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Development of self micro emulsifying drug delivery system: Application to pimozide delivery

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ABSTRACT

The objective of the present investigation was to formulate self micro emulsifying drug delivery system (SMEDDS) of Pimozide and was achieved by using Capmul MCM NF as oily phase, Cremophor RH 40 as Surfactant and PEG-8000 as Co-Surfactant. Pimozide loaded SMEDDS were characterized with respect to Visual Assessment, Phase Separation, Emulsion Droplet Size, Pseudoternary Phase Diagram, HLB Determination, Assessment of Self-Emulsification Efficiency, Drug content and In- vitro dissolution study in comparison with ORAP® 2 mg tablet manufactured by TEVA Pharmaceuticals USA. Prepared Pimozide loaded SMEDDS showed excellent self-emulsification efficiency and released more than 90% of the drug in 45 minutes whereas ORAP® showed about 45% drug release. The mean globule size of optimized Pimozide SMEDDS was 29.39 nm.

Keywords: Pimozide, Self Micro Emulsifying Drug Delivery System (SMEDDS), Lipid based drug delivery system.

INTRODUCTION

Lipid-based formulation approaches, particularly the Self Micro Emulsifying Drug Delivery System (SMEDDS), is well known for its potential as an alternative strategy for delivery of hydrophobic drugs, which are associated with poor water solubility and low oral bioavailability [1, 2]. To overcome such problem, in recent years, much attention has been focused on lipid based formulation with particular emphasis on SMEDDS. SMEDDS formulations are isotropic mixtures of an oil, surfactant, co-surfactant and co-solvent along with drug. The basic principle of this system is its ability to form fine oil-in-water (O/W) micro emulsions under gentle agitation following dilution by aqueous phase. This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. Apart from solubilization, the presence of lipid in the formulation further helps in improving bioavailability by effecting the drug absorption [3, 4]. Pimozide, a diphenylbutylpiperidine derivative having chemical name 1-[1-[4,4-bis(4-fluorophenyl)butyl]-4-piperidinyl]-1,3-dihydro-2H-benzimidazole-2-one, is a white powder, insoluble in water and slightly soluble in most organic solvents and is having a molecular weight of 461.56, molecular formula of $C_{28}H_{29}F_2N_3O$ and melting range of pimozide is 216°C - 220°C. It is lipid soluble and is mainly soluble in vegetable oils. It is an antipsychotic drug for treating schizophrenia and chronic psychosis. Pimozide is a Biopharmaceutical Classification System (BCS) Class II drug with a low dose number [17]. The aim of the present work was to develop, evaluate and optimize SMEDDS of Pimozide, and to compare the in vitro drug release of the

optimised formulation with ORAP® (Pimozide) 2 mg, Tablets, marketed by TEVA Pharmaceuticals USA. Since Pimozide is practically insoluble in water with high lipid solubility and elimination half life of 55 hours; By increasing the aqueous solubility, the drug will be more bioavailable thereby the daily dose of the drug can be reduced and the patient compliance can be improved through once daily dosing.

MATERIALS AND METHODS

Materials

Pimozide was obtained from Anthem Biosciences Bangalore. Capmul MCM NF was obtained from Abitec Corporation, USA; Gelucire 44/14 (PEG-32 Glyceryl Laurate and Polyglycolyzed Glycerides) was obtained from Gattefosse France; Cremophor RH 40 (PEG 40 Hydrogenated Castoroil (Or) Poloxyethylene Castoroil Derivatives) was obtained from BASF Germany; Polyethylene Glycol 8000 was obtained from Dow Chemical USA; Labrasol (Polyoxyglycerides) was obtained from Gattefosse France; Transcutol P (Diethylene Glycol Monoethyl Ether) was obtained from Gattefosse France; Orap® 2 mg (Pimozide) Manufactured by: TEVA Pharmaceuticals USA; Size "1" Hard gelatin capsules Shells was obtained from ACG Associated Capsules Private Limited Mumbai.

Instruments

Magnetic Stirrer: Make - Remi, Mumbai; Thermostat: Make – Remi, Mumbai; Ultrabath Sonicator: Make – Crest, Germany; Micropipette (100-1000 micro liter): Make – Microlit, India; Weighing Balance: Make – Sartorius, Germany; High Performance Liquid Chromatography UV- Visible detector: Model-2695 Make Waters; Dissolution Test Apparatus (XXII) (USP Type –I Basket): Make – Electrolab, India; pH Meter: Model 330, Make – Thermo sciences, USA; Malvern Zetasizer ver. 7.02: Make- Malvern Instruments ltd, UK. Waters HPLC pump equipped with Waters 2489 UV/VIS detector, Redone 7725 injector (Redone, U.S.A.), Empower Chromatography Software (Version 2) integrator software, Inerstil ODS-3V 250×4.6 mm 5.0µ particle size column

Methods

Preparation of Pimozide SMEDDS Formulation

SMEDDS was prepared by mixing 2 mg of Pimozide with oil in a screw-capped glass vial under sonication until the entire drug was completely dissolved. The surfactant was then added to the drug-oily mixture. The vial was placed in a magnetic stirrer platform at 50°C-60°C to facilitate solubilization under stirring, then co-surfactant was added to drug-oil-surfactant mixture and vortex mixed using a magnetic stirrer at 50°C-60°C to obtain a clear, uniform solution, the formulation was then equilibrated at room temperature for at least 48 hrs and examined for signs of turbidity (or) phase separation prior to self micro-emulsification and particle size studies. See Table 1 for further details.

