ORIGINAL ARTICLE

Formulation and development of self-microemulsifying drug delivery system of pioglitazone hydrochloride

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Self-microemulsifying drug delivery system (SMEDDS) is a promising system for the Biopharmaceutics Classification System (BCS) class II drugs. The current research aimed to improve the dissolution of poorly water-soluble antidiabetic drug pioglitazone HCl by formulating it in SMEDDS. Liquid SMEDDS of pioglitazone HCl were formulated with Capmul MCM C8 and oleic acid as oil phase, Cremophor RH 40 and Tween 80 as surfactant phase, and Transcutol P as cosurfactant phase after screening various vehicles. The prepared formulations were evaluated for self-emulsifying ability and phase diagram was constructed to optimize the system. These systems were further characterized for globule size, effect of pH and robustness, zeta potential, drug content, viscosity, self-emulsification time, polydispersity index, % transmittance, thermodynamic stability, surface morphology, and drug release. The system was robust to different pH media and dilution volumes. The optimized system possessed a mean globule size of 122.2 nm, zeta potential around -22.9 mV, drug content 99.66 ± 0.47%, viscosity 0.8874 ± 0.026 cP, emulsification time 38 s, polydispersity index value of 0.5, and transmittance value of 99.3 ± 0.6%. Drug release in hydrochloric acid buffer pH 2 was found to be 99.35 ± 0.38%. More than three-fold increase in dissolution characteristics of pioglitazone HCl in SMEDDS was observed as compared to pure and marketed formulation. Liquid SMEDDS filled in hard gelatin capsule (HGC) shell was found to be compatible. Stability studies show there was no sign of phase separation or precipitation and no change in drug content was observed.

Key words: *Pseudoternary phase diagram, self-microemulsifying drug delivery system, surfactant/cosurfactant ratio*

INTRODUCTION

Diabetes mellitus (Type I and II) is a progressive disease characterized by hyperglycemia, due to inadequate control of levels of blood glucose by the pancreatic hormone insulin and/or abnormal resistance to insulin. Initial treatment includes modifications to diet and exercise, followed by prescription of an oral antidiabetic agent. Pioglitazone HCl (thiazolidinediones) is classified under Biopharmaceutics Classification System (BCS) classification II, that is, highly permeable and low soluble and is a potent antidiabetic drug. Though pioglitazone HCl has good bioavailability, but the poor aqueous solubility and slow dissolution rate of drug may have negative impact on its bioavailability and subtherapeutic plasma drug levels may lead to therapeutic failure. Also presence of foods affect the absorption and delays peak plasma concentration up to 5-6 h.[1]

Recently, much attention has been focused on lipid-based formulations like self-microemulsifying drug delivery system (SMEDDS) and has been an attractive option due to its potential for delivery of hydrophobic drugs and the outstanding advantages including spontaneity of formation, high solubilization capacity, thermodynamic stability, self-preserving nature, low cost, etc. Self-microemulsifying systems are isotropic mixtures of oil, surfactants, and cosurfactants that form fine oil in water (O/W) microemulsion upon mild agitation followed by dilution in aqueous media, such as gastrointestinal tract (GIT) fluids. These formulations

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spread readily in the GIT, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification.[1,2]

MATERIALS AND METHODS

Pioglitazone HCl was gifted by Microlabs Pharma, Bangalore. Capmul MCM C8 obtained as gift sample from Abitech Corporation. Transcutol P and Labrafac Lipophile WL 1349 were gifted by Gattefosse India Ltd; Cremophor RH 40 was gifted by BASF, Mumbai. Tween 80 and oleic acid were purchased from Research Lab Fine Chem Industries, Mumbai.

Experimental

Solubility studies

Screening of excipients was done by determining the equilibrium solubility of pioglitazone HCl in different oils and surfactants. Two milliliter of each of selected oil, surfactant sample was added in glass vial containing excess amount of pioglitazone HCl (200-300 mg), the drug was mixed in oil and surfactant by means of magnetic stirrer for 30 min and the vials were kept in sonicator for 1 h. Further mixing was carried out by keeping the vials on the mechanical shaker for 72 h for reaching the equilibrium. These vials were centrifuged at 7,000-10,000 rpm for 10 min. After centrifugation, undissolved drug was removed by filtering through 0.44 µm Whatman filter paper. The amount of dissolved drug was determined by diluting the supernatant with methanol and analyzing by ultraviolet (UV)-spectrophotometer (Jasco V 630, Japan) at 267 nm.[3-5]

