDS have been formulated using medium chain tri-glyceride oils and non-ionic surfactants, the

latter being less toxic. Upon per oral administration, these systems form fine emulsions (or microemulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility.[9,10,11]

Selection of oils, surfactant and co-solvent based on the solubility of the drug should be considered in the formulation of a SEDDS. The self-emulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs. After self-dispersion, the drug is rapidly distributed throughout the gastrointestinal tract as fine droplets. The SDLFs are of two kinds namely, Self-Emulsifying Drug Delivery Systems (SEDDS) formed using surfactants of HLB < 12 and Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) formed surfactants of HLB > 12. Both SEDDS and SMEDDS are stable preparations and improve the dissolution of the drug due to increased surface area on dispersion.[12,13,14]

Self-emulsifying system (SES) is one of the most prevalent and commercially feasible oil based approaches for the delivery of drugs that show dissolution speed limited absorption. SES is an isotropic mixture of oils, surfactants, co-surfactants, and at times co-solvents, which emulsify extemporaneously to produce oil-in-water or water-in-oil emulsion when introducedinto the gastrointestinal tract (GIT). Based on the droplet size after emulsification, they are classified into two broad classes, namely self-emulsifying drug delivery systems (SEDDS) with a droplet size range of 100–300 nm and self-microemulsifyg drug delivery systems.[15]

Cinacalcet Hydrochloride is the orally bioavailable hydrochloride salt of the calcimimetic cinacalcet. Cinacalcet increases the sensitivity of calcium-sensing receptors on chief cells in the parathyroid gland to extracellular calcium, thereby reducing parathyroid hormone (PTH) secretion. Soluble in methanol, dimethyl sulphonic acid, and ethanol. Slightly soluble in water.

MATERIALS and METHODS

Material: equipment: Electronic balance, Water bath shaker, Magnetic stirrer, Cyclo mixer, Mechanical stirrer, USP apparatus II paddle method, UV-VIS spectrophotometer, FTIR spectrophotometer, Cinacalcet Hydrochloride (Dr.Reddy's), Capmul MCM, Gelucire 44/14, Polyethylene glycol 400,

Calibration Curve of Cinacalcet in 0.1 N HCl: 10mg of Cinacalcet HCl was weighed & dissolved in 0.1N HCL and the volume was made up to the markwith 0.1N HCL to produce a concentration of 1000µg/ml of Cinacalcet HCl which was our standard stocksolution. From, the 1000µg/ml of Cinacalcet HCl 1ml was pipette into the 10ml volumetric flask, volumewas made up to the mark with DMF to produce the concentration of 100µg/ml as working standard solution. From the working standard solution aliquote of solution was transferred to 10ml volumetric flask & volume was made upto the mark with 0.1N HCL to get the concentration of 10mg/ml of Cinacalcet HCl. Then, this solution was used for scanning in the range of 200-400nm to get the λ max. It was found to be 273nm.

Pseudo ternary phase diagram: The pseudo ternary phase diagram is carried out by water titration method by using PRO- SIM TERNARY DIAGRAM INSTALL SOFTWARE to select Smix system. Pseudo ternary phase diagrams of oil, surfactant/ cosurfactant (S/CoS), and water were developed using the water titration method. The mixtures of oil and S/CoS at certain weight ratios were diluted withwater in a drop wise manner. For each phase diagram at a specific ratio of S/CoS (i.e. 1:1, 1:2, 1:3, and 2:3), along with oil or oil-drug mixture is prepared, which is a transparent and homogenous mixture. Then each mixture was titrated with water and visually observed for phase clarity and flow ability. A series of 9 ratios of oil : Smix are made i.e. (1:9, 2:8, 3:7, 4:6,5:5, 6:4, 7:3, 8:2 and 9:1) and individually all are titrated with 0.1 N HCl, then the total mixture was weighed in electronic balance and individual percentages of weight of ingredients are calculated. The concentration of water at which transparency of oil –Smix-drug solution is changed to turbidity at that point the titration is stopped. These values were then used to determine the boundaries of the micro emulsion domain corresponding to the chosen value of oils, as well as the S/CoS mixing ratio. To determine the effect of drug addition on the micro emulsion boundary, phase diagrams were also constructed in the presence of drug using drug-enriched oil as the hydrophobic component. Phase diagrams were then constructed.[16,17,18]

Formulation study: Formulation trials were executed using PEG 400 as co surfactant, Gelucire 44/14 as surfactant. USP Apparatus II paddle method has been used for performing dissolution studies ofSEDDS at 100rpm. Comparison was done between the dissolution rate of pure drug and prepared formulations.