Table: 1 Formulation Trials

Name of the Ingredient		Quantity 352 mg / capsule												
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Pimozide	Drug (mg)	2	2	2	2	2	2	2	2	2	2	2	2	2
Capmul MCM NF	Oil Phase	50	50	50	50	100	100	50	50	50	50	50	50	50
Labrasol	Surfactant	100	200	250	200	200	-	-	-	150	-	-	-	-
Gelucire 44/14	Co-Surfactant	200	100	50	-	-	50	100	50	-	100	-	-	-
Cremophor RH 40	Surfactant	-	-	-	-	-	200	200	250	-	150	250	200	150
PEG 8000	Co-Surfactant	-	-	-	100	50	-	-	-	100	-	50	100	150
Transcutol P	Co-Solvent	-	-	-	-	-	-	-	-	50	50	-	-	-

Filling and Banding of capsules

352 mg of prepared SMEDDS formulations was poured into size 1 (one) hard gelatin capsules. The hard gelatin capsules were banded with 2% W/W aqueous solution of gelatin, which is applied as thin layer on the top inner side of the cap using finer brush and joined tightly by manual pressing. Each capsule represents 2 mg of Pimozide in addition to the specified amount of oil, surfactant, co-surfactant and co-solvent. Filled capsules were stored at room temperature for 24 hrs and observed for any leakage of capsule contents before being used for subsequent studies [5, 6].

Solubility Studies

The solubility of Pimozide in various oil, surfactant, co-surfactant and co-solvent was determined. To 1 g of oil, surfactant, co-surfactant and co-solvent taken individually, Pimozide was added in increments of 1 mg from 1 mg to

25 mg in the screw - capped glass vials and the mixture was heated to 50ºC-60ºC in water bath to facilitate the solubilization and finally the sample was made into homogenous solution using Vortex mixer (or) ultra bath sonicator, these sample were assessed for turbidity, precipitation (or) cloudiness on standing for 7 days at room temperature.

HPLC analysis of Pimozide

The quantity of Pimozide solubilized in various vehicles was determined using HPLC method. The parameters were, mobile phase: Ammonium acetate buffer: Acetonitrile (35:65) at flow rate of 2.0 ml/min, detection at 210 nm in dissolution and 280 nm in assay method with retention time of 8.0 min.

Visual Assessment Test (Dilution Effect)

SMEDDS Formulations (352 mg) were diluted with 1, 25, 50, 100, 150 and 200 fold with pH 4.5 Acetate Buffer. The contents were then mixed gently with magnetic stirrer at room temperature. The tendency to emulsify spontaneously and also the progress of emulsion droplets were observed. The tendency to form an emulsion was judged as "good", when droplets spread easily in the medium and formed a fine milky emulsion and was judged 'bad' when there was poor (or) no emulsion formation with immediate coalescence of oil droplets, especially when stirring was stopped [6, 7].

Phase Separation Study

Each SMEDDS formulation (352 mg) was added to a screw capped glass vials containing 15 fold of pH 4.5 Acetate Buffer at room temperature. After 1 min vortex-mixing, each mixture was stored for a period of 2 hrs and visually the mixtures were observed for phase separation during 2 hour period; the mixtures that didn't showed phase separation were used in the subsequent study [7, 8].

Globule Size Analysis

The globule size of the emulsions was determined by dynamic light scattering (DLS) by monitoring at 25°C at a scattering angle 173° (Zetasizer ver.7.02, Malvern, UK), which measure size range between 6 nm to 0.6 µm. The nanometric size range of the particle was retained even after 100 times dilution with water which proves the compatibility of the system with excess water [7, 8]. Globule size of various formulations is shown in Table 10.

Zeta Potential

Zeta potential is used to identify the charge of the droplets. In conventional SMEDDS, the charge of an oil droplet is negative due to presence of free fatty acids. Zeta potential determined by Zetasizer was monitored at 25°C at a scattering angle 173° (Zetasizer ver.7.02), Malvern, UK). The results are shown in Table.10.

Pseudo Ternary Phase Diagram

A small amount of Water was added drop by drop to the vials containing 352 mg of Pimozide SMEDDS (Pimozide) formulations. Following each water addition, the mixtures in vials were vortex mixed and the mixture was titrated with water until it turned turbid (or) cloudy. The volume of water used was recorded; Water titration was continued till the mixture turned clear and transparent, and the water volume was recorded. The resulting mixture was evaluated by visual observation. Clear, transparent and isotropic solution forming region is micro emulsion. Visibly cloudy region is dispersion. As to particle size, it is generally held that micro emulsion (Clear) have particle size below 150 nm, while emulsions (Visibly cloudy) are in the range of 150 - 1000 nm [9, 10].

HLB Determination

The HLB value of SMEDDS formulation can be determined by following formula.

HLB blend of mixtures = **(A×PA/100) + (B×PB/100) + (C×PC/100)**

A, B, C → HLB value of Oil, Surfactant and Co-Surfactant respectively.
PA, PB, PC → Percentage of Oil, Surfactant and Co-Surfactant respectively.