Selection of surfactant

The selection of best surfactant from a large pool of surfactants was done on the basis of emulsification study, solubility study, and % transmittance study. For emulsification study, oil and surfactant were mixed in 1:1 ratio by weight, heated at 40-50°C and stirred to form homogeneous mixture, ratio of oil to surfactant was decided on the basis of requirement as stated in literature for spontaneously emulsification formation, oil surfactant mixture was added in distilled water in 1:100 ratio, and then visually assessed using the grading system. From the solubility study, best surfactant of choice for SMEDDS formulation was screened. For % transmittance study, oil-surfactant mixture (1 ml) was added in 100 ml distilled water in drop-wise manner and % transmittance was measured using UV-visible (VIS) spectrophotometer.[6-8]

Selection of cosurfactant

Cosurfactant was selected on the basis of enhancement of emulsification in the emulsifying study, solubility study, and % transmittance study. Various cosurfactants were screened by mixing surfactant with selected cosurfactants in 1:1 ratio by weight. Oily phase was added to this mixture in 1:3 ratio by weight, heated, and stirred gently to form homogeneous mixture.[7,9,10]

Construction of pseudoternary phase diagram

Pseudoternary phase diagrams of oil, surfactant/cosurfactant (Smix), and water were developed using the water titration method, each of them represents a side of triangle. Ternary mixtures with varying composition of surfactant, cosurfactant, and oil were prepared. Surfactant and cosurfactant were mixed in different ratios (1:1, 2:1, and 3:1 w/w). For each phase diagram, oil and specific surfactant to cosurfactant ratio were mixed thoroughly in different weight ratios from 1:9 to 9:1 in different test tubes. Nine different combinations of oil and Smix; 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1; were made so that maximum ratios were covered for the study to delineate the boundaries of phase precisely formed in the phase diagrams. A transparent and homogeneous mixture of oil/Smix was formed by stirring for 5 min, and then each mixture was titrated with water and observed for phase clarity and flow ability. The point at which system becomes bluish or turbid, titration was stopped and at this point value of oil, surfactant, and cosurfactant was calculated. Phase diagram were then constructed using CHEMIX School software version 3.0.[11-13]

The following studies were carried out by constructing a pseudoternary phase diagram

1. The influence of various surfactants on the microemulsion formation with the various cosurfactants
2. Influence of various cosurfactants on the microemulsion formation with Cremophor RH 40, Tween 80, and their mixture as a surfactant
3. Influence of surfactant/cosurfactant ratio on the formulation of microemulsion. The microemulsion regions in the diagrams were plotted and the colored region indicates the better self-microemulsification capacity
4. Comparison of the phase diagrams for the selection of best ratio of surfactant to cosurfactant.

Formulation of preliminary trial batches

Based on the pseudoternary phase diagram, four different preliminary batches [Table 1] of SMEDDS were formulated using Capmul MCM and oleic acid as oil, Cremophor RH 40 + Tween 80 combination as a surfactant, and Transcutol P as a cosurfactant.

Formulation and development of pioglitazone HCl SMEDDS

A series of SMEDDS formulation [Table 2] were prepared using Capmul MCM and oleic acid in ratio of 2:1 as oil, Cremophor RH 40 and Tween 80 combination in ratio of 3:1 as a surfactant

Table 1: Formulation of trial batches

Ingredients (mg)	F1	F2	F3	F4
Pioglitazone HCl	15	15	15	15
Capmul MCM+Oleic acid (2:1)	180	420	600	200
Cremophor RH 40+Tween 80 (3:1)	740	480	330	740
Transcutol P	80	100	70	60
Total weight (mg)	1,000	1,000	1,000	1,000

Table 2: Pioglitazone HCl SMEDDS formulation with their composition

Formulation (oil:SmixAB)	Oil (mg) (Capmul MCM+oleic acid-2:1)	SmixAB (3:1) (mg)	Drug (mg)
F1 (2:8)	105	480	15
F2 (3:7)	165	420	15
F3 (4:6)	225	360	15
F4 (5:5)	285	300	15
F5 (6:4)	345	240	15
F6 (7:3)	405	180	15
F7 (8:2)	465	120	15

