WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 11, 530-542. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF SMEDDS CONTAINING EBUXOSTAT BY EMPLOYING COCONUT OIL AND LABRASOL AS OIL AND SURFACTANT SYSTEM

P. Tripura Sundari* and P. Mounika

India.

Article Received on
03 April 2018,

Revised on 24 April 2018,
Accepted on 14 May 2018,

DOI: 10.20959/wjpr201811-11662

***Corresponding Author**
P. Tripura Sundari
India.

ABSTRACT

Solubility is the important process for most of the drug to solubilize in a given solvent to give homogenous solution. The greater the solubility of drug, the greater will be the systemic dissolution showing desired pharmacological response. New techniques have been developed to improve the solubility rate of poorly soluble drugs. Solid dispersion, Complexation, Particle size reduction, co-solvency, etc. Among which, a recent approach lipid base formulations (SMEDDS) are attracting the formulation scientists. These lipid based formulations include SMEDDS, SNEDDS. SMEDDS are nothing but the emulsion containing oil, surfactant, co-surfactant and drug which form oil in water emulsion upon mild agitation with aqueous phase. In the present study SMEDDS containing febuxostat, a BCS class II drug is formulated. As febuxostat is insoluble in water, lipid based formulations SMEDDS are developed by employing coconut oil as lipid phase, Tween 80, PEG400, Labrasol were selected as surfactant mixture. The better formulations were selected based on the evaluation parameters like drug content, %transmittance, drug release studies.

KEYWORDS: SMEDDS (self micro emulsifying drug delivery system), Febuxostat, Labrasol, Ternary diagram.

INTRODUCTION

Oral drug delivery is the most common route used to deliver drugs. Drugs which are highly soluble/hydrophilic can be easily delivered by oral route which increase the bioavailability of drug in body. Drugs which are lipophilic offer least advantage because of their low aqueous.[1-4] solubility. Various solubility enhancement techniques like solid dispersion, complexation, salt formation of drug, co-solvency, use of surfactants etc., are employed to

improve the solubility and bioavailability of poorly aqueous soluble drugs. Each of this technique provides some disadvantages.

Oral delivery of poorly water soluble drugs using lipid as vehicle is a new and recent approach. Lipid based formulations are such as liposome, solid lipid nanoparticle, self-emulsifying administration of lipids along with lipophilc drugs offer better advantages by increasing the bioavailability of drugs and prolongs the GI residence time of drug.

Among the various lipid based formulation self-emulsifying formulations are receiving greater attention by formulation scientist as they are effect in hydrophobic drug delivery, increased stability, self-dispersing nature, ease of scale up.[5-8] These systems are developed by using a lipid carrier which improves the gastro intestinal absorption of poorly water soluble drugs, allows the drug to remain in dissolved state by protecting the drug from enzymatic reaction, thermodynamically stable, easily manufactured and suitable for oral drug delivery. Compounds used in this system include oil, surfactant, and co-surfactant.

The function of oil in this system is to solubilize the lipophilic drug in order to improve the drug loading and bioavailability. Medium chain triglycerides are most commonly used[9-14] as they are resistant to precipitation. Hydrophobic drugs are easily solubilized in oil. As solubility is limited in oils, micro emulsification of oil and surfactant is employed which enhances the drug solubility in oils. Enhancement of drug solubility primarily depends on factors such as efficiency and rapidity to micro emulsify the selected oil, solubility of drug in surfactant. Nonionic surfactants are commonly preferred in formulation as they have less[15-21] CMC value, they are less toxic, provides a greater emulsion stability over a wide range of pH and ionic strength. Concentration of co-surfactant plays a major role in lipid based formulation. Selection of surfactant and co-surfactant is necessary for the solubilization of drug. Organic solvents such as ethanol, propylene glycol, polyethylene glycol are suitable for oral drug delivery.

MATERIALS AND METHOD

Materials

Febuxostat is obtained as gift sample from Sun pharma, Labrasol is gift sample from gatefosse, coconut oil, Tween 80, PEG 400, MCC pH 102, HPMC E15, and all other ingredients used are of pharmacoepial standards.

Solubility study

The solubility of febuxostat is checked in various compounds like oil, surfactants, and co-surfactants respectively. Excess amount of drug was added in each test tube containing 5ml of solvent, the test tubes were placed in orbital shaker for 48hrs to achieve solubility equilibrium. The supernatant was separated and filtered through a membrane filter to remove the undissolved drug. Solubility of Febuxostat was determined by analyzing the filtrate at 315nm.