Assessment of Self Micro Emulsification Efficiency

The efficiency of self micro emulsification was assessed using a standard USP XXIII dissolution apparatus type 2. 352 mg of each formulation was added to 200 ml of pH 4.5 acetate buffer at 37°C, gentle agitation was provided by

a standard stainless steel dissolution paddle rotating at 100 rpm, the lipid based formulation were assessed visually according to the rate of emulsification and the final appearance of the emulsion.

The in-vitro performance of the formulation was visually assessed using the following grading system.
A. Denoting a rapidly forming Micro-emulsion with clear appearance.
B. Denoting a rapidly forming slightly less clear emulsion.
C. Denoting a bright white emulsion (similar in appearance to milk)
D. Denoting a dull white emulsion with a slightly oily appearance that was slow to emulsify.
E. Denoting a formulation which exhibited either poor (or) minimal emulsification with larger oil droplets present on the surface [11].

In -Vitro Dissolution Studies of Pimozide SMEDDS Formulation
Standard Stock Preparation
Weigh accurately and transfer about 40.0 mg of Pimozide WRS/RS into a 100 ml volumetric flask. Add about 70 ml of methanol and sonicate to dissolve. Then dilute to volume with methanol and mix well. Pipette out 5 ml of the above solution and dilute to 100 ml volumetric flask with dissolution medium and mix well. Then pipette out 5 ml of the above solution and dilute to 50 ml of volumetric flask with dissolution medium and mix well. The standard preparation concentration of Pimozide 2µg/ml. [12, 16]

Sample Preparation
In-Vitro release studies were performed using USP XXIII Basket Method Type I Apparatus at 100 rpm, 900 ml of pH 4.5 Acetate buffer and the temperature was maintained at 37°C ± 0.5°C. Samples were taken at intervals of 10, 20, 30 and 45 min. 10 ml of sample was taken and 10 ml of fresh media was replaced at each sampling time, the samples were taken with a glass syringe after filtered through 0.45 µm PTFE filters and the filtered samples were measured by high performance liquid chromatography. The sample preparation have a concentration of 2.2 µg/ml of Pimozide for capsule strength of 2 mg [12, 16].

Assay of Pimozide by HPLC Method
Diluents Preparation
Mix 500 ml of Methanol and 500 ml of Tetrahydrofuran in a suitable container, degas through sonication for about 5 minutes

Internal Standard Solution Preparation
Weigh accurately 250 mg of 3, 4-dimethylbenzophenone transfer in to a 250ml volumetric flask. Add about 150 ml of diluents and sonicate to dissolve. Dilute to volume with diluents and mix well. (Internal standard preparation, concentration of about 1000 µg/ml)

Standard Preparation
Weigh accurately and transfer about 24.0 mg of Pimozide into a 50 ml Volumetric flask. Add 10 ml of internal standard solution. Add 20 ml of diluent and sonicate to dissolve. Dilute to volume with diluent and mix well. (Standard preparation, concentration of about 480 µg/ml of Pimozide)

Test Preparation
30 capsules were accurately weighed, liquids were removed from the capsules and the average weight was determined, SMEDDS liquid equivalent to 12 mg of Pimozide was weighed accurately and transferred into a 25 ml volumetric flask. It was dissolved in 5 ml of internal standard solution. Add about 10 ml of diluents and sonicate for 10 minutes. Dilute to volume with diluents and mix well. Centrifuge a portion of the above solution at 3500 rpm for 10 minute.

Filter the supernatant liquid through a 0.45µm PVDF filter by discarding the first 4 ml of the filter. (Sample preparation, concentration of about 480µg/ml of Pimozide)

Procedure
Inject the standard and test preparation and record the chromatograms at 280 nm and calculate the assay of Pimozide [16].

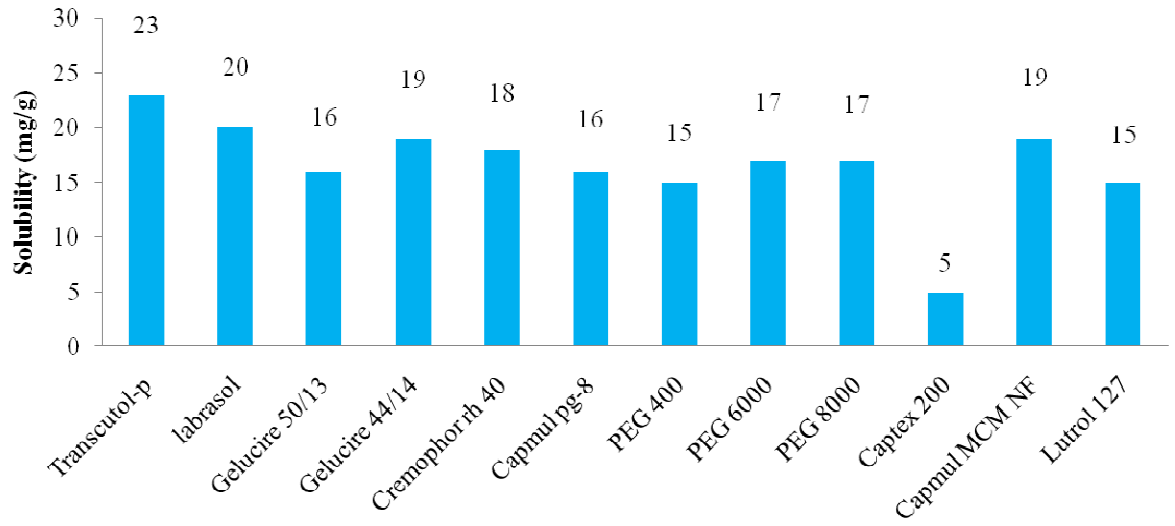
Calculation
Ratio of Pimozide peak area response to the internal standard peak area response

