

DEVELOPMENT AND CHARACTERIZATION OF FLUTAMIDE CONTAINING SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS)

*¹ANURADHA VERMA, ²MANISH K. SINGH, ¹BABITA KUMAR

¹Department of Pharmaceutical Sciences, Shree Ganpati Institute of Technology, Ghaziabad, U.P. India, 201302, ²Promed Research Centre, Gurgaon, Haryana, India, 122001. Email: anuradhampharm@gmail.com

Received: 11 April 2011, Revised and Accepted: 8 May 2011

ABSTRACT

The present work was aimed at formulating a SMEDDS (Self-microemulsifying drug delivery system) for oral drug delivery system containing flutamide. The solubility of flutamide was determined in various vehicles. Pseudo ternary phase diagram was constructed to identify the micro emulsification existence area. SMEDDS formulations were tested for microemulsifying properties, and the resultant formulations loaded with flutamide (ME1, ME2, ME3, ME4 & ME5) were investigated for clarity, phase separation, globule size and shape, zeta potential, effect of various diluents and dilutions, thermodynamic and thermal stability. From the results it is concluded that increase in droplet size is proportional to the concentration of oil in SMEDDS formulation. The optimized formulation's study was composed of Caproyl PGMC (50%), Cremophore RH 40 (37.5%) and PEG-300 (12.5%). Minor difference in the droplet size and zeta potential was observed by varying the diluents (deionized water and 0.1N HCl) and dilutions (1:10, 1:50 and 1:100). Formulations, which were found to be thermodynamically stable (ME1, ME2, ME3 & ME4), were subjected to stability studies as per International Conference on Harmonization (ICH) guidelines. No significant variations were observed in the formulations over a period of three months at accelerated and long-term conditions. TEM photographs of microemulsions formulations further conformed the spherical shape of globules. Among the various SMEDDS formulations, ME4 offer the advantages of good clarity systems at high oil content and thus offer good solubilization of flutamide. Thus this study illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds, such as flutamide by oral route.

Keywords: Flutamide, Antiandrogen, SMEDDS, Microemulsion

INTRODUCTION

It is generally accepted that many of today's New Chemical Entities (NCEs) are poorly water-soluble and pose a challenge in developing an optimum solid oral dosage form. Oral route has been the major route of drug delivery for the treatment of various chronic diseases like cancer. However, oral delivery of approximately 40% of the drug compounds is limited because of low aqueous solubility, which leads to limited oral bioavailability, high intra and inter subject variability and lack of dose proportionality. To overcome the above discussed drawbacks, various other formulation strategies have been adopted including the use of cyclodextrins, nanoparticles, solid dispersions and permeation enhancers^{1,2}. In recent years, much attention has focused on lipid-based formulations to improve the oral bioavailability of poorly water-soluble drug compounds³. In fact, the most popular approach is the incorporation of the drug compound into inert lipid vehicles such as oils and surfactant dispersions⁴, self-emulsifying formulations⁵⁻⁷ emulsions⁸ and liposomes⁹ with particular emphasis on self-microemulsifying drug delivery systems (SMEDDS)^{10,11}. Self micro-emulsifying drug delivery systems (SMEDDS) or self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co solvents/surfactants. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, form the droplets of emulsion (5-100 nm). Because of their unique solubilization properties SMEDDS offer the following advantages^{12,13}.

1. Bio-availability enhancement of poorly aqueous soluble drugs: SMEDDS offer the opportunity to present lipophilic drugs to the gastrointestinal tract in a dissolved state, avoiding the dissolution step (which can limit absorption rate of BCS Class 2 and 4 drugs).
2. Reduction in Inter-Subject and Intra-Subject Variability.
3. Reduction of Food Effect.
4. Ease of Manufacturing and Scale Up.
5. Ability to Deliver Peptides that are Prone to Enzymatic Hydrolysis in GIT.
6. No Influence of Lipid Digestion Process.

Flutamide (Figure-1) chemically (2-methyl-N-[4-nitro-3-(trifluoromethyl) phenyl] propanamide is a nonsteroidal pure antiandrogen that acts by inhibiting the uptake and/or binding of

dihydrotestosterone to the target cell receptor, thus interfering with androgen action. Flutamide is well absorbed orally and extensively metabolized; its active metabolite, 2-hydroxyflutamide, is formed rapidly and excreted almost entirely by the kidneys¹⁴.

