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Research Article

DEVELOPMENT AND EVALUATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM FOR LORNOXICAM

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ABSTRACT

Aim of the present work was to develop and evaluate a solid self-emulsifying drug delivery system (SEDDS) for oral poorly water-soluble drug lornoxicam. The liquid (SEDDS) consisted of capmul MCM as oil phase, tween 20 as surfactant and PEG 400 as co-surfactant. Oil, surfactant and co-surfactant were selected on the basis of solubilisation capacity of drug and emulsification ability of surfactant and co-surfactants. The formulations were optimized by constructing the pseudo-ternary phase diagram. The liquid formulation was solidified by laboratory scale spray dryer, using Aerosil 200 as solid carrier. The solid SEDDS shows greater drug release thus, solid SEDDS improves the oral bioavailability and may provide the useful solid dosage form for oral poorly water soluble drugs.
Keywords: Lornoxicam, Self emulsifying drug delivery system, Bioavailability, Solid-carrier, Capmul MCM, Tween 20, PEG 400.

INTRODUCTION

The low solubility of many new drug candidates is a substantial challenge facing the pharmaceutical industry[1]. The oral delivery of such drugs is frequently associated with implications of low bioavailability and high intra and inter subject variability. To overcome such problems, various formulation strategies are reported in the literature including the use of surfactants, cyclodextrins, solid dispersions, micronization, and enhancers[2]. SEDDS is an oral lipid dosage form. It is a mixture of oils and surfactants that has the ability to form fine oil in water (o/w) emulsions or micro emulsions upon gentle agitation following dilution with the aqueous phase and improves drug dissolution through providing a large interfacial area for partitioning of the drug between the oil and GIT fluid[3-9] . Other advantages include increased stability of drug molecules and possibility of administering the final product as gelatin capsules[10-14]

Lornoxicam (chlortenoxicam) is a non steroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. It is available in oral and parental dosage formulation. Lornoxicam is a Yellow or slightly yellow powder. It is slightly soluble in water, soluble in hydrochloric acid[15]

MATERIALS AND METHODS

Materials

Lornoxicam is obtained as gift sample from Glenmark Pharma Ltd., MCT oil (Labrafac), Caprylic Capric Triglyceride and Mayasol (Labrasol) obtained as gift sample from Subhash Chemicals, Bhosari, Pune (M.S.). Capmul MCM, Captex 200 and Captex 350 obtained as gift sample from

Abitech Corporation, Mumbai, India. Cremophore RH and Cremophore EL obtained as gift sample from BASF Ltd, Mumbai. Tween 20, Tween 80, PEG 400, Soybean oil, Castor oil, Olive oil, Sesame oil were obtained from Prachi Enterprices, Pune, (M.S) India.

Methods

Determination of solubility in various oils, surfactants and co-surfactants

The solubility of drug was determined by adding excess amount of the drug in small vials containing 2 ml of selected oil, surfactants and co-surfactants separately. The drug was mixed in respective oil and surfactant manually with glass rod for 30 minutes, then the vials were kept for sonication about two hours. The vials were tightly stopper and were continuously stirred for 72 hrs in orbital shaking incubator (REMI; RIS 24 BL) at 25^{0}C. oils were centrifuged (REMI; C- 24 BL) at 3500 rpm for 20 min. The supernatant was separated and dissolved in ethanol and solubility was quantified by UV-Spectrophotometer (SHIMADZU UV-1800; 06103) at 383 nm after appropriate dilution with ethanol.

Screening of surfactant & co-surfactant [16]

Various surfactants and co-surfactants (Tween 20, Tween 80, labrasol and PEG 400) were screened for Emulsification ability. 200 mg of Surfactant and 100 mg of co-surfactant was added to the selected oily phase, 100 mg of co-surfactant, 200 mg surfactant and 300 mg oil Phase was used. The mixtures were gently heated at 40–45 °C for 30 seconds to attain homogenization of components. 50 mg of mixture was weighed and diluted in 50 mL of distilled water to obtain a fine emulsion. The emulsion formation was scrutinized by counting the number of volumetric flask inversions to give a uniform emulsion and observed visually for relative turbidity. The resulting emulsions were allowed to stand for 2 hrs and transmittance was observed at 382 nm. The surfactant forming a clear emulsion with fewer inversions and higher transmittance was selected. Observations were shown in table.3.

