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Research Article

FORMULATION DEVELOPMENT AND OPTIMIZATION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS) OF MELOXICAM

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ABSTRACT

Objective: The objective of this study was to develop a self emulsifying drug delivery system (SEDDS) for enhancing the aqueous solubility of meloxicam (BCS class II drug).

Method: In this study, self emulsifying formulations (Batch F_1 to F_{20}) of drug meloxicam by using different concentration of sunflower oil, tween 80 and PEG 400 were prepared. Systematic optimization was carried out using Design Expert Software, with a goal to minimise self emulsification time and maximise percentage drug release using central composite design using three levels of three factors (concentration of sunflower oil, tween 80 and PEG 400).

Result: Self Emulsification time was highest with batch F_{13} and minimum for batch F_{19}.The *in vitro* drug release was maximum in F_{19} and minimum in F_6. Based on desirability approach, the feasibility search yielded one solution to achieve the desired target of minimum emulsification time and maximum dissolution.

Conclusion: The optimized batch yielded faster dissolution than marketed formulation as well as pure drug. It could be concluded that SEDDS can be explored for further dosage form design of drugs with poor aqueous solubility or BCS class-II drugs.

Keywords: Meloxicam, Self Emulsification, Optimization, Solubility, *In vitro* drug release.

INTRODUCTION

SEDDS may be defined as isotropic mixture of natural or synthetic oils, and solid or liquid surfactants or alternatively, one or more hydrophilic solvents & co-solvents/co-surfactants. SEDDS are a promising approach for dosage form development of drugs with poor aqueous solubility and hence can be more useful for BCS Class II and IV drugs. As upon administration, when the dosage form reaches G.I.T, the SEDDS spontaneously forms oil in water emulsion which disperses into fine droplets. The finer droplets provide higher surface area for the drug to dissolve or permeate in surrounding medium. [1-4]

Self Emulsifying Drug Delivery Systems (SEDDS) have gained importance as a promising technology to improve the solubility as well as bioavailability of drugs with low aqueous solubility. A large number of SEDDS formulations have been reported. Successful commercialization of various products such as Agenerase soft gelatin capsules (Amprenavir) and Gengraf soft gelatin capsule (cyclosporine) have successfully established the commercial viability of this delivery system. [5]

Meloxicam, 4-hydroxy-2 methyl-N-(5-methyl-2-thiazolyl)-2H-1, 2-benzothiazine-3-carboxamide-1, 1-dioxide is an oxicam derivative with non steroidal anti inflammatory properties. [6] The therapeutic efficacy of meloxicam is strongly limited by its poor water solubility (0.012 mg/ml). [7] Apart from low aqueous solubility meloxicam also has high degree of enterohepatic circulation and longer half life (15- 20 hrs). [8] The current therapeutic scenario demands a strong need for a delivery strategy that can improve the therapeutic efficacy of Meloxicam by means of increasing its solubility or by reducing first pass metabolism.

Oral absorption of several drugs has been enhanced by SEDDS with different mechanisms. Meloxicam inhibits the synthesis of prostaglandins (PGs) through the inhibition of COX-2 pathway. [9] The dose of meloxicam is 7.5 mg or 15 mg. For the present study 7.5 mg was selected for the development of self emulsifying drug delivery system of meloxicam. The objective of the study was to design, optimize and evaluate the SEDDS of meloxicam.

MATERIALS AND METHODS

Materials

Meloxicam was obtained as gift sample from Sun Pharmaceutical Industries ltd. (Mumbai). Sun flower oil was purchased from Bunge India Private Ltd. (Mumbai). Tween 80 and PEG 400 were supplied by Loba Chemie, Mumbai. All other reagents used were of suitable analytical grade and used as supplied.

Solubility Studies

Equilibrium solubility of meloxicam was measured in various oils viz. castor oil, sunflower oil, soya bean oil, olive oil. An excess amount of meloxicam was added to each of selected vehicles and the mixture was stirred continuously for 72 h at 37 ± 1°C. After equilibrium was attained, the mixture was centrifuged at 3000 rpm for 10 min, and the obtained supernatant was filtered through a membrane filter (Himedia) having pore size of 0.45 µ. [10] Absorbance of the filtrate was measured using a double beam UV/VIS spectrophotometer at λ_{max} of 355 nm. The content of meloxicam was determined using a previously constructed standard calibration curve.