$$= \frac{\text{Pimozide Peak Area}}{\text{Internal Standard Peak Area}}$$

RESULTS AND DISCUSSION

Solubility Studies
Pimozide SMEDDS formulation design involves determination of solubility in various Oil, Surfactant, Co-Surfactant & Co-Solvent and also involves the maximum volume of the final product that could be reasonably encapsulated in hard gelatin capsules. However, in absolute terms Pimozide was less soluble in long chain glycerides compared with medium chain glycerides having C8-C12 numbers. The self micro-emulsifying formulation consisted of one or more surfactants apart from the drug dissolved in oil. The mixture should be a clear, monophasic liquid at ambient temperature and should have good solvent properties to allow presentation of the drug in the solution. The results of the solubility studies of Pimozide in various surfactant, co-surfactant, co-solvent and oils are shown in Table 2. The data indicated that the solubility is related to the hydrophilicity of oil (or) oil surfactant mixture (hydrophilic systems) resulting in greater solubility values. Moreover the components used are soluble in each other and form homogenous liquids. See Figure 1 for further details.

Figure: 1 Solubility Data of Pimozide in Various Oil, Surfactant, Co-Surfactant and Co-Solvent



Visual Assessment Test
SMEDDS form fine oil in water emulsions with gentle agitation upon their introduction into aqueous media. Since the free energy required to form an emulsion is very low, the formation is thermodynamically spontaneous. Surfactant in the system form a layer around the emulsion droplets and hence reduce the interfacial energy as well as providing a mechanical barrier to coalescence. The visual test is a measure of an apparent spontaneity of emulsion formation. A series of SMEDDS were prepared and their self micro-emulsifying properties were observed visually (Table 3, 4, 5 & 6) Visual observations indicated that at higher levels of surfactant, the spontaneity of the self micro-emulsification process was increased. This may be due to excess penetration of water into the bulk oil causing massive interfacial disruptions and ejection of droplets into the bulk aqueous phase. When a co-surfactant is added

to the system, it lowers the interfacial tension, fluidizes the hydrocarbon region of the interfacial film, and decreases the bending stress of the interface. It was reported that when a self micro-emulsified system is diluted by the aqueous phase, various mesomorphic phases are absorbed between the formulation and the water. A delay in the progress of emulsion formation may be due to the time required for the transformation from one liquid crystalline structure to another during the first stages of the disruption process. On the other hand, addition of co-surfactant increase the interfacial fluidity by penetrating into the surfactant film creates void space among surfactant molecules and facilitates the progress of emulsion formation. The inclusion of a greater proportion of surfactant resulted in clearer emulsion and lower emulsion sizes; the emulsification properties appear to be highly dependent on composition, with higher HLB oil and surfactant systems in combination with high co-surfactant content resulting in smaller droplets See Formulation 11, 12 & 13. The surfactant may have the effect of enhancing the solubility of the drug and smaller emulsion droplet possibly due to reverse micelle formation.

Table: 2 Solubility Profile of Pimozide

Solubilizing Excipients	Maximum solubility Initial, mg/g	Maximum solubility after 7 Days, mg/g	Observation for 7 days
Transcutol-P	23	23	Clear
Labrasol	20	20	Clear
Gelucire 50/13	16	16	Clear
Gelucire 44/14	19	19	Clear
Cremophor RH 40	18	18	Clear
Capmul PG-8	16	16	Clear
Polyethylene glycol 400	15	15	Clear
Polyethylene glycol 6000	17	17	Clear
Polyethylene glycol 8000	17	17	Clear
Captex 200	5	5	Colour change
Capmul MCM NF	19	19	Clear
Poloxamer 407 (Lutrol Micro 127)	15	15	Clear

Table: 3 Visual Assessment Tests For SMEDDS Formulation (F1, F2, F3 & F4)

Dilution Media	pH 4.5 Acetate buffer			
Formulation	**F-1**	**F-2**	**F-3**	**F-4**
Dilution (in time)	Clear	Turbid	Clear	Clear
1 in 25, 50, 100, 150, 200	Turbid, cloudy and thick milky white colloidal precipitate	Thick milky white colloidal precipitate	Transperant Solution	Turbid, Milky white solution
Phase Separation	Yes	No	No	No
HLB value	12.86	12.86	12.86	14.57
Pseudo Ternary Phase Diagram	Particle settled at the bottom	Turbid - 100µl, Not clear on further dilution	Oil like transparent solution	Turbid - 100µl, Not clear on further dilution

Table: 4 Visual Assessment Tests For SMEDDS Formulation (F5, F6 & F7)