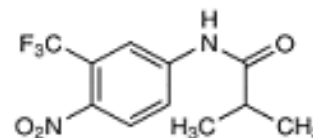


Fig. 1: Flutamide

Flutamide is practically insoluble in water (9.45 mg/L) and have high hydrophobicity (log P 2.6). Flutamide exhibits low bioavailability in various animal models at a single dose of 125 mg. Hence, flutamide was selected as a model drug for this study.

The aim of this study was to evaluate and characterize a system known to produce self- micro emulsifying drug delivery system (SMEDDS) containing poorly water soluble drug (flutamide) with special emphasis on:

1. The solubility in SMEDDS and solubilization capacity after dispersion;
2. The influence of flutamide on dispersion properties and particle size of the identified SMEDDS; and
3. Investigate whether dilution would have any effect on the particle size of the identified SMEDDS and if this was dependent on drug load.

In this study optimized SMEDDS formulation was characterized for various physicochemical parameters (like droplets size and size distribution, Zeta potential, Dilution studies, Morphology, Thermal and thermodynamic stability studies.

MATERIALS AND METHODS

Materials

Flutamide was obtained from Dabur Research Foundation (Ghaziabad, India). Cremophore RH40 (Polyoxyl 40 Hydrogenated Castor Oil) obtained from BASF (India), Tween 80 (Polyoxyethylene

sorbitan monooleate), Labrafil M1944 (Oleoyl macrogol glycerides), Labrafil M2125 (Linoleoyl macroglycerides), Labrafac Lipo (Medium chain triglycerides), PEG 300 (Polyethylene glycol), Lauroglycol FCC (Propylene glycol laurate), Plureol Oleique (Polyglyceryl oleate), Capryol 90 (Propylene glycol monocaprylate), Capryol PGMC (Propylene glycol caprylate) obtained from Gattefosse (Saint Priest, France). Soyabean oil, Olive acid, Castor oil, Iso-propyl Myristate (IPM) obtained from Loba Chem. All other analytical grade chemicals and solvents were purchased from Qualigens fine chemicals (Mumbai, India). All other chemicals and solvents were of analytical grade.

HPLC analysis of Flutamide

The concentration of flutamide was determined by HPLC method. The system consists of Agilent 1100 series with a UV detector. The chromatographic column was Zorbax Eclipse XDB C8 5 μ m, (150 mm and 4.6 mm i.d.) with 5 μ m particle size. The mobile phase (50:50) was acetonitrile and water at a flow rate of 0.5 mL/min and run time was 28.5 mins. A 20- μ L volume was injected into the system and the eluent was monitored at 240 nm. The retention time of flutamide was 19.0 \pm 0.05 min at ambient room temperature. The mean calibration curve was given by the equation-

$$Y = 26.1777X - 0.5930$$

with a correlation coefficient, $R^2 = 0.9999$, where Y represents area under the curve and X the concentration in μ g/mL. The method was validated for accuracy, precision, specificity & solution stability. Linearity curve of flutamide was demonstrated in figure 2.