Construction of ternary phase diagram

Phase behavior of each SMEDDS is studied carefully by using the phase diagram. It is one of the important characteristics of SMEDDS to show the changes when the system is diluted, which may cause drug precipitation. Therefore, phase behavior of each SMEEDS should be carefully studied. Based on solubility shown by drug in different ratios of surfactants the ternary diagrams were developed.

Formulation of SMEEDS of Febuxostat

Based on ternary diagrams, a series of formulations were prepared by using different ratios of oil: S_{mix}. The formulations were stored at room temperature until further use.

Table 1: Different formulations prepared with different ratios of oil: S_{mix}

Formulation	S_{mix} (PEG400:Labrasol)	Oil: S_{mix}
CL1	1:1	1:1
CL2		2:1
CL3		1:2
CL4	1:2	1:1
CL5		2:1
CL6		1:2
CL7	2:1	1:1
CL8		2:1
CL9		1:2

Characterization

Characterization of SMEDDS

SMEDDS pre-concentrate equivalent to dose of drug was diluted with diluted with distilled water. This micro emulsion was taken for in vitro characterization.

Appearance

Appearance of all the formulation SMEDDS (CL1-CL9) was tested visually against white and black background.

Conductance

The electro conductance of resultant micro emulsion system was measured by using conductivity meter (CM 180, ELICO). Each measurement was carried out in triplicate.

%Transmittance

The percentage transmittances of samples (CL1-CL9) are measured by using colorimeter (CL 223 colorimeter, ELICO).

Emulsification of samples

To assess emulsification properties of prepared formulations (CL1-CL9) each formulation was introduced into a 250ml glass beaker containing distilled water at room temperature and contents were agitated gently. The tendency to form clear or transparency emulsion is considered as good, when the formation was poor or milky in appearance then it is considered as bad emulsion.

Stability studies

The stability of lipid based formulation is essential for its performance, which can be adversely effected by the precipitation of drug. In addition formulations having poor stability leads to phase separation affecting the formulation performance and visual appearance. Stability studies of formulations are performed by heat cooling, centrifugation, and freeze thaw cycle.

1. Heat cooling cycle

Six cycles were carried out between 40˚c to 45˚c. In between these temperatures, formulations were stored not less than 48hrs. The formulations which are stable at these temperatures are subjected to centrifugation.

2. Centrifugation

The formulations which passed through above test are centrifuged at 3500rpm for 30min. The formulations that did not show phase separation were taken for freeze thaw test.

3. Freeze thaw cycle

Freeze thaw cycles were carried out between -20˚c to +25˚c. Formulations are stored at each temperature not less than 48hrs.

Droplet size analysis particle size measurements

The droplet size of emulsions were determined by using zetasizer which is able to measure sizes between 10 and 500 nm. Light scattering is monitored at 25˚c at a 90˚ angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the systems compatibility with excess water.

Zeta potential

The charge of the oil droplets in conventional SMEDDS is negative due to presence of free fatty acids. The zeta potential values were determined by using Zetasizer.

Preparation of solid SMEDDS

The prepared SMEDDS are converted into solid dosage forms by adding excipients like MCC pH 102 and HPMC E15 the resultant mixture is weighed and filled in hard gelatin capsule. These are stored for further analysis.

Drug content

The formulated SMEDDS equivalent to 40mg of drug is taken and dissolved in methanol and the resultant sample with proper dilutions are checked for their absorbance in UV (UV-Visible spectrophotometer S164) at 315 nm and percent drug content is calculated.

Uniformity weight of capsule

Fill the capsule shell with formulation (CL1-CL9). Weight of individual capsule should be noted and average weight was calculated. Not more than two individual weight deviate from average weight.

In vitro dissolution rate study

In vitro dissolution rate study of all the prepared formulations (CL1-CL9) containing 40mg of dug febuxostat was performed by using USP dissolution apparatus II (paddle) (USP TDL-14L dissolution tester, electro lab). Phosphate buffer of pH6.0 was used as dissolution media maintained at 37˚c and 75rpm. 5ml of aliquots were withdrawn at specific time intervals and the same amount of fresh buffer was replaced to maintain sink conditions. The collected

aliquots were analyzed for drug content at 315nm using UV-Visible spectrophotometer (UV S164). The test was performed in triplicate. The prepared formulations (CL1-CL9) were compared with the marketed product (uloric 40) of febuxostat, with respect to drug release.

RESULTS AND DISCUSSION

Solubility study

The solubility studies of febuxostat in different compounds.

