



SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM OF LOPERAMIDE HYDROCHLORIDE TABLET

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ABSTRACT

Loperamide hydrochloride is a common antidiarrheal drug and due to its poor aqueous solubility absorbed very slowly and erratically after oral administration. To enhance its solubility, dissolution rate self microemulsifying drug delivery system (SMEDDS) was formulated and evaluated. The solubility of loperamide hydrochloride was determined in various vehicles. Pseudoternary phase diagrams were evaluated for microemulsification existence area, and the release rate of loperamide hydrochloride was investigated using an *in vitro* dissolution test. SMEDDS formulations were tested for microemulsifying properties and the resultant microemulsions were evaluated for clarity, precipitation and particle size distribution. Formulation development and screening was done based on results obtained from phase diagrams and characteristics of resultant microemulsion. The optimized formulation was studied for *in vitro* study and was found that the formulation containing Labrafac CC (28.5%), Tween 60 (53.64%) propylene glycol:ethanol (1:1) showed a complete release in 30 minutes as compared with the pure drug which showed a limited dissolution rate. The stability studies found that the formulations were stable over period of 3 months. Thus the study confirmed that the SMEDDS formulation can be used as a possible alternative to traditional oral formulation of loperamide hydrochloride to improve its solubility and dissolution rate.

Keywords:

Self microemulsifying drug delivery systems; Loperamide hydrochloride; Pseudoternary phase diagram.

INTRODUCTION

Approximately 40 percent of new drug candidates have poor water solubility and such drugs when given orally show low bioavailability, high intra subject variability, and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficiency. Various approaches used to increase bioavailability include the use of cyclodextrins, liposomes, nanoparticles, solid dispersion, micronisation, permeation enhancers, lipid solution and **Microemulsions** have received attention for their potential as drug delivery vehicles due to advantages like excellent thermodynamic stability, longer shelf-life, high solubilisation capacity, improvement in oral bioavailability and protection against enzymatic hydrolysis. However, poor palatability due to lipidic composition leads to poor patient compliance and acceptability.

SMEDDS is an isotropic mixture of an oil, a surfactant, a co-surfactant (or solubiliser) and a drug which forms fine o/w micro emulsion, when introduced into aqueous phase under gentle agitation. The digestive motility of stomach and intestine provide the agitation necessary for self micro emulsification *in vivo* (Patel AR and Vavia PR 2007). SMEDDS is a novel approach to improve the water solubility and ultimately bioavailability of lipophilic drugs. The ability of SMEDDS to form spontaneous emulsion in the gastrointestinal tract presents the drug in a solubilised form, and the small size (1- 100nm) of the formed droplets provides a large inter- facial surface area for drug absorption through the intestinal aqueous border layer and through the absorptive brush border membrane leading to improved bioavailability. SMEDDS is not influenced by lipolysis, emulsification by bile salts, action of pancreatic lipases and mixed micelle formation.

SMEDDS are not digested before the drug is absorbed hence it has no influence of lipid digestion process (Patel AR and Vavia PR 2007). SMEDDS requires very simple and economical manufacturing facilities and therefore it is the most advantageous process when compared to other drug delivery systems like liposomes, nanoparticles, solid dispersion, etc. SMEDDS is superior as compared to other drug delivery systems to deliver macro molecules like peptide, hormones that are prone to enzymatic hydrolysis in GIT. SMEDDS also reduces inter subject and intra subject variability and food effects (Patravale VB *et al*, 2003).

Loperamide hydrochloride is an antidiarrheal drug. Loperamide hydrochloride belongs to biopharmaceutics classification systems (BCS) class II. Thus it is assumed to be absorbed slowly and erratically after oral administration due to limited aqueous solubility. Peak concentration in plasma is usually observed 4 to 8 h after oral ingestion and may be delayed as much as 24 h. For such a drug SMEDDS is a suitable approach for enhancing solubility (McNamara JO, 2001 & Tripathi KD, 2003).

Thus, the present work has been undertaken to explore the utility of the principles of SMEDDS to formulate an oral system for loperamide hydrochloride with enhanced solubility and bioavailability.