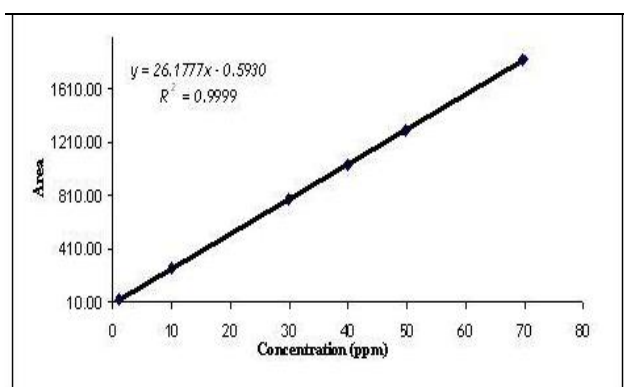


Fig. 2: Linearity curve of flutamide

Solubility studies

The solubility of flutamide in various vehicles i.e. oils, surfactant and co-surfactants were determined. An excess amount of flutamide was introduced into 2 mL of each vehicle and mixture was kept in a sealed vials. Vortex mixer (Heidolph Multi Reax) was used to facilitate the solubilization¹⁵. Sealed vials were stirred in a water bath (Julabo SW 23) at 37°C for 72 hours. After standing for 72 hours and reaching equilibrium, each vial was centrifuged at 15000 rpm for 10 min using a centrifuge (Eppendorf Centrifuge 5810). Undissolved flutamide was removed by filtering with a membrane filter (0.45 μ m). The concentration of dissolved flutamide was determined by HPLC method. Results of solubility studies were reported in (Table 1; Mean \pm S.D.; n = 3).

Construction of phase diagram

The construction of phase diagram makes it easy to find out the concentration range of components for the existence for SMEDDS. On the basis of solubility results non-ionic surfactant Cremophore RH 40 used as a surfactant in the formulation. PEG 300 and Capryol PGMC employed as a co-surfactant and oil phase, respectively. To determine the concentration of components for the existing range of SMEDDS, pseudo-ternary phase diagram was constructed using water titration method at ambient temperature. Surfactant was blended with co-surfactant in the ratio of 1:1, 1:2, 1:3, 1:4, 1:5 and

1:6, (i.e. Km w/w). For each phase diagram the ratio of oil to the S_{mix} was varied (1:9, 1:8.5, 1:8, 1:7.5, 1:7, 1:6.5, 1:6, 1:5.5, 1:5, 1:4.5, 1:4, 1:3.5, 1:3, 1:2.5, 1:2, 1:1.5, 1:1, 1.5:1 and 2:1). Deionized water was used as diluting medium and added in drop wise manner into the each Oil- S_{mix} pre-concentrate mixture under gentle shake condition at 37°C. For any mixture, the total of surfactant, co-surfactant and oil concentrations always added to 100%. After equilibrium, the samples were visually checked and determined as being clear microemulsions, or emulsions or gels. The percentage of surfactant, cosurfactant, oil and water used herein was decided on the basis of the requirements for the spontaneously emulsifying systems (16).

Table 1: Solubility results of flutamide in various vehicles

S.No.	Vehicle	Function in SMEDDS	Solubility (mg/mL)
01	Soyabean Oil	Oil	7.6 \pm 0.5
02	Castor Oil	Oil	12.9 \pm 0.7
03	Oleic Acid	Oil	9.1 \pm 0.9
04	Iso Propyl Myristate (IPM)	Oil	12.0 \pm 0.5
05	Labrafil M 2125	Oil	17.1 \pm 1.0
06	Labrafil M 1944	Oil	35.9 \pm 0.9
07	Labrafac Lipo	Oil	4.2 \pm 0.8
08	Capryol 90	Oil	42.5 \pm 0.8
09	Capryol PGMC	Oil	59.47 \pm 0.6
10	PEG 300	Co-surfactant	39.65 \pm 0.5
11	Lauroglycol FCC	Co-surfactant	23.24 \pm 0.8
12	Plureol Oleique	Co-surfactant	6.12 \pm 0.8
13	Cremophore RH 40	Surfactant	6.12 \pm 0.7
14	Tween 80	Surfactant	5.02 \pm 0.6

The pseudo-ternary phase diagrams of the formulation composed of Capryol PGMC, Cremophore RH 40 and PEG 300 is described in figure 3. Pseudo-ternary plot was constructed using Sigma Plot 10 software.

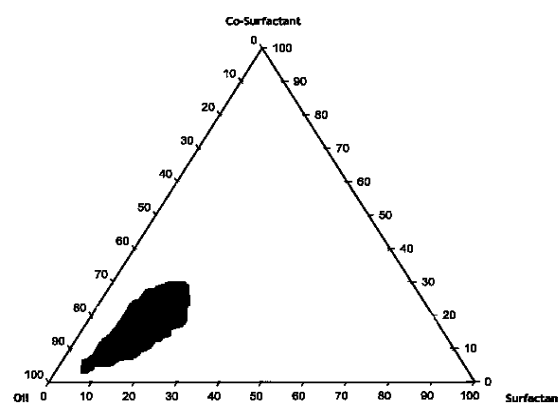


Fig. 3: Pseudo-ternary phase diagrams of the formulation

After being equilibrated, the efficiency of self-emulsification, dispersibility, and appearance and flow ability was observed according to the five grading systems shown in table 3. Above observations were recorded in table 4. By the investigation of pseudo ternary phase diagram, some optimal placebo formulations, containing various ratios of oil, surfactant and co-surfactant, were selected to develop flutamide loaded SMEDDS formulations.