Table 2: Solubility of drug in different surfactant.

S.No.	Solvent(ml)	Amount of drug dissolved(mg)
1	Coconut oil	48
2	PEG 400	42
3	Tween 80	44
4	labrasol	20
5	Arachis oil	49
6	labrafac	23

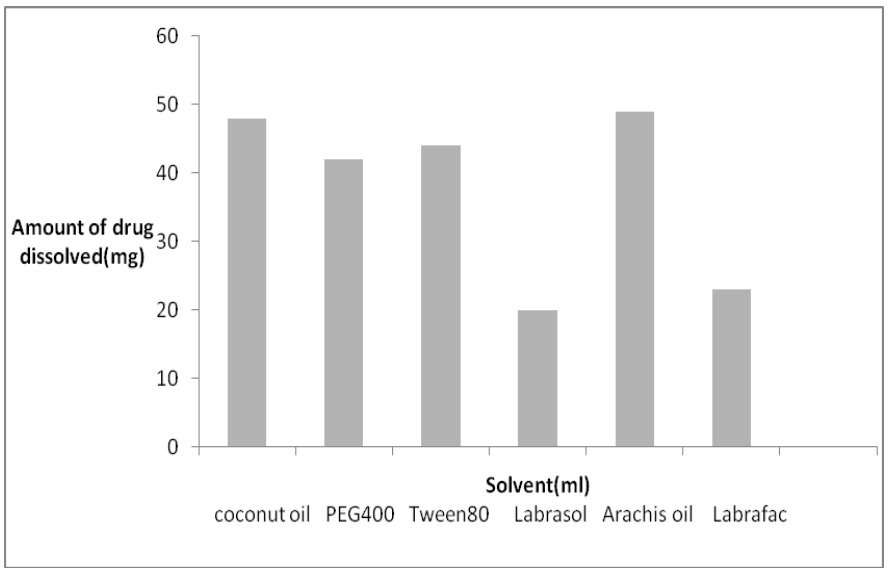

Fig 1: Solubility profile of Febuxostat in various surfactant and co-surfactant.

Solubility study of febuxostat in various compounds

The solubility of drug was checked in various compounds and the values ranges from 23-48mg/ml. Based on solubility studies coconut oil was selected as oil phase. Tween 80 PEG 400 and labrasol selected as surfactant and co-surfactant further the ratios of surfactant: co-surfactant was fixed from solubility data obtained from the studies of different ratios of surfactant: co-surfactant.

Table 3: Solubility of drug in different ratios of surfactant and co-surfactant(S mix).

S.No.	S: Co S(S_{mix})	Amount of drug dissolved (mg)
1	1:1	38
2	1:2	40
3	1:3	15
4	1:4	21
5	2:1	33
6	3:1	18
7	4:1	19

From the above study 1:1, 1:2 and 2:1 were selected further for formulation of SMEDDS

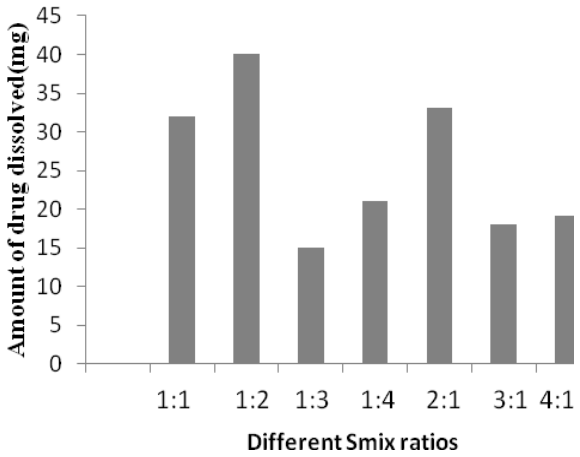

Fig. 2: solubility profile of drug in different S mix ratio.

The solubility studies of febuxostat in different ratios of Smix were carried out and it was clear from the studies that 1:1, 1:2, 2:1 ratio of Smix has shown better solubility of drug when compared to other ratios.

Construction of ternary phase diagram

Oil, water and S_{mix} were taken as each apex of ternary graph and ternary diagrams were constructed separately for each group to identify the micro emulsion region.