Total weight: 600 mg

phase (SmixA), and Transcutol P as a cosurfactant. The mixture of surfactant phase and cosurfactant phase in the ratio of 3:1 is called SmixAB. Proportion of oil, surfactant, and cosurfactant was determined by pseudoternary phase diagram. In all the formulations, the level of pioglitazone HCl was kept constant (15 mg). Briefly accurately weighed pioglitazone HCl was placed in glass vial, and oil, surfactant, and cosurfactant were added. The ingredients were further mixed by gentle stirring and were heated at 40-50°C (30 min) until pioglitazone HCl was perfectly dissolved. The mixture was stored at room temperature until further use. The formulation batches were selected to cover low concentration of oil to high concentration as to get optimum oil and surfactant concentration, and hence, oil concentration from 20 to 80% and surfactant concentration 80 to 20% were selected for formulation (oil:SmixAB = 2:8:8:2).

Filling of SMEDDS in hard gelatin capsule

The liquid SMEDDS of the selected batch was filled in the Hard Gelatin Capsule (HGC) shell (Qualicaps, Japan). The size of the capsule shell selected according to the final volume of the formulation. The leakage problem of the liquid filled in the HGC was solved by the band sealing process (5% gelatin solution was prepared and in this solution approximately 10 empty HGC shells were soaked for about 10-12 h, this solution was used for band sealing).[14,15]

Evaluation of SMEDDS

Robustness

Robustness to dilution was studied by diluting the final liquid SMEDDS 100 and 1,000 times with various dissolution media viz. 0.1N HCl and Phosphate buffer pH 6.8. The diluted microemulsions were stored for 12 h and observed for any signs of phase separation or drug precipitation.[10,16]

Self-emulsification and dispersibility test

Evaluation of the self-emulsifying properties of SMEDDS formulations was performed by visual assessment. The formulations were subjected to test for speed of emulsification, clarity, and apparent stability of the resultant emulsion and further categorized as per grading system (A-bluish clear microemulsion and B-milky white microemulsion, both these type emulsify within 1 min.). Visual assessment was performed by drop-wise addition of the preconcentrates (SMEDDS) into 250 ml of distilled water. This was done in a glass beaker at room temperature, and the contents were gently stirred magnetically at ~100 rpm.[14,16,17]

Droplet size measurement

SMEDDS formulation (1 ml) was diluted with 100 ml deionized water in a beaker with constant stirring using a glass rod. The resultant emulsion was then subjected to particle size analysis. The droplet size distribution, polydispersity index of the resultant microemulsion was determined by dynamic light scattering with particle size apparatus (Malvern Zetasizer, UK). After equilibrium, the particle (droplet) size was recorded. The reduction of the droplet size to values below 200 nm lead to the formation of SMEDDS; which are stable, isotropic, and clear oil/water (o/w) dispersions. All studies were repeated in triplicate. This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion.[11,12,18]

Percentage transmittance

A total of 1 ml of SMEDDS formulation was diluted with 100 ml distilled water. Percentage transmittance was then measured spectrophotometrically at 638.2 nm using distilled water as a blank by UV-spectrophotometer.[17]

Thermodynamic stability studies

SMEDDS was diluted with deionized water and then centrifuged at 10,000 rpm for 10 min and formulation was observed visually for phase separation. The formulations that did not show any sign of phase separation after centrifugation were subjected to three to four freeze-thaw cycles, which included freezing at −4°C for 24 h followed by thawing at 40°C for 24 h. Centrifugation was performed at 3,000 rpm for 5 min. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies.[19]

Drug content determination

SMEDDS (100 mg) was dissolved in 10 ml of methanol in a 10 ml volumetric flask separately and then 0.1 ml of stock solution measured accurately and then transferred to 10 ml volumetric flask to which 10 ml methanol was added and filtered through Whatman filter paper. The above solution was analyzed by UV spectrophotometer at 267 nm. The amount of drug present in the formulation was determined using the prepared standard calibration curves of drug in methanol.[16]

Viscosity determination of SMEDDS

Ten to twenty grams of each formulation was weighed and transferred to beaker, and the viscosity of formulation was determined with the help of Brookfield Viscometer DV-E model, spindle no. 6, at 10 rpm for 5 min.