MATERIALS AND METHODS

SOLUBILITY STUDIES

The solubility of loperamide hydrochloride in various oils (Labrafac CC, Labrafil 1944, Lauroglycol FCC, α -tocopherol acetate, Almond oil, Castor oil and Sunflower oil), surfactants (Tween 60, Tween 80, Span 20) and co-surfactants (PEG-400, Propylene Glycerol, Glycerol) was determined as follows. Loperamide hydrochloride (2 g) was added to a vial containing above selected vehicles (5 ml of each). After sealing, the vials were kept in sonicator and the mixture was heated at 40°C in a water bath to facilitate the solubilization. Mixing of system was performed using cyclomixer. Mixture was shaken in mechanical shaker at 25°C for 72 h. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 min, and excess insoluble loperamide hydrochloride was discarded by filtration using whatman filter paper (Patel AR and Vavia PR 2007 & Kale AA and Patravale VB, 2008).

Estimation of drug from oil, surfactant and co-surfactant

Transfer 1 ml of the above filtrate into a 100 ml volumetric flask and diluted with ethanol sufficiently and the free drug concentration of loperamide hydrochloride in suitable vehicle was quantified by UV spectroscopy at 214 nm.

PSEUDO TERNARY PHASE DIAGRAM STUDY

Pseudo ternary phase diagrams of oil (labrafac CC), surfactant (tween 60), co-surfactant (propylene glycol) and co-solvent (ethanol) were developed using the water titration method. Mixtures of labrafac CC, tween 60 and propylene glycol with ethanol in the ratio of 1:1, were prepared at different ratios (in percentage w/w) of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9 in different vials. For each phase diagram at a specific ratio of S/CoS (surfactant to co-surfactant ratio), i.e., 1:1, 2:1, 3:1 and 5:1, were added to oil phase, followed by ethanol and vortexed for 5 min. to get a transparent homogenous mixture. Then each mixture was titrated with water. After each addition, the mixtures in the vials were vortexed for 2-3 min and were allowed to equilibrate at 25°C for 30 min. After equilibration the mixtures were visually examined for phase separation, transparency and flowability. The concentration of water at which turbidity to transparency and transparency to turbidity transition occurred was derived from the weight measurements. These values were then used to determine the boundaries of the microemulsion domain corresponding to the chosen value of oils as well as S/CoS mixing ratio (Patel AR and Vavia PR 2007, Quan D *et al* 2007 & Patel D and Sawant KK, 2007). Phase diagrams were then constructed using Chemix software.

THE EFFECT OF DRUG ON THE PHASE DIAGRAM

The experiment was carried out to investigate the effect of loperamide hydrochloride on the SMEDDS performance. Loperamide hydrochloride (100 mg) was added to the mixture containing labrafac CC, tween 60, and propylene glycol with ethanol in the ratio of 1:1, and SMEDDS were prepared at different ratios (in percentage w/w) of 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 1:9 in different vials. The remaining procedure was followed as mentioned above.

PREPARATION OF SMEDDS FORMULATION

A series of SMEDDS were prepared using Tween 60 with propylene glycol and ethanol in the ratio of 1:1, as S/CoS and labrafac CC as oil. In all the formulations concentration of loperamide hydrochloride was kept constant (100 mg) and the varying ratio of oil, surfactant, co- surfactant and co-solvent were added. Accurate quantity of ethanol : propylene glycol (1:1), labrafac CC, was added into a vial containing fixed amount of loperamide hydrochloride and mixed by gentle stirring for 15 min, followed by vortexed for 30 min. Then the mixture was heated at 30 – 40°C and kept in sonicator till the drug gets solubilized. The mixture was cooled to ambient temperature. Tween 60 was added into vials and stirred on magnetic stirrer until loperamide hydrochloride was dissolved. The mixture was stored at room temperature for further evaluation (Patel AR and Vavia PR 2007 & Patel D and Sawant KK, 2007). Various formulation ratios are given in Table 1.

Formulation code	Loperamide hydrochloride	Labrafac CC (ml)	S/CoS ratio	Tween 60 (ml)	Propylene glycol (ml)	Ethanol (ml)
F1	100 mg	28.5	3:1	53.64	8.94	8.94
F2	100 mg	29.0	3:1	53.25	8.88	8.88
F3	100 mg	29.5	3:1	52.88	8.82	8.82
F4	100 mg	30.0	3:1	52.5	8.75	8.75
F5	100 mg	30.5	3:1	52.13	8.69	8.69
F6	100 mg	31.0	3:1	51.75	8.63	8.63
F7	100 mg	31.5	3:1	51.38	8.57	8.57
F8	100 mg	31.5	3:2	41.1	13.7	13.7
F9	100 mg	32.5	3:1	50.63	8.44	8.4