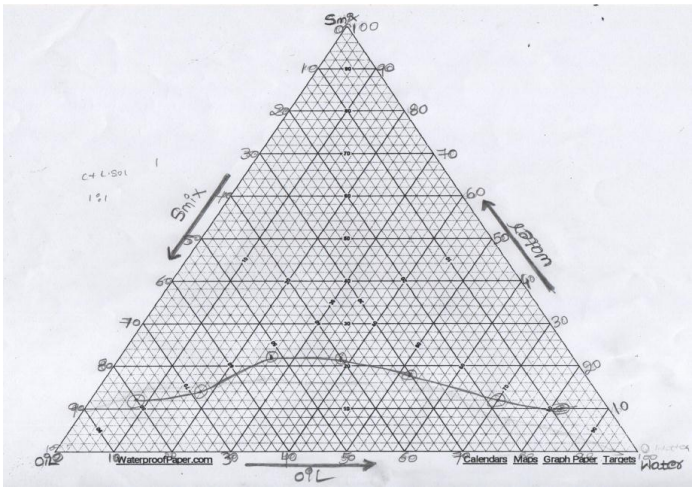

Fig. 3a: Ternary phase diagram of 1:1 ratio of coconut oil:Smix (labrasol: PEG 400) and water.

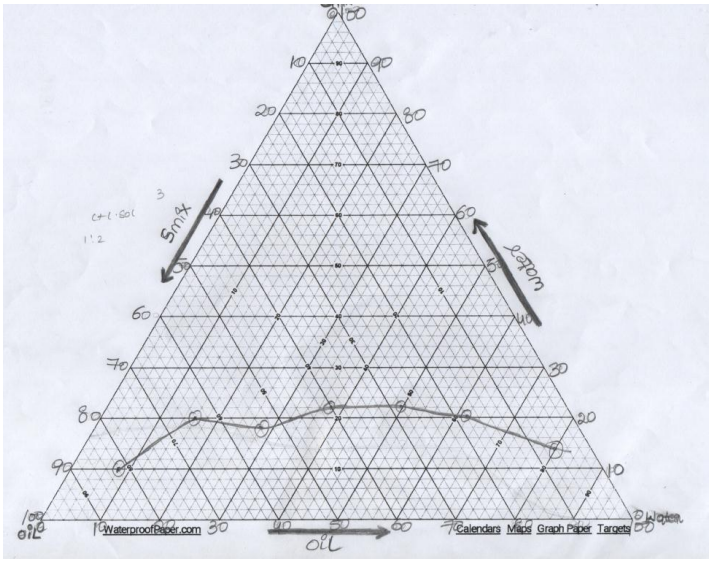

Fig. 3b: Ternary phase diagram of 1:2 ratio of coconut oil: s mix (labrasol:PEG 400) and water.

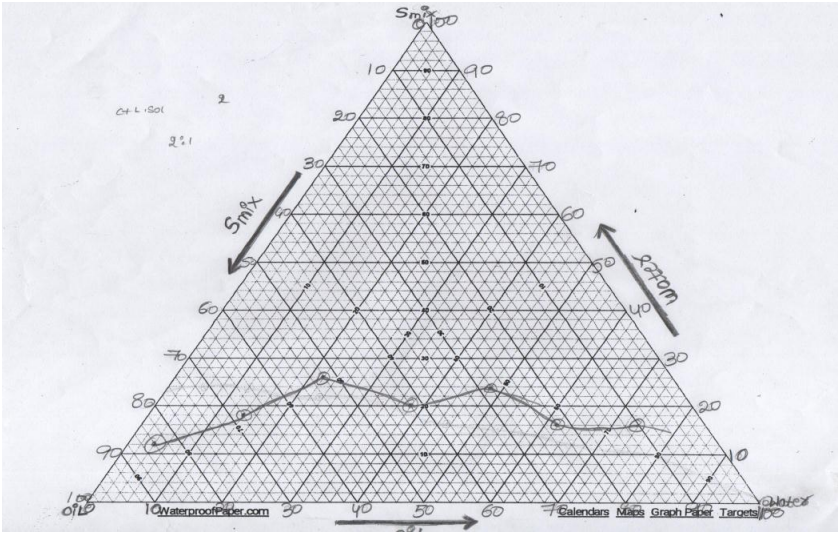

Fig. 3c: Ternary phase diagram of 2:1 ratio of coconut oil: s mix (labrasol:PEG 400) water.

From the above ternary diagrams, we can select the better emulsification zone for each ratio of S mix without getting the drug precipitated out of each system.

Characterization of SMEDDS

Appearance

At the end of 24 hrs the emulsions were visually inspected for clarity, phase separation and precipitation of drug.

Table 4: Assessment of physical compatibility by visual observation of prepared formulation.