Dilution Media	pH 4.5 Acetate buffer		
Formulation	**F-5**	**F-6**	**F-7**
Dilution (in time)	Clear	Clear	Clear
1 in 25, 50, 100, 150, 200	Turbid, cloudy and thick milky white colloidal precipitate	Transparent solution	Transparent solution
Phase Separation	No	No	No
HLB value	12.54	12.29	13.43
Pseudo Ternary Phase Diagram	Turbid- 100µl, Not clear on further dilutions	Oil like transparent solution	Oil like transparent solution

Table: 5 Visual Assessment Tests For SMEDDS Formulation (F8, F9 & F10)

Dilution Media	pH 4.5 Acetate buffer		
Formulation	**F-8**	**F-9**	**F-10**
Dilution (in time)	Clear	Turbid	Clear
1 in 25, 50, 100, 150, 200	Turbid, cloudy and thick milky white colloidal precipitate	Turbid, cloudy and thick milky white colloidal precipitate	Transparent solution
Phase separation	Yes	No	No
HLB value	13.57	13.14	11.86
Pseudo Ternary Phase Diagram	Particle settled at the bottom	Turbid - 100µl, Not clear on further dilution	Oil like transparent solution

Table: 6 Visual assessment tests for SMEDDS Formulation (F11, F12, F13)

Dilution Media	pH 4.5 Acetate buffer		
Formulation	**F-11**	**F-12**	**F-13**
Dilution (in time)	Clear	Clear	Clear
1 in 25, 50, 100, 150, 200	Translucent Solution and Glossy Micro emulsion	Translucent Solution and Glossy Micro emulsion	Translucent Solution and Glossy Micro emulsion
Phase Separation	No	No	No
HLB value	14.57	15.14	15.86
Pseudo Ternary Phase Diagram	Turbid - 0.1 ml, Clear and translucent - 0.8 ml maintained upto 250 ml	Turbid - 0.1 ml, Clear and translucent - 1 ml maintained upto 250 ml	Turbid - 0.1 ml, Clear and translucent – 1.3 ml maintained upto 250 ml

Phase Separation Study

The results of the phase separation study of SMEDDS formulation were shown in Table 3,4,5 & 6. The data indicated that the phase separation did not occur in the Formulation 2, 3, 4, 5, 6, 7, 9, 10, 11, 12 & 13 but occurs in the Formulation 1 and 8.

Pseudo Ternary Phase Diagram

Pseudo ternary phase diagram was constructed to identify the self micro-emulsifying regions and to establish the optimum concentration of Oil, Surfactant and Co-surfactant. It was reported that the mechanism of self micro-emulsification involves erosion of a fine cloud of small droplets from the surface of large droplets, rather than progressive reduction in droplet size. Micro-emulsion preparation requires adjusting the HLB value of the formulation by including a co-surfactant, which makes the polar solvent less hydrophilic. The phase diagrams of the systems containing oil, surfactant, and co-surfactant are shown in Figure 2. The results indicate that the area of the micro-emulsion region increased in the system containing co-surfactant. Efficiency of emulsification was good when the surfactant concentration was more than 40%. It was observed that increasing the concentration of co-surfactant within the self micro-emulsifying region increased the spontaneity of the self-emulsification process. When co-surfactant is added to the system it further lowered the interfacial tension between the oil and water interface and also influences the interfacial film curvature, which thereby readily deforms around oil droplets. It can also be seen that formulation 13 with combined use of two surfactants appeared to have the largest region of micro-emulsion among the 13 formulations. This is evident in Pseudoternary phase diagram of Figure 2 where as much as 14.2% oil can be incorporated in the pre concentrate and be diluted into micro-emulsion. This is significant in the pre concentrate formulation development, as more oil in the composition help to solubilize poorly water-soluble drug in the pre concentrate; this is an important observation, suggesting that the combined use of surfactants is significantly more effective in generating micro-emulsions.

Figure: 2, Pseudo Ternary Phase Diagram for Optimized Formulation (F13)

Ingredients		Qty(µl)/ capsule	Percentage (%)
Capmul MCM NF	Oil phase	50	3.03
Cremophor RH 40	Surfactant	150	18.18
PEG- 8000	Co-Surfactant	150	
Water	-	1300	78.78
Pseudo Ternary Phase Diagram		Turbid-0.1 ml, Clear and Translucent-1.3 ml. Maintained upto 250 ml	

Assessment of the Efficiency of Self-Emulsification

The assessment of the efficiency of self-emulsification was adopted to evaluate the formulation in pH 4.5 Acetate Buffer. Table 7 & 8 represents the results of the assessment of self micro-emulsification efficiency. The emulsification characteristics were observed when the formulations were dispersed in the pH 4.5 Acetate Buffer. The visual grading and emulsions formed on dispersion are shown in the Table 7 & 8. The SMEDDS formulation 11, 12 and 13 formed micro-emulsions which were visually graded A; SMEDDS formulation 1 and 8 formed emulsions which are turbid and less clear and were graded B; SMEDDS formulation 2, 4, 5 and 9 formed milky emulsion and were graded C; SMEDDS formulation 3, 6, 7 & 10 remained as unemulsified oily liquid and were graded E.