RESULTS AND DISCUSSION

Linearity graph for Cinacalcet in buffer dissolution medium was established for the range of

5-80 mcg/ml. presented in figure-1 and table-1.

Table 1: linearity study for Cinacalcet HCl in 0.1N HCl.

Concentration (µg/ml)	Absorbance
0	0
5	0.086
10	0.148
20	0.296
30	0.422
40	0.569
50	0.700
60	0.839
70	0.980
80	1.051

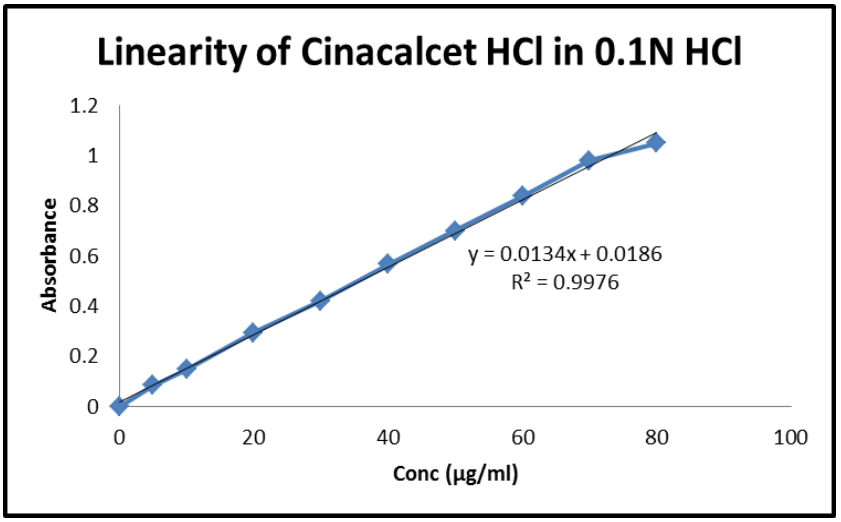

Figure 1: Linearity of Cinacalcet HCl in 0.1N HCl.

Construction of pseudo-ternary phase diagram: A series of SEDDS were prepared and their self-emulsifying properties were observed visually. Pseudo-ternary phase diagrams were constructed without using the drug Cinacalcet HCl to identify the self-emulsifying regions and to optimize the concentration of oil, surfactant and co surfactant in the SEDDS formulations. The phase diagrams containing Gelucire 44/14 as surfactant, Capmul MCM as oil and PEG 400 as co surfactant was observed thatthe efficiency of emulsification was good when the S/CoS concentration was more than 65% of SEDDS formulation.

Different ratios of Smix were selected (1:1, 1:2, 2:3) for Gelucire 44/14 as surfactant, PEG 400 as co-surfactant by HLB value calculation procedure. In our presentstudy Capmul-MCM as the oil phase and Gelucire 44/14 with PEG 400 as the surfactant and co surfactant respectively in combination and titrated with water in all nine ratios of S: CoS from 1:9 to

9:1. Various Smix ratios selected to find out the nano emulsion region are enlisted in the table-2,3,4 & 5.

Table 2: Phase diagram for 1:1 ratio of Smix of Gelucire 44/14 with PEG 400.