Zeta potential

Zeta potential is used to identify the charge of the droplets. In conventional SMEDDS, the charge on an oil droplet is

negative due to presence of free fatty acids. Zeta potential determined by Zetameter was monitored at 25°C at a scattering angle 173° (Zetasizer Nano-ZS, Malvern, UK).[16]

Scanning electron microscopy

The liquid Scanning electron microscopy (SEM) analysis was done to assess SMEDDS morphology, microemulsion appearance, and droplet size range.

In vitro dissolution studies

The quantitative *in vitro* release test was performed in hydrochloric acid buffer pH 2 as per United States Food and Drug Administration (USFDA) Guideline, using US Pharmacopoeia XXIV dissolution apparatus, Paddle apparatus at 50 rpm speed and temperature 37 ± 0.5°C. The SMEDDS formulations were filled into HGCs (00 size) followed by band sealing and used for drug release studies. During dissolution study, the HGC was tied to paddle with wire to avoid floating of capsule, results were compared with those of plain drug in HGC and marketed formulation. During the release studies, sample of medium was withdrawn at various time intervals and subjected to drug analysis using UV spectrophotometer (Jasco V-630, Japan) at 267 nm. The removed volume was replaced each time with 10 ml of fresh medium.[16,19,20]

Stability study

The SMEDDS formulations were filled into empty HGCs (size 00) and subjected to stability studies at 4°C, 25 ± 2°C/65 ± 5% (relative humidity (RH)), and 40 ± 2°C/75 ± 5% RH. Samples were charged in stability chambers with humidity and temperature control. They were withdrawn at specified intervals for analysis over a period of 3 months. The SMEDDS was evaluated by visual inspection for physical changes such as color and drug precipitation and also for drug content.[21-23]

RESULT AND DISCUSSION

Solubility studies

One important consideration when formulating a self-emulsifying drug delivery formulation is to avoid 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 selected drug. Solubility of pioglitazone HCl in various oils, surfactants, and cosurfactants is shown in the Table 3. Pioglitazone HCl exhibited good solubility in the Capmul MCM C8 and oleic acid among the oils. Data suggest that drug has more solubility in medium chain triglycerides (MCT) rather than long chain triglycerides (LCT) because MCT possess higher ester content per gram than LCT, so drug has higher solubility in MCT than LCT. Thus, for further studies Capmul MCM and oleic acid as oils were selected. In case of surfactants, the drug exhibited good solubility in Cremophor RH 40 and Tween 80. In case of cosurfactants, Transcutol P shows good solubility.

Table 3: Solubility profile of pioglitazone HCl in various oils and surfactants

Oils/surfactant	Solubility (mg/ml)
Olive oil	14.90±0.4
Capmul MCM	32.4±0.65
Sesame oil	12.18±0.74
Soybean oil	20.79±0.2
Castor oil	13.39±0.5
Oleic acid	27.11±0.32
Labrafac Lipophile WL 1349	17.08±0.43
Labrafil M 1944CS	5.93±0.4
IPM	7.46±0.5
Cremophor RH 40	22.10±0.83
Propylene glycol	7.27±0.1
PEG 400	14.64±0.33
Ethanol	13.39±0.26
Lauroglycol 90	10.41±0.72
Tween 80	17.096±0.25
Tween 20	12.18±0.14
Transcutol P	48.2±0.42
Labrasol	9.2±0.32

PEG: Polyethylene glycol, IPM: Isopropylmyristate

Selection of surfactant

Surfactant was selected collectively on the basis of the emulsification study [Table 4], solubility study [Table 3], and % transmittance study as shown in Table 4, which clearly distinguished ability of surfactant to emulsify selected oil phases. The study indicated that combination of surfactants showed better ability to emulsify oil compared to single surfactant. Combination of Cremophor RH 40 and Tween 80 showed very good ability to emulsify Capmul MCM C8, whereas, none of the surfactant alone emulsify combination of oils to a higher extent. Although, hydrophilic-lipophilic balance (HLB) value of surfactants used in study were ≥15, there were considerable differences in their ability to emulsify oils. Among the oils, both Capmul MCM C8 and oleic acid were emulsified easily. This is explained by the fact that ease of emulsification is affected by its molecular volume, as number and chain length of hydrophobic alkyl chain increases the emulsification capacity decreases.