Table 1: Composition of formulations

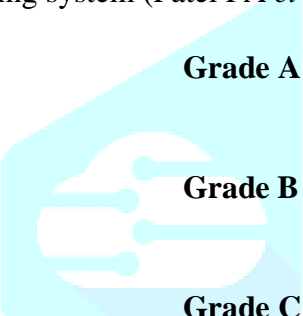
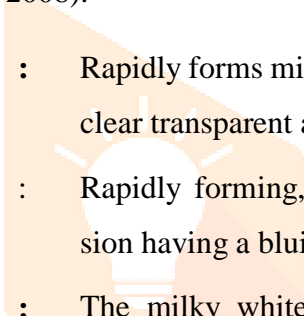
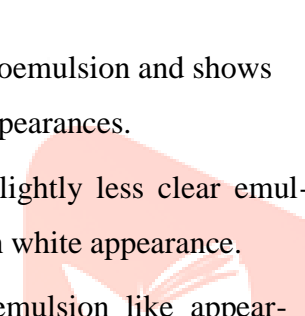
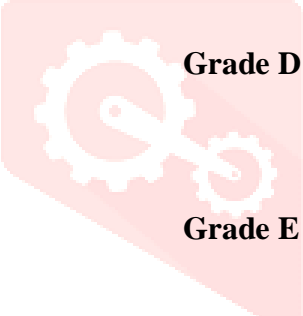
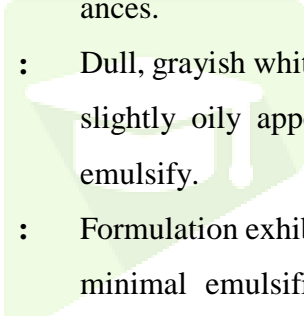
CHARACTERIZATION AND EVALUATION

Freeze thawing

Freeze thawing was employed to evaluate the stability of formulation. The SMEDDS pre concentrate of various formulations were subjected to 3 to 4 freeze thaw cycles, which included freezing at 2° C for 24 h, followed by thawing at 40 °C for 24 h. The various formulations were then subjected to centrifugation at 3000 rpm for 5 min. The formulations were visually observed for phase separation.

Dispersibility test

The efficiency of SMEDDS is assessed using standard USP XXIII dissolution apparatus II. Each formulation (1 ml) was added to 500 ml of distilled water at 37°C ± 0.5°C. The paddle was made to rotate at 50 rpm. The *in vitro* performance of the formulations was visually assessed using the following grading system (Patel PA *et al* 2008).

	Grade A : Rapidly forms microemulsion and shows clear transparent appearances.
	Grade B : Rapidly forming, slightly less clear emulsion having a bluish white appearance.
	Grade C : The milky white emulsion like appearances.
	Grade D : Dull, grayish white emulsion is having slightly oily appearances that are slow to emulsify.
	Grade E : Formulation exhibiting either poor or minimal emulsification with larger oil globules.

Percentage transmittance

Percentage transmittance was carried out to prove that the SMEDDS are transparent in nature and form clear monophasic solution. A 100 µl of each pre concentrate of SMEDDS of loperamide hydrochloride was diluted to 250 ml with distilled water in a beaker and was gently mixed using a glass rod. Percentage transmittance was measured by U.V. spectrophotometer (Shimadzu V- 530, Japan) at 400 nm using water as blank (Patel D and Sawant KK, 2007).

Speed of emulsification

SMEDDS forms spontaneously fine oil-in-water micro emulsion in gastrointestinal tract under gentle agitation which is provided by digestive motility of the stomach and the intestine. The rate of formation of micro emulsion is an important index for assessment of efficiency of micro emulsion. A 100 µl of each pre concentrate of SMEDDS of loperamide hydrochloride was diluted to 250 ml with distilled water in a beaker and agitated at 20 rpm the time taken to form emulsion was noted using stopwatch (Patel AR and Vavia PR 2007).

Determination of Particle size, viscosity, zeta potential and polydispersive index

A 100 µl of each pre concentrate of SMEDDS of carbamazepine was diluted to 250 ml with distilled water in a beaker with constant stirring on a magnetic stirrer. The droplet size and size distribution, viscosity, zeta potential and polydispersive index of resultant micro emulsion were determined (Patel AR and Vavia PR 2007, Gao ZG *et al* 1998)) after 1 h, by laser scattering particle size analyzer (Malvern Nano Zeta sizer Instrument).

Uniformity of weight (weight variation)

Weight variation test was performed as per Indian Pharmacopoeia (IP).