Pseudo ternary phase diagram construction

Pseudo-ternary phase diagrams were constructed using sigma plot 12.0 software by titrating three components, consisting of mixtures of surfactant and co-surfactant with water at the ambient temperature. The mixture was observed visually following equilibration. A series of pseudo-ternary phase diagrams were also constructed to precisely identify the regions of emulsification. For 1:1, Tween 80 and PEG 400 were mixed in a ratio of 1:1 and then oil is mixed in ratio of 9:1, 8:2, 7:3, 1:9. Finally aqueous titration was carried out by decreasing 0.5 g of mixture at each step. For 2:1, Tween 80 and PEG 400 were mixed in a ratio of 2:1 instead of 1:1. The plotted pseudo-ternary phase diagrams revealed that region of emulsification was more with Tween 80 and PEG 400 ratio of 2:1. [11]

Preparation of SEDDS

The liquid SEDDS formulations were prepared by standard admixture method. [11] Drug was dissolved in the sunflower oil. Tween 80 (surfactant) and PEG 400 (co surfactant) were mixed

separately and then surfactant/co surfactant mixture was added to oil drug mixture, while stirring at high speed using magnetic stirrer at optimum temperature. On the basis of region of emulsification in pseudo ternary phase diagram, Sunflower oil, Tween 80, PEG 400 were taken as three factors at three levels each (-1, 0, +1) using Central Composite Design for further formulation and optimization studies. Limits for all three factors were also ascertained for subsequent detailed studies. Overall a set of 20 experimental runs were formulated as per experimental design matrix. (Table 1) The response variables considered for optimization were self emulsification time and % drug release in 3 hrs.

Table 1: 20 Experimental Runs

Run	Sun flower oil conc.(mg)	Tween 80 conc.(mg)	PEG 400 conc.(mg)
1	0.00	0.00	0.00
2	0.00	0.00	0.00
3	1.00	-1.00	-1.00
4	0.00	0.00	0.00
5	-1.00	-1.00	1.00
6	0.00	0.00	0.00
7	0.00	-1.68	0.00
8	1.00	1.00	1.00
9	-1.68	0.00	0.00
10	1.68	0.00	0.00
11	0.00	0.00	0.00
12	0.00	0.00	1.68
13	-1.00	1.00	1.00
14	1.00	-1.00	1.00
15	-1.00	-1.00	-1.00
16	0.00	1.68	0.00
17	0.00	0.00	0.00
18	0.00	0.00	-1.68
19	1.00	1.00	-1.00
20	-1.00	1.00	-1.00

Formulation Characterization

Self Emulsification Time

Self Emulsification time was determined by the method described by Singh B. *et al.* [11] 1.0 g of each of the formulations was added to 0.1N HCl (500 ml) under continuous stirring (50 rpm) using a USP type II (paddle type) at 37 ± 0.5°C. The time required to disperse the system completely and uniformly was recorded as the self emulsification time.

***In vitro* Drug Release**

In vitro drug release study was carried out by dialysis bag technique. 1 ml of the SEDDS formulation along with 0.5 ml of dialysing medium (0.1 N HCl) were filled in the dialysis membrane (0.45 µ). Both ends of the membrane were tied with thread. One end is then tied with paddle and allowed to rotate in dialysing medium at 100 rpm using a USP type II (paddle type) at 37 ± 0.5°C. Samples were withdrawn at different time intervals (15, 30, 45, 60, 75, 90, 105, 120, 135,150,165,180 minutes) and then after suitable dilutions, were analyzed by UV spectrophotometer at λmax of 355 nm. Volumes of samples withdrawn (5ml) were replaced with fresh dialysing medium. (0.1 N HCl)

Optimization Data Analysis

Self emulsification time and % drug release were selected for optimization studies as response variables. Design expert 8.0.7.1 was used for formulation optimization of self emulsifying drug delivery of meloxicam with an objective to keep Sun flower oil conc, tween 80 and PEG conc within the range of experimental level. The goal of optimization was to minimize the self emulsification time and maximizing the drug solubility i.e. to emulsify the dosage form in minimum time with maximum drug release in GIT. Since optimization techniques are basically meant to make compromises, in order to achieve the desired goals and in order to get the desired goal lower limits and upper limits were set for different time points. The observed values were compared with predicted values. Linear correlation plots and the residual graphs were plotted between observed values and predicted values.