Selection of cosurfactant

Table 4 shows relative efficacy of cosurfactants to improve emulsification of surfactants. Span 20, Span 80, and polyethylene glycol (PEG) could not form clear solution with selected oil and mixed surfactants and also have very less % transmittance. Propylene glycol (PG) and Transcutol P, hydrophilic cosurfactants increased spontaneity of microemulsion formation and showed clear solution along with good water uptake capacity, and therefore, were selected for further studies. As ratio of surfactant to cosurfactant is constant, study clearly distinguished ability of cosurfactants to improve emulsification of surfactants. Span 20 and 80 have oleate and laurate backbone, whereas, Transcutol P has less alkyl chains. This increase molecular

Table 4: Oils-surfactants-cosurfactant compatibility study

Oil:Surfactant/cosurfactant (1:1)		Water uptake capacity	Emulsification	Transmittance (%)	Result
Capmul MCM	Cremophor RH 40	Good	Emulsifies	99.23	Passes
Oleic acid	Cremophor RH 40	Good	Emulsifies	99.56	Passes
Capmul MCM	Tween 80	Good	Emulsifies	99.24	Passes
Oleic acid	Tween 80	Good	Emulsifies	99.74	Passes
Capmul MCM	Transcutol P	Good	Emulsifies	99.88	Passes
Oleic acid	Transcutol P	Good	Emulsifies	99.45	Passes
Capmul MCM	Span 20	Intermediate	Do not emulsify	37.89	Rejected
Oleic acid	Span 20	Intermediate	Do not emulsify	23.11	Rejected
Capmul MCM	Span 80	Intermediate	Do not emulsify	12.54	Rejected
Oleic acid	Span 80	Intermediate	Do not emulsify	26.87	Rejected
Capmul MCM	PEG	Intermediate	Do not emulsify	47.33	Rejected
Oleic acid	PEG	Intermediate	Do not emulsify	56.29	Rejected
Capmul MCM	PG	Good	Emulsifies	99.05	Passes
Oleic acid	PG	Good	Emulsifies	98.27	Passes

PG: Polyethylene glycol, PG: Propylene glycol

volume and affect penetration at interface. In contrast, PG is short chain amphiphiles, can penetrate perfectly at oil-water interface. Transcutol P shows better solubility than PG [Table 3] for pioglitazone HCl. Therefore, Transcutol P was selected for construction of ternary phase diagram.

Construction of pseudoternary phase diagram

The construction of pseudoternary phase diagram was used to obtain appropriate concentration ranges of components for the formation of microemulsions. Self-microemulsifying systems form fine oil water emulsions with only gentle agitation, upon their introduction into aqueous media. Therefore, the selection of oil and surfactant, and the mixing ratio of oil to Smix, play an important role in the formation of the microemulsion.

Figures 1b-e show pseudoternary phase diagram for Capmul MCM C8 + oleic acid (2:1), Cremophor RH 40 + Tween 80 (3:1), Transcutol P, as oil, surfactant, and cosurfactant phases, respectively, and here surfactant to cosurfactant ratio 1:1, 2:1, and 3:1 were used. The colored region indicates the better self-microemulsification capacity. Single surfactant study for pseudoternary diagram was also done for comparison with combination of surfactants as shown in Figure 1a. The size of microemulsion region was compared; larger the size, greater is the self microemulsification efficiency. Microemulsion formation area was increased with an increase in surfactant to cosurfactant (S:Cos) ratio; 3:1 shows more microemulsion area, hence used for formulation. On comparing Figure 1a and d, it is evident that the combination of surfactants have larger microemulsification region compared to single surfactant used in the SMEDDS system. Therefore, due to larger microemulsification area and greater capacity for oil incorporation, which is desirable to improve drug loading, Capmul MCM C8 + oleic acid (2:1) + Cremophor RH 40 + Tween 80 (3:1) + Transcutol P, where SmixAB 3:1 systems were selected for formulation. Thus, it helped to determine a suitable surfactant to cosurfactant ratio and concentration