Determination of percentage drug content

One tablet of each formulation was taken in a 100 ml volumetric flask, and added 100 ml of ethanol as extracting solvent. This was shaken for 1 h in mechanical shaker and kept a side for 24 h. After 24 h, filtered the solution through Whatman filter paper (0.45µm) to collect the filtrate. The filtrate was then analyzed in Jasco-V-530 spectrophotometer at 214 nm using ethanol as blank. The concentration of drug in solution was calculated from absorbance and standard graph (Patil P *et al* 2007).

Determination of disintegration time

The *in vitro* disintegration test was determined as per IP, using disintegration test apparatus. The medium used for the study was 0.1N HCl, maintained at $37 \pm 2^\circ\text{C}$. The time taken for the tablet to disintegrate completely with no palpable mass remaining in apparatus was noted (Patel AR and Vavia PR 2007).

Sr. No	Ingredient	Solubility in mg/ml* ± SD
OILS		
1.	Labrafac CC	30.82 ± 0.0242
2.	Labrafil 1944	16.71 ± 0.1437
3.	Lauroglycol FCC	14.59 ± 0.2231
4.	Almond OIL	13.67 ± 0.0134
5.	Castor oil	9.86 ± 0.0756
6.	Sunflower oil	12.69 ± 0.0267
7.	α-tocopherol acetate	27.85 ± 0.0553
SURFACTANTS		
1.	Tween 60	80.21 ± 0.0682
2.	Tween 80	68.51 ± 0.0267
3.	Span 20	26.21 ± 0.1972
COSURFACTANTS		
1.	PEG 400	72.20 ± 0.0685
2.	Propylene glycol	86.20 ± 0.1154
3.	Glycerol	14.57 ± 0.0213

* Each value is average of 3 readings

Table 2: Solubility Study of loperamide hydrochloride in various components

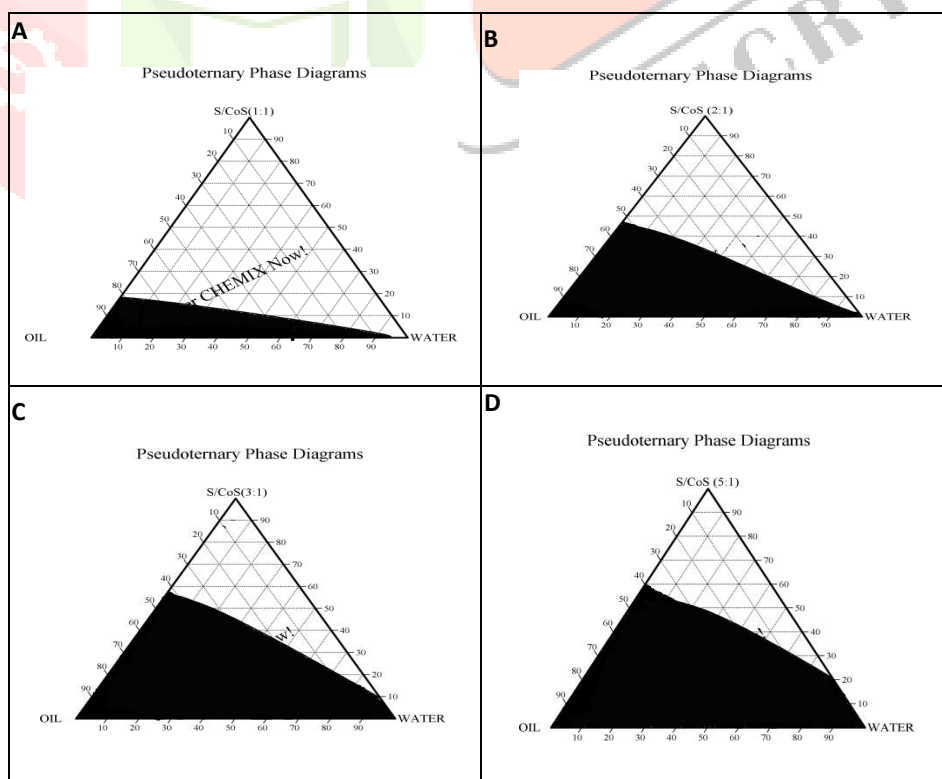


Figure 1: Pseudo-ternary phase diagram (identification of self micro emulsifying region)

In vitro drug release studies

In vitro dissolution studies were carried out by using paddle type USP XXIII dissolution test apparatus II. Dissolution tests were done separately for pure drug and prepared SMEDDS. Pure drug and SMEDDS capsules containing drug equivalent to 100 mg of the pure drug were used for dissolution studies. Dissolution was carried out in 900 ml of 0.1 N HCl (pH 1.2) at 50 rpm and at temperature of $37 \pm 0.5^\circ\text{C}$. Sample aliquots (5 ml) of dissolution medium were withdrawn at definite time intervals, filtered and replaced with fresh medium. The samples were assayed spectrometrically at 214 nm (Patel D and Sawant KK, 2007).