Construction of pseudo-ternary phase diagram [17]

The pseudo-ternary phase diagrams were constructed by water titration method at room temperature. The ratios of surfactant and co-surfactant (Smix) were used 1:1, 2:1, 3:1 and 1:2. Tween 20 and PEG 400 was used as surfactant and co-surfactant and Capmul MCM was used as an oil phase. Mixtures of Smix and Oil ratio from 9:1 to 1:9 were titrated by adding the water drop by drop. During the titration samples were stirred to allow equilibration and at the same time examined for the transparency. Samples with low viscosity, single phase and transparent nature were considered as stable SEDDS formulation. The data obtain after titration was used for the construction of pseudo-ternary phase diagram. The ternary-phase diagrams for different ratios are shown in fig. 3.

Preparation of SEDDS [18]

Lornoxicam (8 mg) was dissolved in 1 ml of the mixture of Capmul MCM, Tween 20 and PEG 400 as oil, surfactant and co-surfactant respectively. The ratio of S/CS (Smix) 1:1 was used for preparation of SEDDS. Compositions of liquid SEDDS formulations are shown in table 1.

A laboratory scale spray dryer (LABULTIMA; LU 222-ADV) was used for the preparation of solid SEDDS. 1 gm. of Aerosil 200 was suspended in 100 ml ethanol. 2 ml of liquid SEDDS was added to this solution and continuously stirred at room temperature for 30 min. This solution was then delivered to the nozzle (0.7 mm diameter) at a flow rate of 3 ml/min with peristaltic pump and spray dried at inlet temperature of 100 and 60^{o}C and outlet temperature of 80 and 40^{o}C respectively. The spray air pressure was 4kg/cm^2.

Table. 1- Composition Of Sedds Formulations

Formulation code	Lornoxicam (mg)	Capmul MCM	Tween 80 + PEG 400 (1:1)
F1	08	10 (%)	90 (%)
F2	08	20 (%)	80 (%)
F3	08	30 (%)	70 (%)
F4	08	40 (%)	60 (%)
F5	08	50 (%)	50 (%)
F6	08	60 (%)	40 (%)
F7	08	70 (%)	30 (%)
F8	08	80 (%)	20 (%)
F9	08	90 (%)	10 (%)

Evaluation of SEDDS

Drug content [19]

Prepared SEDDS containing 08 mg Lornoxicam was dissolved in 100 ml of ethanol. This stock solution was then further diluted with ethanol and drug content was determined by UV-spectrophotometer at 382 nm. Results of drug content study are shown in table 4.

Viscosity determination[19]

Viscosity of various formulations was determined by Brookfield Viscometer (OSWAL'S SCINTIFIC; RVDV II + PRO), at 10 rpm for 5 min. Results are shown in table 5.

Thermodynamic stability study[20]

Following tests were performed for thermodynamic stability studies.

Centrifugation study

Formulations were centrifuged at the 5000 rpm for 30 mins and observed for phase separation, creaming and cracking. The formulations which showed maximum stability (no creaming, cracking, phase separation) were selected and studied for heating-cooling cycle, freeze-thaw cycles.

Heating cooling cycles

In this study each formulation was kept at 45^0 C and at 0^0C temperature for 48 hrs for each temperature cycle by using stability chamber (THERMOLAB; TX 0000310 G).

Freeze–thaw cycles

In this study the formulations were exposed at two different temperatures i.e. -21^0C and 21^0C for each temperature cycles not less than 24 hrs. For the better estimation of accelerated stability studies three such cycles were run for each batch of formulation.

Dispersibility test [21]

Self-emulsification efficiency of formulation was assessed using a standard dissolution apparatus (ELECTROLAB; TDT-06 L). One ml of each formulation was added to 500 mL of distilled water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitroperformance of the formulations was visually assessed using the following grading system (Table.2).