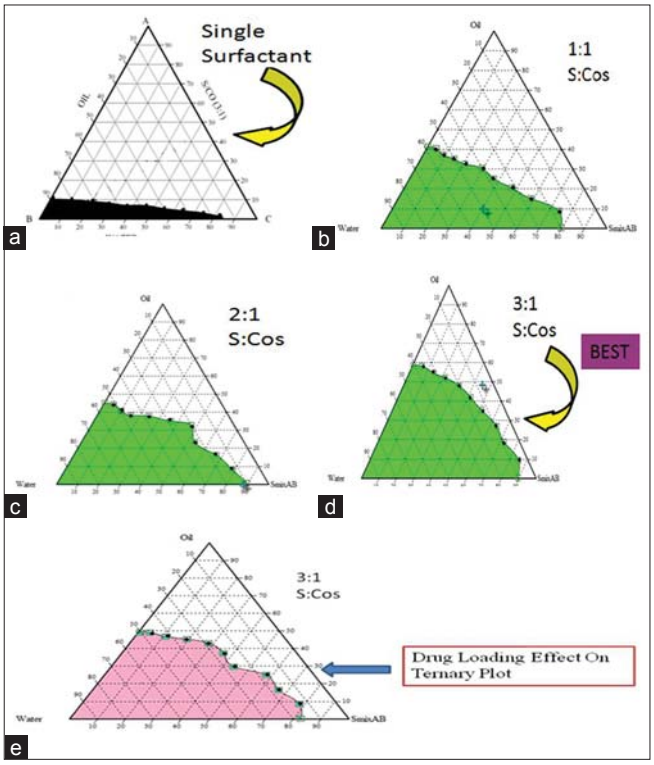

Figure 1: Ternary phase diagram of Capmul MCM + oleic acid–Cremophor RH40 + Tween 80 + Transcutol P-Water System. S/Cos = Surfactant to cosurfactant ratio in w/w

range of various components for formation of SMEDDS. Figure 1e shows phase diagrams in the presence of the drug, the inclusion of drug (15 mg/g) narrowed the microemulsion existence area because inclusion of the drug in the lipid phase lead to expansion of the lipid phase and consequently a need for a higher surfactant: Cosurfactant ratio for stabilization.

Robustness

The influence of dilution (i.e., 100 and 1000 times) with various diluents (i.e., acid buffer pH 2 and buffer pH 6.8)

was evaluated. Larger dilutions may mimic conditions better in the stomach following oral administration of SMEDDS (preconcentrate). On dilution with all the diluents there was no change in the visual clarity even after 8 h at room temperature for all formulations. Observation of the dilution studies showed that none of the formulation show phase separation or drug precipitation, because the selected oils and surfactants show high water uptake capacity. It was also observed that pH of dilution media does not affect SMEDDS stability.

Self-emulsification and dispersibility test

The result of self-emulsification and dispersibility studies is given in Table 5. It was observed that as the oil component increases in the formulation beyond a certain limit there was generation of nonclear dispersion. Among seven formulation, F1-F5 show grade A, while F6 and F7 exhibited grade B. Also self-emulsification time for F6 and F7 were more (57 s and 1.05 min, respectively). Therefore, these two batches were not taken for further study.

Droplet size measurement

The mean droplet size of the diluted SMEDDS preconcentrates was very low and all were found to be in the nanometric range (<200 nm). The mean droplet size of the formulation is shown in the Table 5. F4 was found to have the mean droplet size of 122.2 nm as indicated in Figure 2 with optimum concentration of oils and surfactants, therefore it was considered to be the best formulation. In all five formulations tested, the droplet size increased upon decreasing weight of Smix. All the polydispersity values were below 0.6, suggesting good uniformity in the droplet size distribution after dilution with water. Table 5 confirms the average size of pioglitazone HCl SMEDDS formulations to be in the range of 98.84-168.3 nm.

Percentage transmittance

Percentage transmittance of optimized F4 SMEDDS after diluting 100 times with deionized water was 99.30%. Transmittance value [Table 5] of SMEDDS formulation was in proximity to 100%; it indicated that clear microemulsion was obtained when SMEDDS was diluted 100 times with deionized water.

Thermodynamic stability studies

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variation on SMEDDS formulations. The SMEDDS formulation is found to be stable in these conditions; metastable formulation is thus avoided and frequent test need not to be performed during storage. All the formulations were stable to centrifugation and did not show any phase separation. No changes in visual description of samples after freeze thaw cycles were observed. Transmittance study observations showed % transmittance after freeze thaw cycle in the range of 99.18-99.35% for all formulations.

Drug content determination

The percentage drug content of formulations was determined spectrophotometrically at 267 nm by preparing the calibration curve of pure pioglitazone HCl in methanol. The drug content of various batches is given in Table 5. The F4 formulation shows drug content of 99.66 ± 0.47%.