DRUG RELEASE KINETICS

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models (Reddy KR *et al* 2003): Zero order (cumulative amount of drug released v/s time), first order (log cumulative percentage of drug remaining v/s time) and Hixson Crowell cube root law model (cube root of the percentage of drug remaining in the matrix v/s time).

STABILITY STUDIES

Stability studies were carried out as follows. From each batch 20 tablets were selected at random and kept at refrigerator temperature (4°C), room temperature $25^\circ\text{C} / \pm 60\% \text{ RH} \pm 5\%$ and accelerated temperature ($40^\circ\text{C} \pm 75\% \text{ RH} \pm 5\%$) for a period of 90 days. The formulations were evaluated for particle size, speed of emulsification, clarity of micro emulsion, zeta-potential, viscosity, polydispersive index, weight variation, disintegration time, % drug content and *in vitro* drug release studies. The sampling was done on 7th, 15th, 30th, 45th, 60th, and 90th day.

RESULTS AND DISCUSSION

SOLUBILITY STUDIES

SMEDDS are clear, monophasic liquid at ambient temperature and consideration has to be given to avoid precipitation of drug on dilution in the gut lumen *in vivo*.

Therefore the components used should have high solubilization of the drug in the resultant dispersion. The solubility study was carried out to determine the drug solubilizing capacity in the given oils, surfactants and co surfactants. Result of the solubility studies are reported in Table-2. From the above result, tween 60, propylene glycol showed the highest solubilisation capacity followed by labrafac CC. Thus in the present study labrafac CC was selected as oil phase, tween 60 and propylene glycol was selected as surfactant and co-surfactant respectively.

Pseudo-ternary phase diagrams were constructed to identify self micro emulsifying region and to select suitable concentration of oil (labrafac CC), surfactant (tween 60), cosurfactant (propylene glycol) and co-solvent (Ethanol) for the formulation of SMEDDS. In the present study labrafac CC, was tested for phase behaviour studies with tween 60, propylene glycol and ethanol. As seen from the ternary plot (Figure 1) the microemulsion existing area increases as the S/CoS ratio increases. However it was observed that increasing the surfactant ratio resulted in a loss of flowability. Thus an S/CoS ratio of 3:1 was selected for the formulation.

THE EFFECT OF DRUG ON THE PHASE DIAGRAM

The effect of drug on the phase diagram was studied using pseudoternary phase diagram. Oil = Labrafac CC, Surfactant = Tween 60, Co-surfactant = Propylene glycol and Co-solvent = Ethanol. S/CoS ratio of A is 1:1, B is 2:1, C is 3:1 and D is 5:1. In the present study it was found that the drug incorporation in the SMEDDS had no significant difference in micro emulsion existing area when compared with the corresponding formulation without loperamide hydrochloride as shown in Figure-2.

CHARACTERIZATION AND EVALUATION OF SELF MICRO-EMULSIFYING DRUG DELIVERY SYSTEMS OF LOPERAMIDE HYDROCHLORIDE

Freeze thawing

Freeze thawing was carried out to evaluate the stability of formulation. For the development of SMEDDS formulation, right blend of emulsifier is necessary to form stable micro emulsion. It was observed that in formulations F7, F8 and F9, there was separation of two layers, and hence these formulations were excluded for further studies. It was also observed that the solubility of drug was more in S/CoS phase, when compared with oil phase. Hence higher the concentration of oil, more unstable was the emulsion. Thus formulation F1, F2, F3, F4, F5 and F6, which were stable to freeze thawing were used for further evaluation.

Dispersibility test

The efficiency of self emulsification of oral micro emulsion was assessed using dispersibility test. Grade A and grade B formulations remained as micro emulsion when dispersed in GIT, while formulations of grade C are recommended as SEDDS formulation. The formulation F1 and F2 showed clear transparent appearance therefore it rapidly forms micro emulsion and thus these systems are called as SMEDDS. The formulation F3 and F4 formed less clear emulsion with bluish

white appearance, whereas formulation F5 and F6 showed milky white appearance and therefore these systems are termed as Self Emulsifying Drug Delivery Systems.