***In-vitro* Dissolution Study** [22]

Dissolution study of SEDDS formulations were determined using rotating paddle dissolution apparatus (USP type II) (Electrolab; TDT-06 L) used at 37°C ± 0.5°C and a rotating speed of 100 rpm in 900 ml of Phosphate buffer (pH 6.8). The SEDDS formulation was placed in a hard gelatine capsule held to the bottom of the vessel using copper sinkers. During the release studies, samples were withdrawn and subjected to UV-spectrophotometric analysis. The sample volume was replaced each time with equal quantity of fresh medium. The results are presented graphically in Fig.4.

RESULTS AND DISCUSSIONS

Solubility study

Lornoxicam showed highest solubility in Capmul MCM than other oils Captex 200, Captex 350, Labrafil M 1944 CS, labrafac, Transcutol, Soybean oil, Castor oil, Olive oil, Sesame oil and Isopropyl myristate.

Lornoxicam showed highest solubility in Tween 20 as Surfactant than Tween 80, Span 20, Span 80, Cremophore RH 40 and Cremophore EL. PEG 400 as a co-surfactant showed highest solubility other than co-surfactants Labrasol, Labrafac, Transcutol and Propylene glycol (Fig. 1 and 2). Hence these excipients were selected for SEDDS formulation.

Screening of surfactant and co-surfactant

On the basis of solubility of drug in oils, surfactants and co-surfactants following excipients were chosen for per cent transmittance (%T) study. Capmul MCM with Tween 20 and PEG 400 showed highest transparency and have rapid emulsification ability than other combination shown in table 3.

Table. 2 Grades of Dispersibility Test

Sr.no.	Observations	Grades
1	Rapidly forming (within 1 min) nanoemulsion, having a clear or slight bluish	A
2	Rapidly forming, slightly less clear emulsion, in bluish colour	B
3	Fines milky emulsion that formed within 2 min.	C
4	Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).	D
5	Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.	E