Droplet Size Measurement

Aliquots (1ml) of the samples serially diluted 1000 folds with purified water were employed to assess the globule size. The emulsion droplet size was determined by using a particle size analyzer. Each study was carried out in triplicate to ensure reproducibility and the mean values were reported. [12]

Zeta potential Determination

Aliquots (1ml) of the samples serially diluted 1000 folds with purified water were employed to determine zeta potential. Zeta potential was determined by Malvern zeta sizer. Each study was carried out in triplicate to ensure reproducibility. [13]

Drug Release Comparison with Marketed Formulation

Drug release profile of optimized formulation was compared with marketed brand having dose of 7.5 mg.

Release Kinetics of Optimized Batch

The drug release data of optimized was evaluated for various kinetic models viz. Zero order, first order, Higuchi model, Hixcon Crowell model and Korsmeyer Peppas model. [14,15] The study was carried out to determine the mode of drug release from the formulation.

RESULTS AND DISCUSSION

Solubility Studies

Solubility studies were carried out to identify the oil, surfactant and co surfactant that possess good solubilization potential for meloxicam. Solubility of meloxicam in various oils is shown in figure 1 and solubility of drug in surfactant and co surfactant were observed to be 0.391 in Tween 80 and 7.0 in PEG 400. [16] Sunflower oil was selected as an oil phase for further studies due to its higher solubilization potential (6.3mg/ml) for meloxicam.

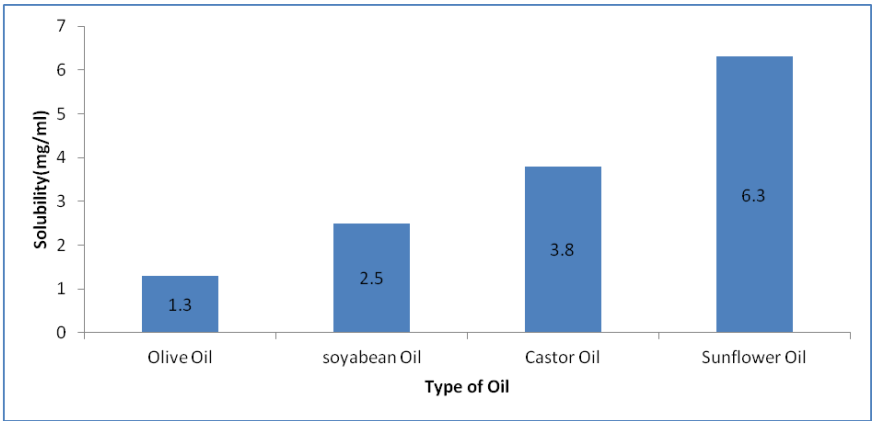

Fig. 1: Solubility analysis of drug in various oils

Pseudo ternary phase diagram study

Pseudo ternary phase diagrams were constructed to determine regions of emulsification and to optimize surfactant to co surfactant ratio and the concentration of oil. The studied systems were composed of sunflower oil, tween 80, PEG 400 and water. The pseudo ternary phase diagrams with different ratios of surfactant and co surfactant are shown in figure 2

On the basis of ternary phase diagrams shown here in figure 2, it was observed that region of emulsification in case of tween 80 and PEG 400 ratio 1:1 is 75 -95% and in case of tween 80 and PEG 400 ratio 2:1, it is 65- 95 %. Since the emulsification region obtained was more with 2:1 ratio of tween 80 and PEG 400, it was therefore, decided to use tween 80 and PEG 400 ratio 2:1 for further development of self emulsifying system of meloxicam.