Table 2: Composition and Content of flutamide in optimized SMEDDS Formulation

Composition	Quantitative Composition
Flutamide	125 mg
Cremophore RH 40	43.0 %
PEG 300	7.0 %
Capryol PGMC	50.0 %
Assay (By HPLC)	98.9 % \pm 1.20

Table 3: Visual assessment of efficiency of self-microemulsification

Grade	Dispersibility and appearance	Time of Self-micro emulsification
I	Rapid forming microemulsion, which is clear or slightly bluish in appearance	< 1 min
II	Rapid forming, slight less clear emulsion, which has a bluish white appearance	< 2 min
III	Bright white emulsion (similar to milk in appearance)	< 2 min
IV	Dull, grayish white emulsion with a slight oily appearance that is slow to emulsify	> 3 min
V	Exhibit poor or minimal emulsification with large oils droplets present on the surface	> 3 min

Table 4: Visual observation of SMEDDS formulation

Surfactant (S) Co-surfactant (Co-S) Lipophilic Phase (Oil) Oil to S _{mix} ratio	Surfactant/ Co-surfactant ratio (S _{mix})					
	1:1	1:2	1:3	1:4	1:5	1:6
	Cremophore RH 40					
	PEG 300					
	Caproyl PGMC					
1:9	III	II	I	I	I	I
1:8:5	III	II	I	I	I	I
1:8	III	II	I	I	I	I
1:7.5	III	II	I	I	I	I
1:7	III	II	I	II	I	I
1:6.5	III	II	I	I/II	I	I
1:6	III/IV	II	I	I	I	I
1:5.5	III/IV	II/III	II	I	I	I
1:5	III/IV	II/III	II	I/II	I/II	I
1:4.5	III	II/III	II	II	I/II	I
1:4	III	III	II/III	II	II	I/II
1:3.5	III/IV	III	II/III	III	II	II
1:3	III/IV	III	II/III	III	II	II
1:2.5	IV	III	II/III	III	II/III	II
1:2	IV	III	II	IV	II/III	II/III
1:1.5	V	III/IV	I/II	III	II/III	II/III
1:1	V	III	I/II	III	II/III	I/II
1.5:1	V	IV	II	IV	III	III
2:1	V	V	IV	V	IV	III

Preparation of Flutamide SMEDDS

Flutamide was added in the oily phase in small increment with continues stirring. The surfactant system was prepared by mixing separately the chosen surfactant and co-surfactant in their determined ratios. Flutamide containing oil solution was added in

the surfactant system solution with continuous stirring and vortex mixing. Continued the stirring till the homogenous mixture formed. Finally, the mixture was kept at 25°C. Flutamide loaded SMEDDS formulations (ME1, ME2, ME3, ME4 & ME5) were subjected to further characterization. Detailed compositions of SMEDDS formulations were summarized in table 5.