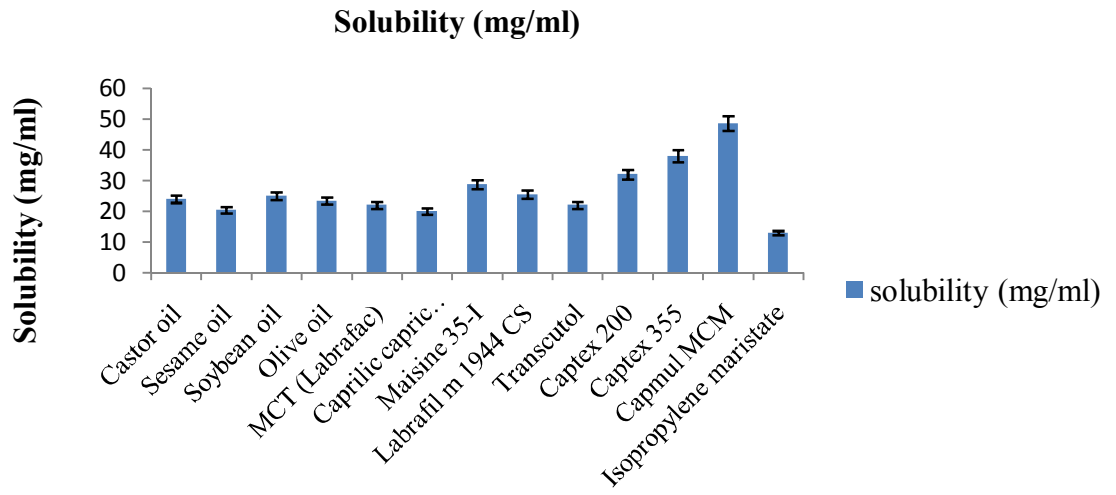


Fig.1 - Solubility of drug in various oils

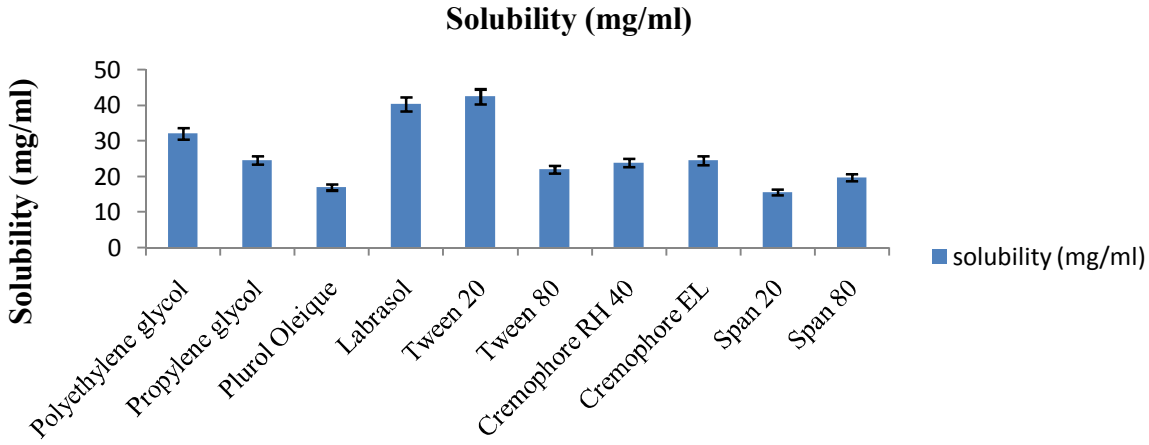


Fig.2 - Solubility of drug in various surfactants & co-surfactants

Table.3- Percent Transmittance (% T) Observations For Surfactants And Co-Surfactants

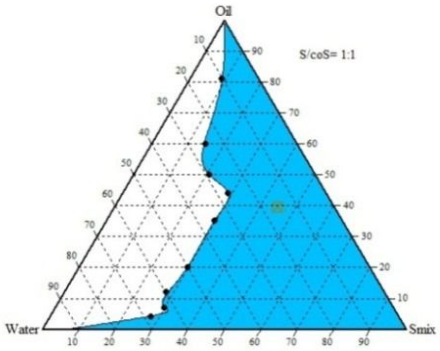
Oils/ Surfactants	Tween 20	Tween 20 + Labrasol	Tween 20 + PEG 400	Tween 80	Tween 80 + Labrasol	Tween 80 + PEG 400
Capmul MCM	85.66 %	89.4 %	**99.56 %**	89.2 %	91.2 %	97.3 %
Captex 200	88.3 %	92.34 %	97.54 %	94.22 %	95.36 %	98.26 %
Captex 350	90.6 %	94.88 %	98.89 %	92.41 %	96.25 %	99.2 %
Labrafil M 1944 CS	87.72 %	89.21 %	92.34 %	80.96 %	84.3 %	88.85 %

Construction of pseudo-ternary phase diagram

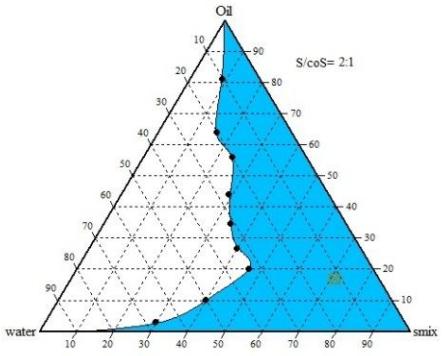
Pseudo-ternary phase diagram were constructed by using a series of SEDDS, to identify the self-emulsifying region and to optimize the concentration of oil, surfactant and co-surfactant in the SEDDS formulation. The phase diagram of the system containing Capmul MCM, Tween 20 and PEG 400 as oil, surfactant and co-surfactant respectively, with different ratios of surfactant and co-surfactant is shown in fig. 3.

It was observed that the mixture of surfactant and co-surfactant (Smix) ratio 1:1 [Fig.3 (A)] showed the greater self -emulsifying (microemulsifying) region than the other ratios such as, 2:1[Fig.3 (B)], 3:1 [Fig.3 (C)], and 1:2[Fig.3 (D)].The assessment of self-emulsification by visual evaluation in the SEDDS and the efficiency of self-emulsification can be estimated by the determination of globule size distribution and the rate of emulsification. From the ternary phase diagram Capmul MCM as oil, Tween 20 as surfactant and PEG 400 as co-surfactant were chosen for liquid SEDDS formulation.