Viscosity determination of SMEDDS

The viscosity of microemulsion systems can be monitored by standard rheological techniques (Brookfield Viscometer DV-E). It depends on oils and surfactants used. It was observed that the viscosity of all the formulations is less than 0.8877 cP [Table 5]. Formulation; F4 has the minimum viscosity

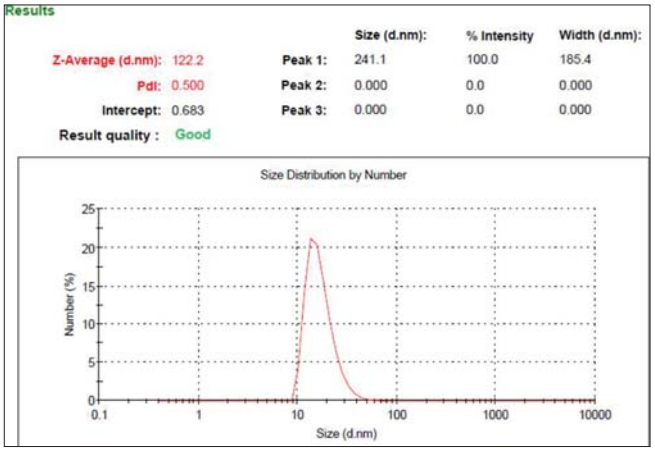

Figure 2: Droplet size of pioglitazone HCl self-microemulsifying drug delivery system (SMEDDS) F4 Formulation

Table 5: Viscosity, % transmittance, droplet size, polydispersity index (PDI), drug content, % drug release, dispersibility grade, self-emulsification time, and zeta potential of various SMEDDS

Batch	Viscosity (cP)	% Transmittance	Droplet size (nm)	PDI	Drug content (%)	Drug release (%)	Dispersibility grade	Emulsification time (min:s)	Zeta potential (mV)
F1	0.8873±0.043	98.4±0.5	98.84	0.332	98.68±0.18	100.85±0.65	A	00:29	
F2	0.8869±0.012	98.8±0.4	122.69	0.312	99.09±0.102	100.18±0.97	A	00:32	
F3	0.8871±0.077	99.1±0.1	152.8	0.551	99.91±0.38	98.41±0.25	A	00:35	
F4	0.8874±0.026	99.3±0.6	122.2	0.5	99.66±0.47	99.35±0.38	A	00:38	−22.9
F5	0.8877±0.042	99.7±0.2	168.3	0.263	98.43±0.24	98.03±0.77	A	00:44	
F6	-	-	-	-	-	-	B	00:57	
F7	-	-	-	-	-	-	B	1:05	

SMEDDS: Self-microemulsifying drug delivery system

0.8874 cP, which is highly similar to that of water, that is, 1.0. Thus, it shows that SMEDDS forms o/w microemulsion, water remains as external phase and viscosity of SMEDDS is near to that of water. This reveals that formulation F4 is very clear, transparent, and low viscous liquid.

Zeta potential

The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. If all the particles have a large negative or positive zeta potential they will repel each other and there is dispersion stability. Zeta potential of the system negative (−) mV, which indicates the droplets of microemulsion have negative charge. The zeta potential of optimized F4 formulation was found to be −22.9 and Figure 3 confirms the zeta potential of F4 pioglitazone HCl SMEDDS.

In vitro dissolution studies

Pioglitazone HCl is insoluble in water and showed pH-dependent solubility. As shown in Figure 4, plain drug showed very less release 26% even after 40 min in pH 2 buffer. Marketed (Actos Tablet, 15 mg) formulation showed about 38% release after 40 min in pH 2. Whereas, SMEDDS showed rapid release of drug in buffer pH 2. At 20 min about 45% of pioglitazone HCl from SMEDDS (F4) was released and more than 86% was released after 35 min, complete release was observed in 40 min. In other words, SMEDDS could quickly form clear and transparent solution under the condition of dissolution. It was also evident that release of pioglitazone HCl from SMEDDS was independent of pH dissolution medium.