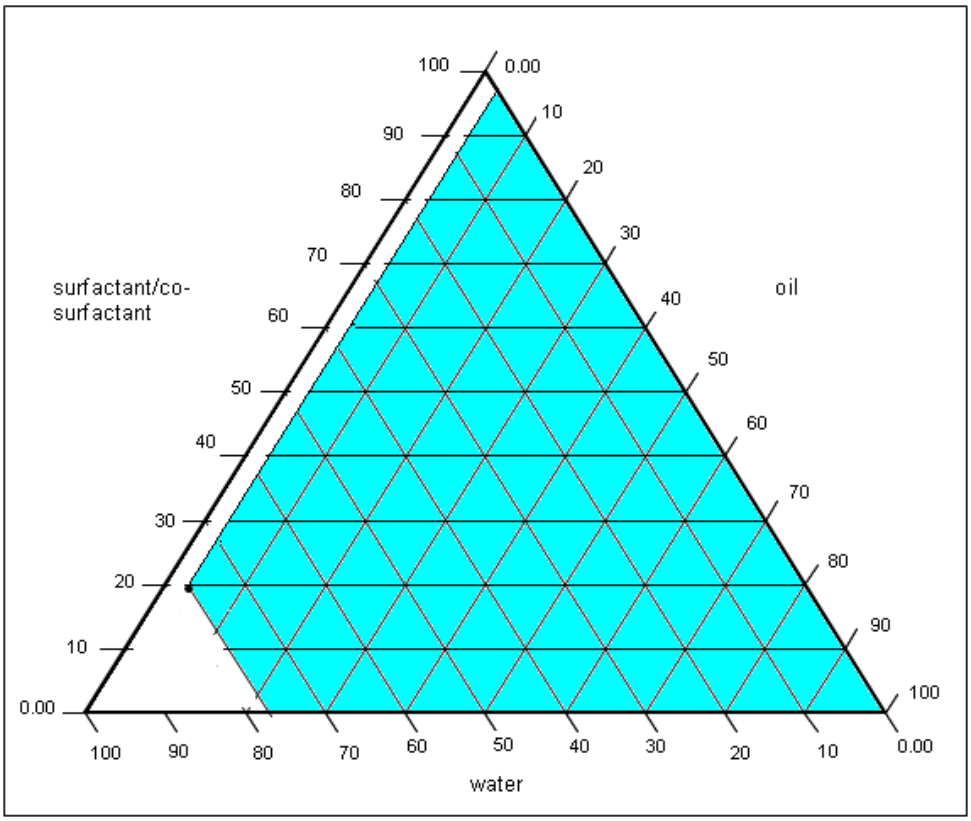


Table: 7 Assessment of Self-Emulsification Efficiency (Formulation F1, F2, F3, F4, F5, F6)

Formulation	F1	F2	F3	F4	F5	F6
Rate of Emulsification (min)	10	10	10	10	10	10
Final appearance of Emulsion	Turbid less Clear	Milky	Oily	Milky	Milky	Oily
Visual Grading System	B	C	E	C	C	E

Table: 8 Assessment of Self-Emulsification Efficiency (Formulation F7, F8, F9, F10, F11, F12, F13)

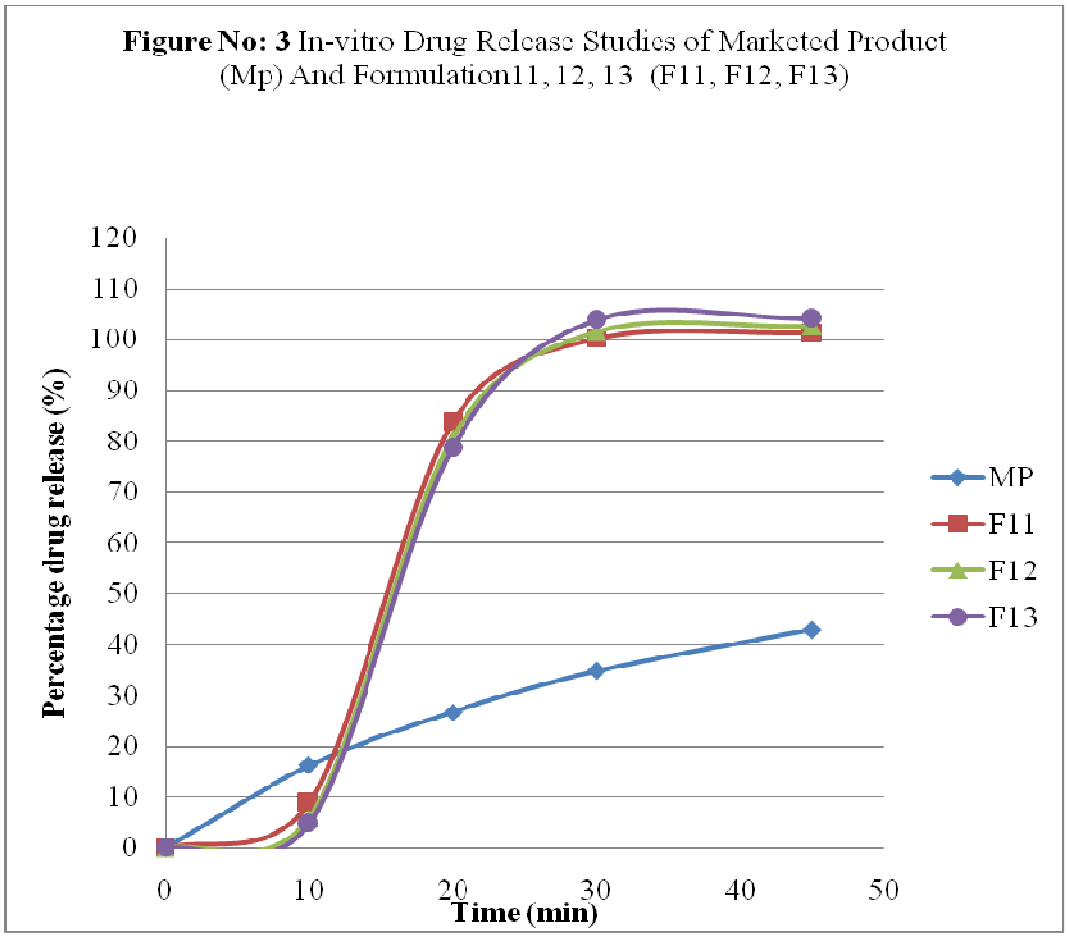
Formulation	F7	F8	F9	F10	F11	F12	F13
Rate of Emulsification (min)	10	10	10	15	5	5	4
Final appearance of Emulsion	Oily	Turbid less clear	Milky	Oily	Clear	Clear	Clear
Visual Grading System	E	B	C	E	A	A	A