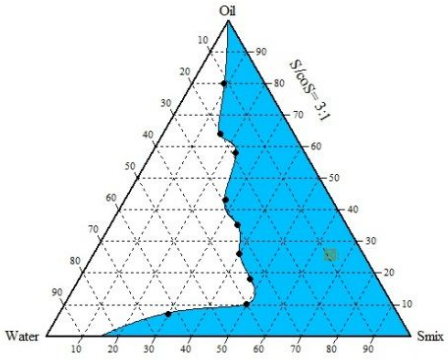
Fig.3– Pseudo-ternary phase diagram for different surfactant and co-surfactant ratios



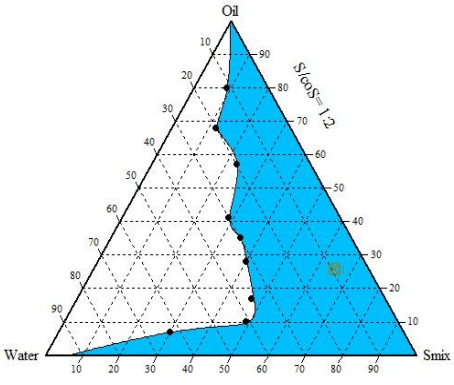
(A) S/coS= 1:1



(B)S/coS= 2:1



(C)S/coS= 3:1



(D)S/coS= 1:2

Drug content of SEDDS

Drug content of different formulation were shown in table 4. It was observed that the formulation F1 and F2 have highest drug content because of higher concentration of surfactant and co-surfactant as they have high solubilisation capacity.

TABLE.4- % DRUG CONTENT OF SEDDS

Formulation	% Drug content*Mean ± S.D.
F1	99.88 ± 0.221
F2	100.02 ± 0.128
F3	98.24 ± 0.155
F4	97.23 ± 0.427
F5	95.64 ± 0.223
F6	93.84 ± 0.315
F7	92.43 ± 0.316
F8	92.24 ± 0.413
F9	92.16 ± 0.415

* (n = 6)

Viscosity determination

From viscosity determination it was observed that formulation F1 and F2 has highest viscosity as they contain higher concentration of surfactant and co-surfactant. As the concentration of Smix increased viscosity of formulation also get increased (Table 5).

TABLE.5- VISCOSITY OF SEDDS FORMULATIONS

Formulation code	Viscosity (mPas)* Mean ± S.D.
F1	4072 ± 0.012
F2	3925 ± 0.014
F3	3657 ± 0.012
F4	3354 ± 0.015
F5	3052 ± 0.018
F6	2826 ± 0.022
F7	2659 ± 0.024
F8	2355 ± 0.027
F9	2054 ± 0.018

* (n = 6)

Thermodynamic stability study

All the formulations were subjected to the different thermodynamic stability by using centrifugation, heating cooling cycle and freeze thaw cycle tests. Thermodynamic stability of nano and micro emulsions (formulations) differentiate them from the emulsions. It was observed that the formulation F1 to F4 survived the thermodynamic stability test while others get separated. Formulations F1 to F4 have fine globule size because of which these formulations have a higher stability.

Dispersibility test

All the formulations were subjected to this test. Formulation F1 and F2 rapidly formed a clear emulsion, hence falls into grade A, while F3 and F4 were of B grade formulations as they formed slightly less clear emulsion. Results of this test are shown in table 6.

TABLE.6 – VISUAL OBSERVATION FOR DISPERSIBILITY TEST

Formulations	Observations	Grade
F1	Rapidly forming clear emulsion	**A**
F2	Rapidly forming clear emulsion	**A**
F3	Rapidly forming, slightly less clear emulsion	**B**
F4	Rapidly forming, slightly less clear emulsion	**B**
F5	Milky emulsion formed within 2 min	**C**
F6	Dull, greyish white emulsion slow to emulsify longer than 2 min.	**D**
F7	Formulation with poor emulsification, large globules on the surface	**E**
F8	Formulation with poor emulsification, large globules on the surface	**E**
F9	Formulation with poor emulsification, large globules on the surface	**E**

In-vitroDissolution Study

Dissolution study indicates that the release of lornoxicam from SEDDS varied with respect to the concentration and O/Smix ratio. It was observed that the formulation F2 have faster drug release as compared to the other formulations (fig.4).