S. No.	Formulation	Phase separation	Clarity
1	CL1	Not observed	cloudy
2	CL2	Not observed	opaque
3	Cl3	Not observed	cloudy
4	CL4	Not observed	turbid
5	CL5	Not observed	clear
6	CL6	Not observed	cloudy
7	CL7	Not observed	cloudy
8	CL8	Not observed	clear
9	CL9	Not observed	opaque

CLF5 and CL8 were observed to be clear after 24 hrs. whereas other formulations were either cloudy or opaque in physical appearance which may due to drug precipitation.

Conductance

Presence of oil in water emulsion formulation was confirmed by measuring conductivity. All SMEDDS are water continuous emulsion systems, some decrease in conductance were due to presence of oil droplets showing resistance to conductance and so decrease in conductance was observed.

Table 5: Electro conductivity of SMEDDS containing Febuxostat.

S.No.	Formulation	Conductance(us/cm)
1	CL1	40
2	CL2	43.2
3	CL3	41.6
4	CL4	46.2
5	CL5	59.4
6	CL6	41.0
7	CL7	48
8	CL8	59.2
9	CL9	46.6

The conductance values for all prepared formulations were ranging from(CL1-CL9) 40-60, among which CL5,CL8 were showing higher conductance (59.4,59.2).

Percentage transmittance

The clarity of micro emulsions was checked by transparency in terms of percentage transmittance (%T).

Table 6: Transmittance of SMEDDS containing Febuxostat.

S. No	Formulations	Transmittance (%T)
1	CL1	54
2	CL2	56.2
3	CL3	48
4	CL4	64
5	CL5	96
6	CL6	61
7	CL7	56.7
8	CL8	96.1
9	CL9	57

The % transmittance for all the formulations ranging from (CL1-Cl9) 53-97.1, and the formulations CL5, CL8 were showing higher values (96, 97.1).

Characteristics of solid SMEDDS

Drug content

The drug content of Febuxostat SMEDDS formulation was measured by using UV-Visible spectroscopic method. (UVS164).

Table 7: Drug content values of prepared formulations.

S. No.	Formulations	Drug content(%W/W)
1	CL1	91
2	CL2	93.4
3	CL3	92
4	CL4	95.2
5	CL5	98
6	CL6	89
7	CL7	91.1
8	CL8	98.4
9	CL9	94.2

The drug content values for all prepared formulations were ranging from (CL1-CL9) 91-98.5, among which CL5, CL8 showing high drug content(98, 98.4).

Uniformity of weight of capsule

Uniformity weight of capsule was determined for all formulations. The value of average weight of capsule range from 525.7-527.5mg. The weight variation was observed within acceptable limit i.e., less then ±7.5% capsule as per IP 2007.

In vitro dissolution studies

In vitro dissolution studies have been performed on all formulations (CL1-CL9) and drug release is observed. Among all CL5 and CL8 had shown 101 and 102% of drug release which are comparatively higher than the other formulations.

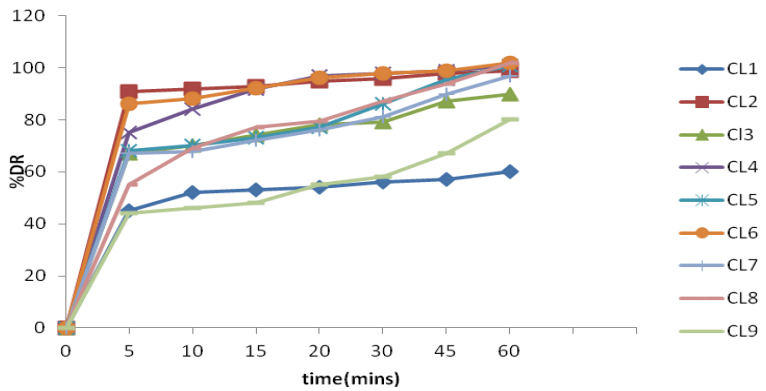

Fig. 4: Dissolution profile of all the prepared SMEDDS containing Febuxostat.

The formulation batches CL5, CL8 are compared with marketed product and pure drug (febuxostat) with respect to drug dissolution profile.