In-Vitro Dissolution Study

In-Vitro drug release study was performed using USP-I (Basket) apparatus, 100 RPM, 900 mL of pH 4.5 Acetate buffer. The percentage release of Pimozide from Formulation 11, 12 & 13 was found to be more than 99% at the end of 45 minutes and 100% micelles was formed in Formulation l1, 12 and 13. These formulations showed clear transparent solution, broad micro-emulsion region, more percentage release of drug and less rate of emulsification (min). The dissolution profile of marketed product ORAP® (Pimozide) Tablets, 2 mg showed only 42.9% of drug release. As per the USFDA's Dissolution data base, dissolution profile for pimozide needs to be generated in 0.01N HCl medium. Pimozide is less soluble in pH 4.5 Acetate buffer and is a perfect discriminative dissolution medium to check on the dissolution enhancement. The dissolution results of Pimozide SMEDDS in comparison with marketed product ORAP® suggests that changing the concentration of oil, surfactant and co-surfactant in SMEDDS improved the solubility through in situ micro emulsion resulting in more release of drug in the discriminative dissolution medium. See Table 9 and Figure 3.

TABLE: 9 In-Vitro Drug Release Studies of Marketed Product (MP) and Formulation 11, 12 and 13

TIME	% Drug Dissolved			
	Marketed Product (ORAP® 2 mg Tablet)	Formulation-11	Formulation-12	Formulation-13
10	16.2	8.9	5.8	4.8
20	26.7	83.7	80.5	78.6
30	34.8	100.2	101.5	103.8
45	42.9	101.4	102.6	104.1
Medium: 900 mL of pH 4.5 Acetate Buffer Apparatus: USP-I (Basket), 100 RPM				



Drug Content Determination

Drug content was estimated for the optimized Pimozide SMEDDS formulation by HPLC method, and is within the limit of not less than 95% and not more than 105% in Formulation 11, 12 and 13.

Globule Size Distribution and Zeta Potential

The globule size and zeta potential was determined using Malvern Zetasizer. The average globule size was taken into consideration. The average diameters of vesicles were in nano size range. Droplet size distribution is one of the most important characteristics of emulsion for stability and *in vivo* absorption. Poly dispersity index (PDI) below 0.3 indicates good uniformity in the droplet size distribution after dilution with water. In this study the poly dispersity index below 0.3 was obtained for formulation 11, 12 & 13. The zeta potential of the liquid systems is of considerable importance from the stability point of view. In this study the zeta potential of formulation 11, 12 & 13 was less then –30, indicating good stability. See Table 10 and Figure 4 & 5.

Table.10 Globule Size, Polydispersity Index and Zeta Potential of Various SMEDDS

Formulation No	Average Globule size (nm)	Poly dispersity Index	Zeta Potential (mV)
13	29.39	0.261	-11.5