S. No	Oil/Smix	Oil (g)	Smix (g)	Water consumed(g)	Total (g)	Oil %	Smix %	Water %
1	1:9	0.1	0.9	1.62	2.62	3.8	34.3	61.9
2	2:8	0.2	0.8	0.16	1.16	17.2	69.0	13.8
3	3:7	0.3	0.7	0.20	1.20	25	58.3	16.7
4	4:6	0.4	0.6	0.14	1.14	35.1	52.6	12.3
5	5:5	0.5	0.5	0.14	1.14	43.8	43.8	12.4
6	6:4	0.6	0.4	0.08	1.08	55.6	37.0	7.4
7	7:3	0.7	0.3	0.08	1.08	64.8	27.8	7.4
8	8:2	0.8	0.2	0.09	1.09	73.8	18.3	8.3
9	9:1	0.9	0.1	0.08	1.08	83.3	9.3	7.4

Table 3: Phase diagram for 1:2 ratio of Smix of Gelucire 44/14 with PEG 400.

S. No	Oil/Smix	Oil (g)	Smix (g)	Water consumed(g)	Total (g)	Oil %	Smix %	Water %
1	1:9	0.1	0.9	1.81	2.81	3.6	32.0	64.4
2	2:8	0.2	0.8	1.76	2.76	7.3	29.0	63.7
3	3:7	0.3	0.7	0.22	1.22	24.6	57.4	18.0
4	4:6	0.4	0.6	0.16	1.16	34.5	51.7	13.8
5	5:5	0.5	0.5	0.21	1.21	41.3	41.3	17.4
6	6:4	0.6	0.4	0.09	1.09	55	36.7	8.3
7	7:3	0.7	0.3	0.18	1.18	59.3	25.4	15.3
8	8:2	0.8	0.2	0.20	1.20	66.6	16.7	16.7
9	9:1	0.9	0.1	0.17	1.17	77.0	8.5	14.5

Table 4: Phase diagram for 2 :3 ratio of Smix of Gelucire 44/14 with PEG 400.

S. No	Oil/Smix	Oil (g)	Smix (g)	Water consumed(g)	Total (g)	Oil %	Smix %	Water %
1	1:9	0.1	0.9	1.48	2.48	4.0	36.3	59.7
2	2:8	0.2	0.8	2.08	3.08	6.5	26.0	67.5
3	3:7	0.3	0.7	0.36	1.36	22.0	51.5	26.5
4	4:6	0.4	0.6	0.10	1.10	36.4	54.5	9.1
5	5:5	0.5	0.5	0.13	1.13	44.2	44.2	11.6
6	6:4	0.6	0.4	0.12	1.12	53.6	35.7	10.7
7	7:3	0.7	0.3	0.09	1.09	64.2	27.5	8.3
8	8:2	0.8	0.2	0.11	1.11	72.1	18.0	9.9
9	9:1	0.9	0.1	0.12	1.12	80.4	8.9	10.7

It was observed that increasing the concentration of the surfactants, Gelucire 44/14 within the self-emulsifying region increased the spontaneity of the self-emulsification process. It was observed that the emulsification was not efficient with lessthan 50% of surfactant ratio. Thus,

an S/CoS ratio 2:3 for Gelucire 44/14 and PEG 400 were selected for the nano emulsion formulation. It has been reported that the drug incorporated in the SEDDS may have some effect on the self-emulsifying performance.[1,5] In our study, no significant differences were found in self emulsifying performance when compared with the corresponding formulations with Cinacalcet HCl. The composition of 6 formulations, mixed with different proportion of component is presented in table-5.

Table 5: Composition of Self Emulsifying Drug Delivery System.

Formulation	Pure drug	CAPMULMCM	Gelucire 44/14	PEG 400
F1	30	100	150	200
F2	30	150	200	150
F3	30	200	200	200
F4	30	100	200	200
F5	30	150	150	150
F6	30	200	150	150

The formulation was evaluated for physico-chemical properties, the results are presented in table 6, 7 and figure -2.

Table 6: Physico chemical characterization of SEDDS formulation.

Formulation	Turbidity in 0.1N HCl	Self Emulsifying time	Drug content (%)
F1	Clear Slightlybluish	<1 min	90
F2	Clear Slightlybluish	<1 min	89
F3	Clear Slightlybluish	<1 min	93
F4	Bluish Appearance	<1 min	91
F5	Bluish Appearance	<1 min	94
F6	Milky Appearances	<1 min	90

Table 7: In-vitro dissolution profile of SEDDS formulation.