Percentage transmittance

Percentage transmittance was carried out to prove that SEDDS are clear, transparent systems. The per-centage transmittance of F1, F2 and F3 was found to be 98.6, 98.0 and 96.4% respectively which is very closer to 100%. This indicated that clear micro emul- sion was formed when diluted with distilled water. Whereas F5 and F6 appeared non transparent or milky white, due to decreased concentration of surfactant. Thus lower concentration of surfactant was found to have very less ability to emulsify large amount of oil globules in water phase.

Speed of emulsification

The rate of emulsification is an important index for assessment of the efficiency of emulsification. It was observed that F1 showed less dispersion time 30 sec, when compared with F6 which showed 80 sec. The result showed the order of dispersion time as follows- $F1 < F2 < F3 < F4 < F5 < F6$. Thus, an increase in the proportion of labrafac CC in the composition resulted in the increase in self-emulsification time, beyond the concentration of 31% w/w of labrafac CC resulted in formation of non-clear dispersion. The decrease in self emulsification time of F6 can be assumed to be due to the relative decrease in surfactant concentration, lead- ing to decreased viscosity of the formulation. The S/CoS ratio of 3:1 was kept constant for the initial for- mulation study. However it was found water, propylene glycol being water soluble is antici- pated to enter the water phase and redistribute mainly between the water phase and the emulsion water in- terface, resulting in a loss of solvent capacity of the vehicle. Therefore ethanol was used as co-solvent which aid to increase drug solubilization in oil phase and to increase the fluidity of interfacial surface area of oil globules.

Table 3: Polydispersive index and viscosity profile of formulation F1 to F6

Formulation Code	Polydispersive Index*	Viscosity (cps)
F1	0.319	0.8873
F2	0.282	0.8867
F3	0.225	0,8873
F4	0.352	0.8865
F5	0.417	0.8867
F6	0.365	0.8865

*Each value is an average of three readings.