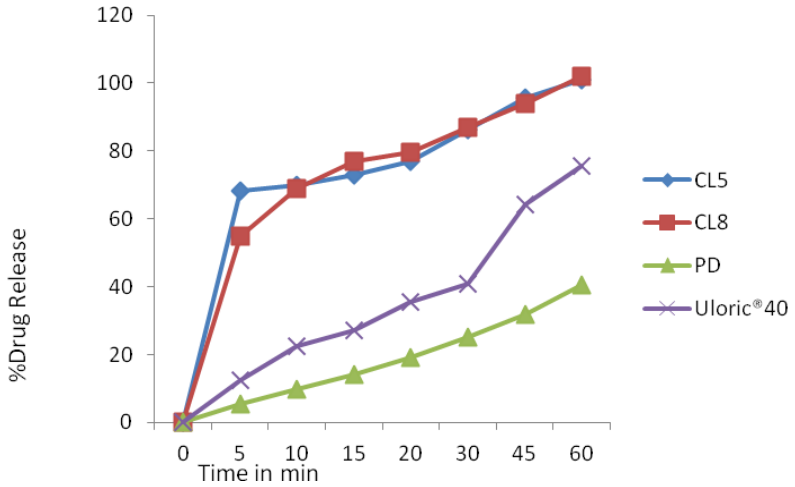

Fig. 5: Comparison of finalized formulations with marketed preparation and pure drug.

The formulations CL5 and CL8 were compared with marketed preparation (uloric) and pure drug. The prepared formulations had shown very high dissolution studies than the marketed product and pure drug.

CONCLUSION

In this study, the SMEDDS of febuxostat were prepared using coconut oil, labrasol, PEG 400. Based on ternary phase diagrams PEG 400, labrasol were selected as surfactant, co-surfactant respectively. The ratios of surfactant, co-surfactant was fixed based on solubility studies. Among all the prepared formulations CL5, CL8 were showing better drug content values, %transmittance and conductivity values, further the drug release values also proved that among all the formulations CL5, CL8 are showing better profile, these formulations were compared with marketed formulation with respect to drug release data. Hence from all the studies carried out SMEDDS of febuxostat can be successfully prepared by using oil, smix (PEG 400: labrasol) to improve its solubility profile.

REFERENCES

1. Adhvait R. Dixit, sadhana J. Rajput, “preparation and bioavailability assessment of SMEDDS containing valsartan” AAPS Pharm Sci Tech, 2010; 11(1): 314-21.
2. Chaudhary A, Nagaich U, Gulati N, Sharma V and Khosa R, “Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review.” J. Adv. Pharm. Edu. Res., 2012; 2(1): 32-67.

3. Kang J, Dong H, Chul Y and Han G, "Effects of solid carriers on the crystalline properties, dissolution and bioavailability of flurbiprofen in solid self nano emulsifying drug delivery system (solid SNEDDS)." Eur. J. Pharm. Biophrm., 2012; 80: 289–297.
4. Kumar S, Gupta S and Sharma P, "Self-emulsifying drug delivery systems for oral delivery of lipid based formulations - A review." African J. Bas. Appl. Sci., 2012; 4(1).
5. Kalhapure R, Krishnacharya G and Kamanchi A, "Oleic acid based heterolipid synthesis, characterization and application in self-microemulsifying drug delivery system." Int. J. Pharm., 2012; 425: 9-18.
6. Mittal P, Rana AC, Bala R, Seth N, Lipid based self microemulsifying drug delivery system (smedds) for lipophilic drugs: an acquainted review. Int Res J of pharm, 2011; 2(12).
7. Mistry R and Sheth N, "A review: Self emulsifying drug delivery system." Int.J.Pharm. Pharm. Sci. 2011; 3(2): 23-28.
8. Nekkanti V, Karatgi P, Prabhu R and Pillai, "Solid self-microemulsifying formulation for Candesartan Cilexetil." AAPS Pharm. Sci. Tech., 2010; 11(1): 9-17.
9. Pouton CW, "Lipid formulations for oral administration of drugs "Nonemulsifying, self emulsifying and self-micro emulsifying drug delivery systems."Eur. J. Pharm. Sci. 2000; (11): 93-98.
10. Patil RV, Patil KK, Mahajan VR, Dhake AS, "Self emulsifying therapeutic-a review".Int J of pharma. Bio Archives, 2012; 3(3): 481-486.
11. Kim, C. K., Ryun, S.A., Park, K.M., Lim, S. J., Hwang, S. J., Int J Pharmaceutics. 1997; 147: 131-4.
12. Khoo, S. H., Humber stone, A. J., Porter, C. J. H., Edwards, G. A., Charman, W. N., Int J Pharmaceutics., 1998; 167: 155- 164.
13. Kim, H. J., Yoon, K. A., Hahn, M., Park, E. S., Chi, S. C., Drug Dev and Ind Pharm., 2000; 26(5): 523-5224.