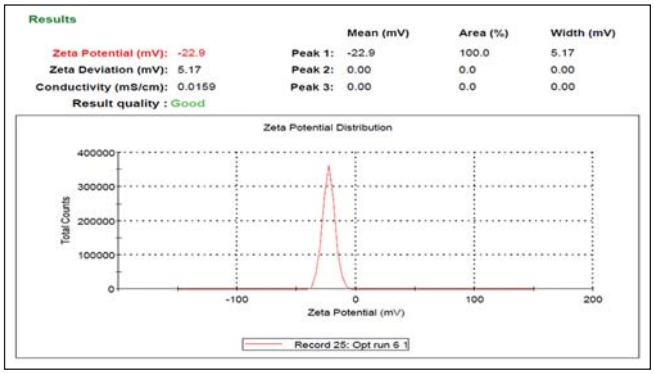

Figure 3: Zeta potential of pioglitazone HCl SMEDDS F4 formulation

SEM

Liquid SMEDDS micrographs suggesting that the drug is present in a completely dissolved state in the SMEDDS. From Figure 5, it was concluded that, the particle are globular, uniform in size, and well-separated. There was no agglomeration and globule size is in the nanometer scale.

Stability study

At the end of stability study, no phase separation and drug precipitation was observed in SMEDDS formulations. The drug content at the end of stability study for various SMEDDS formulation ranges from 99.04 to 99.58%.

CONCLUSION

SMEDDS preparations of pioglitazone HCl were successfully prepared using Capmul MCM C8 and oleic acid (2:1) as oil phase, Cremophor RH 40 and Tween 80 (3:1) as surfactant phase, and Transcutol P as cosurfactant phase. Liquid SMEDDS were filled in the HGC shell and it was found to be compatible. Based on *in vitro* dissolution studies, it was concluded that the pioglitazone HCl SMEDDS with optimum concentration

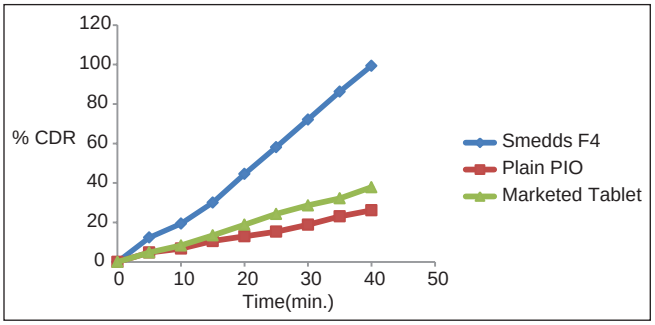

Figure 4: *In vitro* % cumulative drug release (%CDR) study of marketed tablet, plain drug, and SMEDDS formulation in acid buffer pH 2

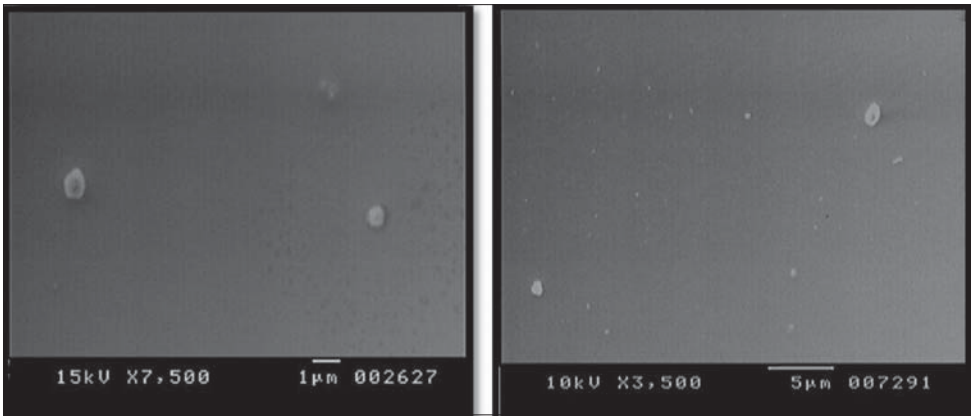

Figure 5: Liquid scanning electron microscopy (SEM) images of pioglitazone F4 SMEDDS formulation

of oil and surfactant showed complete and faster dissolution profile as compared to marketed formulation of pioglitazone HCl (ACTOS 15 mg tablet). pH independent dissolution profile of SMEDDS compared to ACTOS tablet may definitely improve the oral bioavailability of pioglitazone HCl with reduced dose and variability.

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