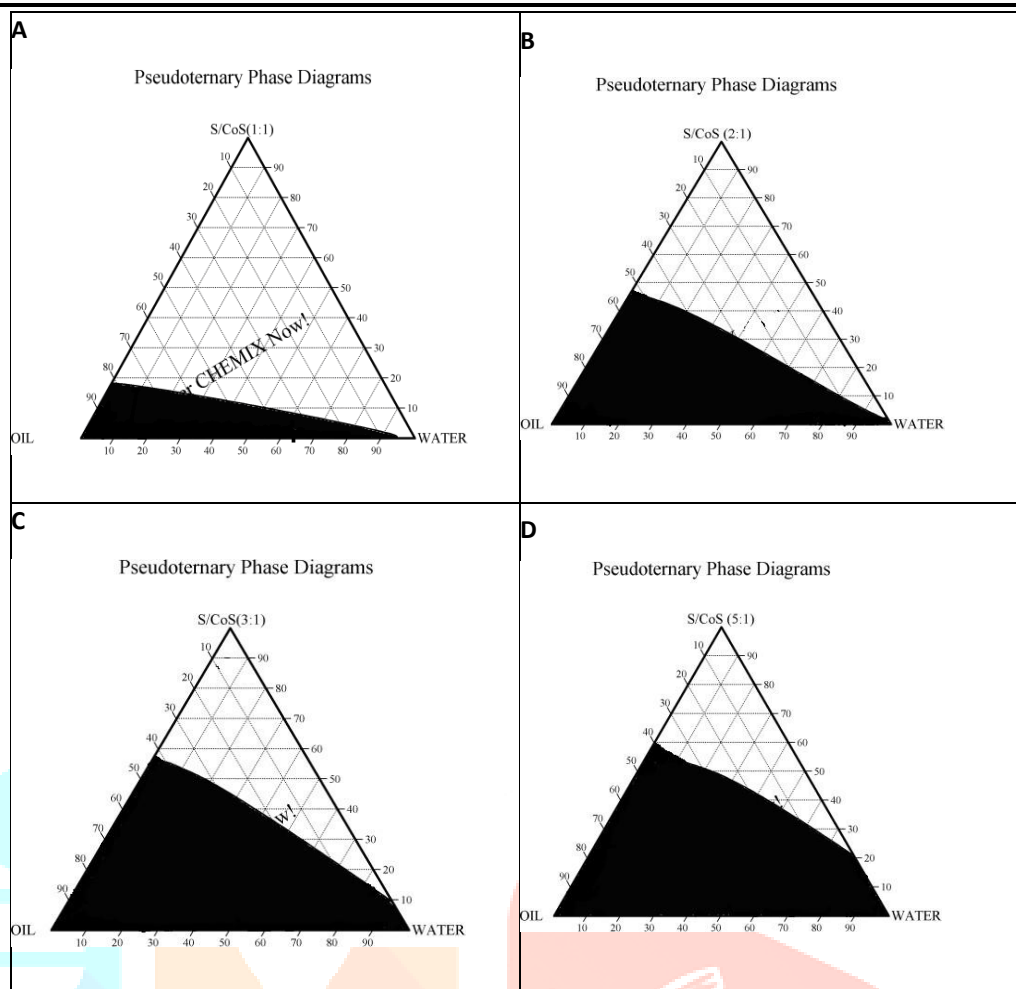


Figure 2: Pseudoternary phase diagram (effect of drug on the phase diagram)

Particle size analysis

Formulation F1 with the highest proportion of surfactant (53.55% w/w tween 60) at a fixed amount of oil (28.5% w/w), showed the lowest mean particle diameter, whereas F6 with the lowest proportion of surfactant (51.38% w/w tween 60) and a fixed amount of oil (31.5% w/w), showed the highest mean particle diameter. Thus an increase in the ratio of the oil phase (Ibrafac CC) resulted in proportional increase in particle size, because of the simultaneous decrease in the S/CoS proportion. Addition of surfactants to the micro emulsion system causes the interfacial film to stabilize and condense, while the addition of co-surfactant causes the film to expand. An increase in the S/CoS ratio leads to a decrease in mean droplet size. This could be attributed to an increased surfactant proportion relative to co-surfactant. Thus, the relative proportion of surfactant to co-surfactant had varied effects on the droplet size.

Determination of Viscosity and Polydispersive Index

All the formulations showed very low poly dispersive index and low viscosity. Hence, all the formulations rapidly formed emulsion and remained stable for longer time (Table 3). The formulation F1 showed lower value of zeta-potential, i.e., -19.8mV, where as F6 showed higher value of zeta-potential, i.e., -14.2mV.

Weight Variation Test

The maximum percentage weight variation observed was -2.4578 to + 2.7451 for F6 and minimum observed was -1.2762 to +2.1115 for F1. The maximum allowed percentage weight variation for tablets weighing 800 mg as per IP is 7.5% and hence no formulations were exceeding the limits. Thus all formulations were found to comply with the IP specifications. The drug content values for all the formulation comes in the range of 92.0% to 98.0%. As per the USP standard, loperamide hydrochloride tablets must contain not less than 92% and not more than 108.0% of the stated amount of loperamide hydrochloride. Thus all the SMEDDS formulations of loperamide hydrochloride comply with USP limits for assay.

Uniformity of Drug Content

Uniformity of drug content should be carried out only after the drug content estimation (assay) in a pooled sample of loperamide hydrochloride. It was found that uniformity of drug content remained to be within the limit of the stated amounts (USP Limit: loperamide hydrochloride tablets contain not less than 92.0% and not more than 108.0 % of loperamide hydrochloride). The assay value for all the formulations were found to comply with USP limits for assay. The range of uniformity of content for all the formulations was found to be 92.23%w/w to 99.74%w/w. The average disintegration time of all the SMEDDS formulations was found to be in the range of 3.1 to 3.5 min.

IN VITRO DISSOLUTION TESTING

In vitro drug release studies were performed as per the method described in methodology section 4.10. The result of *in vitro* drug release studies from the pure drug and SMEDDS formulations of loperamide hydrochloride are described in table 22-28. The percentage cumulative drug release of SMEDDS of loperamide hydrochloride and pure drug was plotted against time. A comparison of *in vitro* drug release profile of pure drug and SMEDDS formulation are given in Figure-3.

Based on the drug release comparison studies, it was observed that the drug release from the SMEDDS from F1 was found to be significantly higher when compared with that of pure drug loperamide hydrochloride (Figure-3). Also it was found that there was 100% drug release from

F1 at the end of 30 min. No significant difference in drug release was observed between the formulations. The order of drug release decreased as follows: F1>F2>F3>F4>F5>F6. It was suggested that the SMEDDS formulation resulted in spontaneous formation of a micro emulsion with a small droplet size, which permitted a faster rate of drug release into the aqueous phase, much faster than that of pure drug loperamide hydrochloride. Thus, this greater availability of dissolved loperamide hydrochloride from the SMEDDS formulation could lead to higher absorption and oral bioavailability.