Table 5: Composition and assessment of SMEDDS formulations

Composition	Formulation (g)				
	ME1	ME2	ME3	ME4	ME5
Flutamide	125 mg	125 mg	125 mg	125 mg	125 mg
Caproyl PGMC	140 mg	200 mg	400 mg	500 mg	500 mg
PEG 300	260 mg	220 mg	170 mg	130 mg	200 mg
Cremophore RH 40	600 mg	580 mg	430 mg	370 mg	300 mg
Assessment of SMEDDS diluted with purified water					
Grade	I	I	I	I/II	I/II
Droplet size (After 0.5 hrs) nm	10.5	13.5	24.6	29.8	34.5
Polydispersity Index (After 0.5 hrs)	0.09	0.18	0.15	0.04	0.15
Zeta potential (After 0.5 hrs) mv	-0.8	-9.1	-0.5	-0.6	-8.4
Droplet size (After 24 hrs) nm	12.8	16.3	29.5	30.9	36.5
Polydispersity Index (After 24 hrs)	0.03	0.07	0.31	0.27	0.10
Zeta potential (After 24 hrs) mv	-1.1	-9.9	-1.5	-1.9	-9.2
Assessment of SMEDDS diluted with 0.1N HCl					
Grade	I	I	I	I/II	II
Droplet size (After 0.5 hrs) nm	13.5	14.7	23.5	28.5	35.5
Polydispersity Index (After 0.5 hrs)	0.08	0.05	0.11	0.26	0.17
Zeta potential (After 0.5 hrs) mv	-2.5	-7.8	-3.1	-8.6	-6.5
Droplet size (After 24 hrs) nm	16.1	15.8	25.6	30.5	37.8
Polydispersity Index (After 24 hrs)	0.13	0.15	0.08	0.03	0.34
Zeta potential (After 24 hrs) mv	-2.9	-7.8	-1.6	-11.8	-4.1

Flutamide content in SMEDDS formulation

Content of Flutamide was determined by the HPLC method described in solubility studies. Result of assay is shown in (Table 2).

Determination of droplets size distribution and zeta potential

The droplet size, size distribution and zeta potential were analysed by dynamic light scattering with particle size apparatus (Malvern Zetasizer 3000 HS). Flutamide SMEDDS were diluted with deionized water and 0.1N HCl in a drop-wise manner at 25°C under gentle

shaking. After equilibrium droplet size and zeta potential were recorded in table 5.

Dilution studies

Dilution may better mimic conditions in the stomach following oral administration of SMEDDS pre-concentrate. Dilution study was done to access the effect of dilution on SMEDDS pre-concentrates. In this study selected formulations were subjected to various dilutions (i.e.1: 10, 1:50 & 1:100) with various diluents (i.e. deionized water, 0.1N HCl) and the visual observation were recorded in table 6.

Table 6: Observation of dilution studies

S. No.	Formulation Code	Caproyl PGMC (%)	PEG 300 (%)	Cremophore RH40 (%)	Dilution with Water			Dilution with 0.1N HCl		
					1:1	1:50	1:100	1:1	1:50	1:100
01	ME1	14.0	26.0	60.0	I	I	I	I	I	I
02	ME2	20.0	22.0	58.0	I	I	I	I	I/II	I/II
03	ME3	40.0	17.0	43.0	I	I/II	I/II	I/II	II	II
04	ME4	50.0	13.0	37.0	I	I	I	I	I/II	I/II
05	ME5	50.0	20.0	30.0	I/II	I/II	II	II	I/II	I/II

Thermodynamic stability studies of flutamide SMEDDS

The objective of thermodynamic stability is to evaluate the phase separation and effect of temperature variation on SMEDDS formulations. Flutamide SMEDDS were diluted with aqueous medium and centrifuged at 15000 rpm for 15 minutes and formulations were observed visually for phase separation. Phase separation was observed in ME5 sample. Formulations were subjected to freeze thaw cycles (-20°C for 2 days followed by +40°C for 2 days) (17). No change in the visual description of samples after freeze-thaw cycles. Formulations, which are thermodynamically stable, were selected for further characterization.

Transmission electron microscopy

From the results of thermodynamic stability studies four formulations (i.e. ME1, ME2, ME3 & ME4) were selected for morphological characterization using transmission electron microscopy (TEM). Transmission electron microscope (TEM) (Philips CM12 Electron Microscope, Eindhoven, Netherlands) was used as a visualizing aid. SMEDDS formulations were diluted with water (1/100). A drop of the diluted microemulsion was directly deposited on the holey film grid and observed the morphology of formulations figure 4 (a, b, c, d).