All the SEDDS formulations showed faster drug release than the API. The formulation F2 shown the highest and quick drug release i.e. 100 % within 1.5 hrs while API shows only 8.21% drug release.

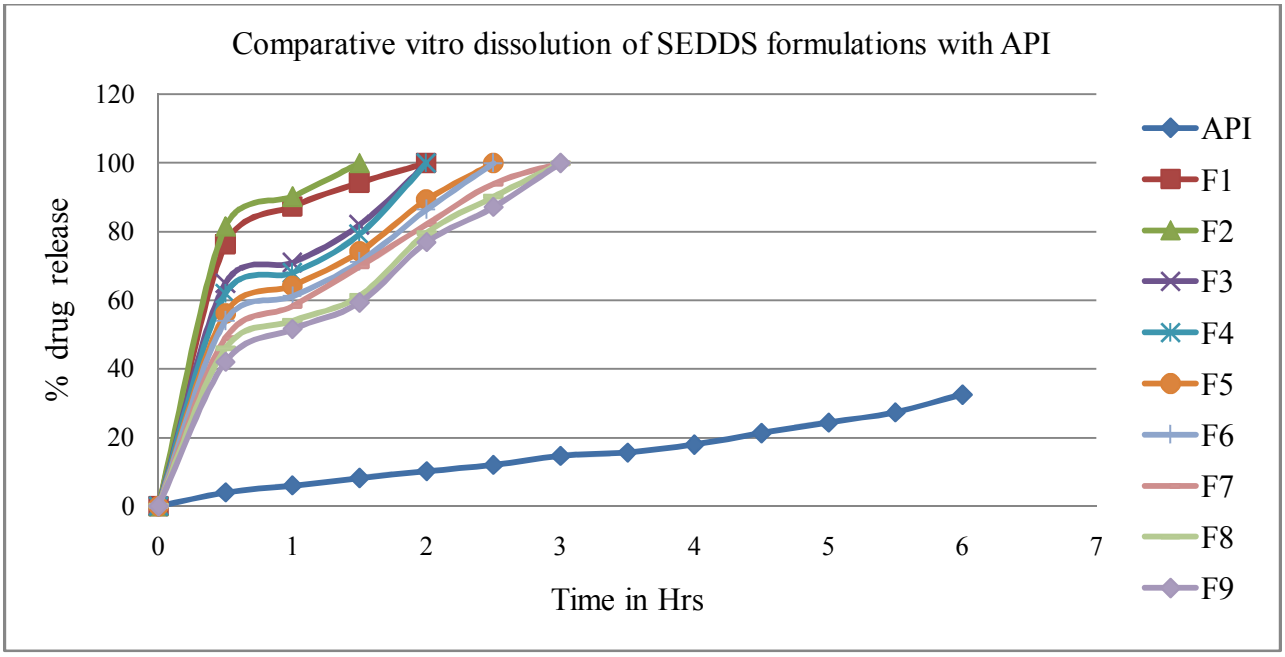


Fig.4- in vitro dissolution of SEDDS formulations with API

CONCLUSION

Self-emulsifying drug delivery system, consisting of Tween 20 (S)/Polyethylene glycol 400 (CS) Capmul MCM (O), was formulated, using Smix ratio 1:1, as well as Smix /Oil ratio 8:2. Established SEDDS showed high solubilisation capacity. Solid SEDDS prepared with Aerosil 200 as solid carrier showed greater drug release. Amongst the various oils, surfactants and co-surfactants Capmul MCM, Tween 20 and PEG 400 respectively, showed high solubilisation capacity. Various formulations were prepared with varying ratios of O/Smix, amongst the formulation F2 showed promising results. All the SEDDS formulations were successfully formulated and dried by spray drier. The results of this study concluded that the SEDDS of lornoxicam can be formulated by using Capmul MCM (20 %), Tween 20 (40 %) and PEG 400 (40 %) as oil, surfactant and co-surfactant respectively.

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