DRUG RELEASE KINETIC STUDIES

The drug release data of loperamide hydrochloride were fitted to zero order, first order, and Hixson-Crowell cube root model kinetics. The data were processed for regression analysis using MS-EXCEL statistical function. The drug release kinetic study indicated that the release of drug from formulation followed first order as the R^2 values ranged from 0.9421 to 0.9954 for first order kinetics and also obeyed Hixson- Crowell cube root law as R^2 values ranged from 0.9596 to 0.9949 . Hence the release mechanism was found to be diffusion through the formulation.

STABILITY STUDIES

All the formulations showed good stability at 25° C/ 60% RH. The data showed that there were no significant changes in visual appearance, particle size, speed of emulsification, % drug content, weight variation and disintegration time and *in vitro* drug release studies. During the stability period, % drug content did not deviate by more than 2 % , indicated that the drug is stable in SMEDDS formulations and also there was no significant variation in *in vitro* release study at the end of 3 months. Formulation F1 and F2 were found to be stable at 4°C, and 40 °C/60 % RH.. Formulation F3 was stable only up to 45th day at 45°C/75 % RH, whereas F4 was stable only up to 30 days. It was also found that the remaining formulations i.e., F5 and F6 were not stable beyond 15th day. It was found that the formulations were not stable when exposed to higher temperature except F1 and F2 formulation. Hence it was concluded that 45 °C/75 % RH, is not suitable for SMEDDS. However F1 and F2 were found to be stable for 3 months at 4° C, 25° C and 45° C 75 % RH.. There were no significant changes in the drug content, drug release ($t_{90\%}$) or particle size of the resultant micro emulsion. It was also seen that the formulation was compatible with the tablet, as there was no sign of tablet shell deformation. Further, no changes in the appearance, disintegration time or micro emulsifying property were observed. The formulations were found to show no phase separation, drug precipitation.

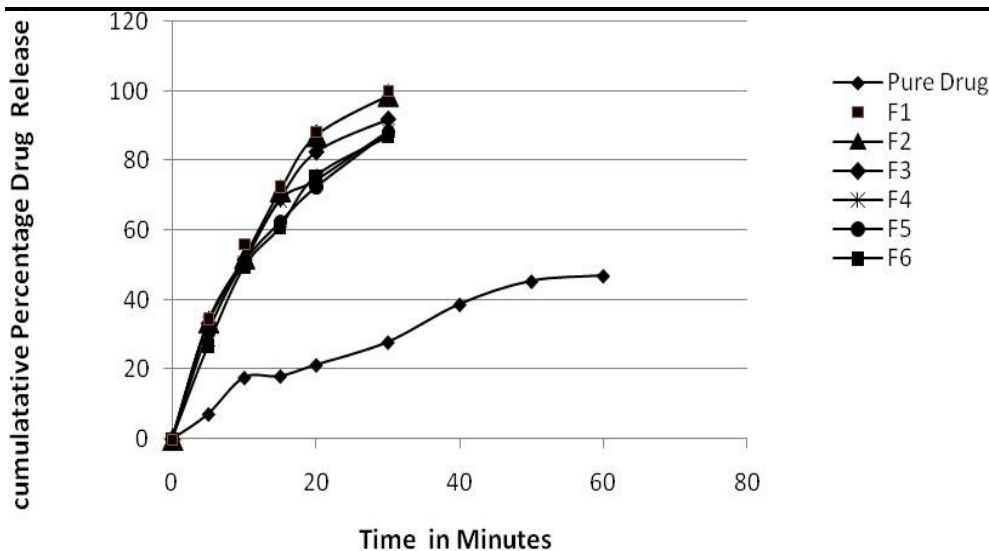


Figure 3: Comparative results of drug release from pure drug loperamide hydrochloride and the SMEDDS formulations F1-F6 in 0.1 N HCl dissolution media

CONCLUSION

SMEDDS formulations of loperamide hydrochloride were tested for microemulsifying properties and the resultant micro emulsions were evaluated for clarity, precipitation and particle size distribution. Formulation development and screening was done based on results obtained from phase diagrams and characteristics of resultant micro emulsion. SMEDDS formulation showed a complete release in 30 min as compared with the plain drug which showed a limited dissolution rate. Thus the study confirmed that SMEDDS formulation can be used as a possible alternative to traditional oral formulation of loperamide hydrochloride to improve its solubility and oral bioavailability.

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