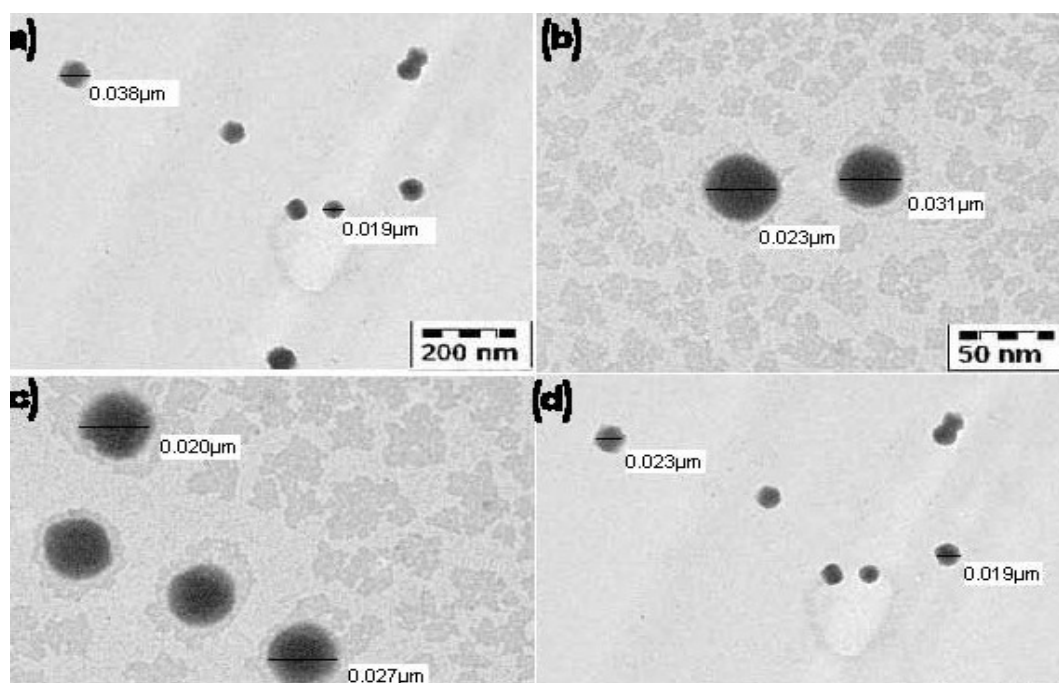


Fig. 4: Morphology of formulations (a, b, c, d)

Table 7: Observation of thermodynamic stability studies

S. No.	Formulation Code	Freeze-thaw	Centrifugation
01	ME1	No phase separation	No phase separation
02	ME2	No phase separation	No phase separation
03	ME3	No phase separation	No phase separation
04	ME4	No phase separation	No phase separation
05	ME5	No phase separation	Phase separation

Stability studies

Formulations, which were found to be thermodynamically stable, were subjected to stability studies. Samples of stability studies were charged on $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60 \pm 5\%$ RH (Newtronics stability chamber) and $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75 \pm 5\%$ RH (Newtronics stability chamber). Samples were subjected to stability studies for three months period. Observations of stability studies were recorded in the table 7.

RESULTS

Solubility of flutamide in various oils was determined by HPLC method. Since the flutamide exhibit maximum solubility in Capryol PGMC than other oils, Capryol PGMC was selected as an oil phase for flutamide SMEDDS formulation. Considering the safety and biocompatibility of the excipients, the selected system, known to produce SMEDDS consist of a nonionic surfactant (Cremophore RH 40), propylene glycol caprylate (Capryol PGMC) and Polyethylene Glycol (PEG 300) was selected for the development of flutamide SMEDDS. Pseudo-ternary plot was constructed by using Capryol PGMC, Cremophore RH 40 and PEG 300 as presented in the figure 3. Formation of microemulsion systems was observed at room temperature.

Microemulsion region that contains the oil component approximately 10-50% resulting in an extensive microemulsion region of SMEDDS. From this region five different ratio of Oil/S/Co-S were selected. In the selected pre-concentrate mixture flutamide was incorporated and the formulations (ME1, ME2, ME3, ME4 & ME5) were subjected to further characterization. The effect of concentration of oil on the droplet size was investigated after SMEDDS formulations were dispersed with deionized water at 25°C . The droplet increased from 10.5 nm to 34.5 nm, when the concentration of oil added increased from 12.4% to 44.4%. ME1, with the highest proportion of surfactant (53.3 % w/w), had the lowest mean particle diameter. This could be attributed to an increased surfactant proportion relative to co-surfactant. To investigate the effect of the dispersing medium on zeta potential, SMEDDS formulations were dispersed with deionized water and 0.1N HCl, respectively. Minor difference in zeta potential was observed between the two dispersing media at the same dilution. Composition and detailed assessment of optimized formulations are summarized in table 4.