Figure No: 4 Emulsion Droplet Size Analysis of Formulation 11, 12 & 13

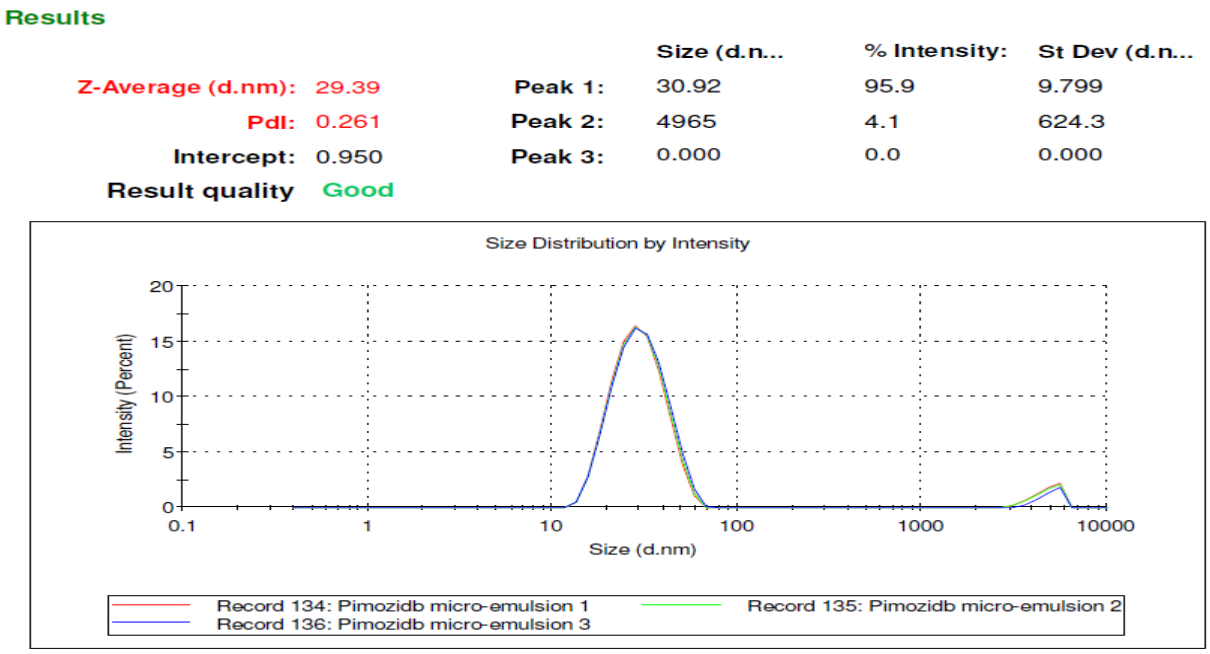
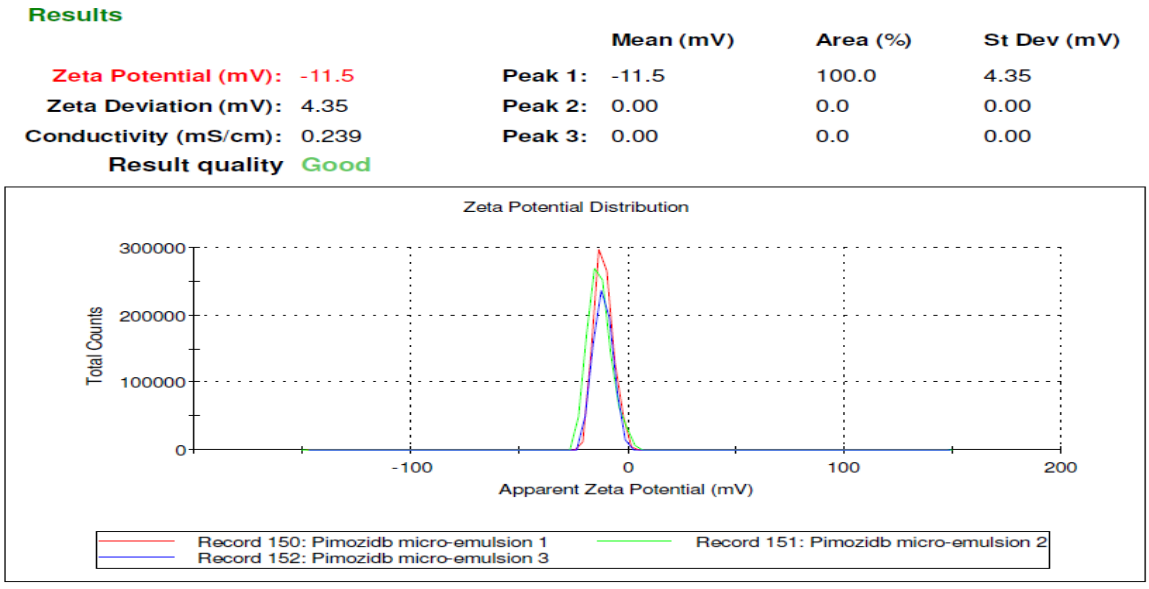


Figure No: 5 Zeta Potential of Formulation 11, 12 & 13



CONCLUSION

Pimozide SMEDDS was prepared using Capmul MCM NF as oil phase, Cremophor RH 40 as Surfactant and PEG-8000 as Co-Surfactant. Pimozide loaded SMEDDS were characterized with respect to Visual Assessment, Phase Separation, Emulsion Droplet Size, Pseudoternary Phase Diagram, HLB Determination, Assessment of Self-

Emulsification Efficiency, Drug Content and In- Vitro dissolution study in comparison with ORAP® 2 mg tablet manufactured by TEVA Pharmaceuticals USA. Prepared Pimozide loaded SMEDDS showed excellent self-emulsification efficiency and released more than 90% of the drug in 45 minutes whereas ORAP® showed about 45% drug release. The mean globule size of optimized Pimozide SMEDDS was 29.39 nm. The positive outcome of this research is Pimozide SMEDDS improved the solubility of drug which is evident from the drug release in discriminative dissolution medium (pH 4.5 Acetate Buffer). Hence we can expect a better in vivo bioavailability. Based on the bioavailability results, the daily dose of the drug can be reduced and patient compliance can be improved through once daily dosing for effective anti psychosis in treating Schizophrenia and Chronic psychosis.

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