TIME (mins)	Cumulative Percentage Drug Release (Cinacalcet HCl) in 0.1N HCl						
	Drug	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
5	5.4	77	38.9	27.7	45.6	32.2	83.7
10	18.8	83.7	52.3	38.9	54.6	45.6	94.9
15	25.5	99.4	77	50.1	72.5	54.6	99.4
30	21	94.9	99.4	63.5	94.9	72.5	100.1
45	23.2	97.1	100.1	74.7	97.1	88.2	100.1
60	25.5	98.2	100.3	85.9	98.3	97.1	100.3

The in-vitro dissolution data indicates, the complete release of cinacalcet was achieved with the aid of SEDDS system. The drug as such has been observed with only 25% of drug

release.

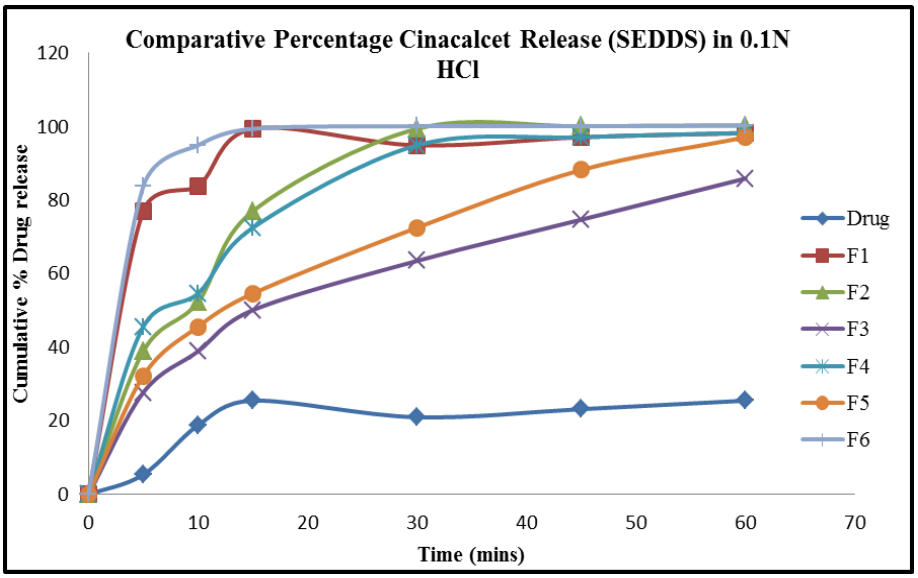

Figure 2: Comparative Percentage drug release of Cinacalcet in 0.1N HCl as SEDDS.

CONCLUSION

The SEDDS are promising formulation approaches to solve that problem. According to Bio pharmaceutical classification system, the class IV drugs have poor water soluble property this restricts the permeation through the GI tract which leads to the lower bioavailability. This lipid based SEDDS formulation improves the dissolution behavior and hence bioavailability. In this formulation different combination of oil, surfactant, co surfactants are taken in different proportion having different HLB value to prepare a stable and effective formulation of nano sized globule. Cinacalcet HCl as drug, oil (Capmul MCM), surfactant (gelucire 44/14) and co surfactant (PEG 400) were taken and after that different evaluative tests were performed. Ternary phase diagram are plotted in titration method by taking in different combination of Smix with oil-drug combination and it is found that the emulsion region is more in the ratio of 2:3. This study reveals that solid SEDDS formulations can improve the solubility and dissolution of poorly water soluble drugs like Cinacalcet, potentially leading to improved therapeutic performance.

CONFLICT OF INTEREST

The authors have no conflict of interest.

ACKNOWLEDGEMENT

The authors thank to Tagore college of Pharmacy, Chennai, for providing all necessary

facilities for this project work.

FUNDING SOURCE

There is no source of funding.

DATA AVAILABILITY

Not declared.

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