The influence of increasing the dilution factor from (1:10, 1:50 and 1:100) was evaluated; larger dilutions may better mimic conditions in the stomach following oral administration of SMEDDS (pre-concentrate). In all cases, increased dilution resulted in the microemulsion remaining with the same clarity. Thermodynamic stability of formulations is directly proportional to content of surfactant (Cremophore RH 40) in the formulation. ME5 formulation of flutamide, which contains 26.67% of Cremophore RH 40, found to be thermodynamically unstable. Formulations that found to be thermodynamically stable were considered for further characterization. Samples of flutamide SMEDDS were charged on accelerated and long term stability conditions. Chemical and visual observations of samples were shown in table 6. No significant change in the drug content in the formulations was observed over the period of three months at accelerated and long-term stability conditions. However flutamide SMEDDS demonstrate insignificant difference in the particle size and polydispersity results when diluted with deionized water and 0.1N HCl.

The morphology of microemulsion was examined with a transmission electron microscope. The droplet on the microemulsion appears dark with the bright surroundings. TEM photographs [figure 4 (a, b, c, d)] further conformed that the globules are spherical in shape.

DISCUSSION

SMEDDS is a homogenous mixture of lipids, surfactants and co-surfactants, which get emulsified on contact with aqueous phase under gentle agitation. It is considered that the excipients in the SMEDDS could enhance the dissolution and permeability of drug by significantly decreasing the droplet size. To develop an optimum self-emulsifying formulation (SMEDDS), it is very important to

evaluate (a) the drug solubility in various components; (b) area of self-emulsifying region in the phase diagram; (c) and distribution of droplet size¹⁸. The components used for developing a SMEDDS formulation should have high solubilization capacity for the drug, ensuring maximum solubilization of drug in the resultant dispersion. Self-microemulsifying systems form fine oil-water emulsions with only gentle agitations, upon their introduction into aqueous media. Surfactant and co-surfactant get preferentially absorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decreases in the free energy required for the emulsion formation consequently improve the thermodynamic stability of the microemulsion formulations. The efficiency of self-emulsification of surfactant and co-surfactant is much related to their hydrophilic-lipophilic balance (HLB) value. Generally surfactants with HLB 12-15 are regarded as being of good efficiency for self emulsification¹⁹. The construction of Pseudo-ternary phase diagram makes it easy to find out the concentration range of components for the existence range of SMEDDS. Phase behavior investigation of this system demonstrated the suitable approach to determining an optimum oil, surfactant and co-surfactant ratio with which transparent microemulsion system was formed. An increase in the ratio of the oil phase (Capryol PGMC) resulted in a proportional increase in particle size, because of the simultaneous decrease in the S/CoS proportion. Increasing the S/CoS ratio led to a decrease in mean droplet size. It is well known that the addition of surfactants to the microemulsion systems causes the interfacial film to stabilize and condense, while the addition of co-surfactant causes the film to expand; thus, the relative proportion of surfactant to co-surfactant has varied effects on the droplet size. Thermodynamic stability study was designed to identify and avoid the metastable SMEDDS formulations. In thermodynamic stability studies, formulations selected were subjected to different stress tests like centrifugation and freeze-thaw test. If the SMEDDS formulations are stable in this condition, metastable formulations thus avoided and frequent tests need not to be performed during storage.

CONCLUSION

An optimized flutamide loaded formulation consisting of Capryol PGMC (35.55% w/w), Cremophore RH 40 (38.22%), PEG 300 (15.11%) offers the advantage of good clarity systems at high oil content and thus should offer good solubilization of flutamide. Thus our studies conformed that SMEDDS can be used as a possible alternative to conventional oral formulation of flutamide. Results further conclude that SMEDDS can be explored as a potential drug carrier for dissolution enhancement of flutamide and other lipophilic drug.

ACKNOWLEDGEMENT

The authors would like to thank Gattefosse (Saint Priest, France) and GPS Pharma (Delhi, India) for providing the excipients for this study.

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