Self Emulsification time determination

Emulsification times of the prepared formulations are shown in figure 3, it was observed that emulsification time varied from 1.23 to 5.01 minutes. It was less in case where co surfactant concentration was low and maximum emulsification time was observed in case where all three components were at their higher levels. Emulsification time was minimum in F_{19} (1.23 min) and maximum with formulation $F_{13.}$ (5.01 min)

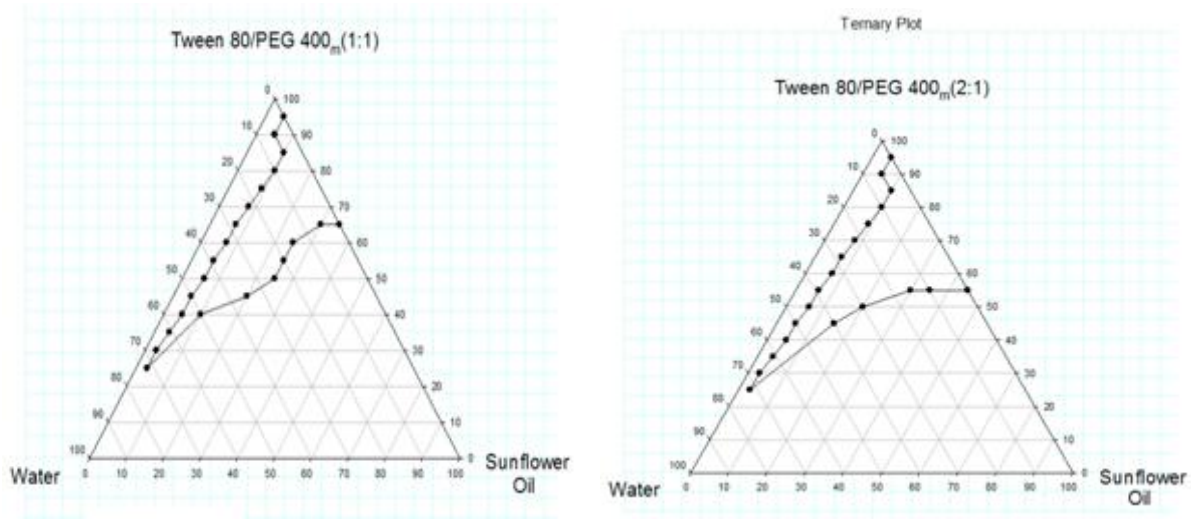

Fig. 2: Pseudo ternary diagram of surfactant and co surfactant in various ratios

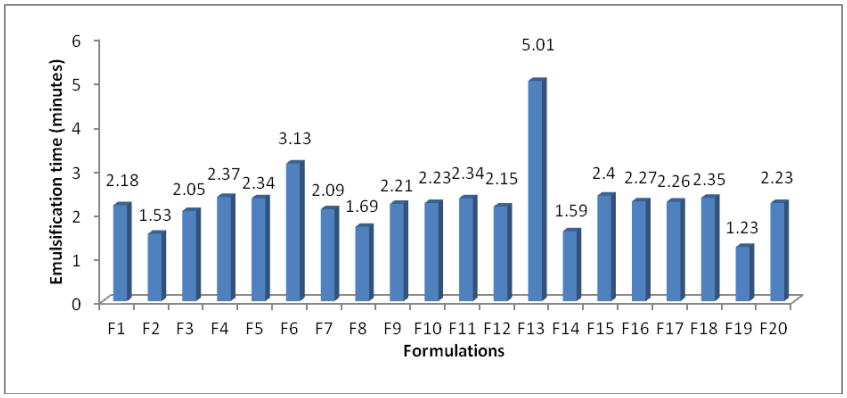

Fig. 3: Emulsification time of 20 trial runs

Dissolution Studies

The dissolution studies were carried out using USP type II paddle type dissolution apparatus and cumulative percent drug release of formulations F_1 to F_{20} at various time intervals were analyzed and their dissolution profiles are shown in figures 4 and 5. *In vitro* drug release study revealed that there was marked increase in the dissolution rate of meloxicam in all the 20 formulations and maximum release (96.35%) was observed with formulation F_{19} where co surfactant was at its lower level i.e. at -1 level, and oil &surfactant were at their higher levels i.e. at + 1 level. The minimum release (64.22%) was in F_6 where all the components were at their base levels. This revealed that drug release was more when concentration of co surfactant i.e. PEG 400 was less than the other two components i.e. sunflower oil and Tween 80.

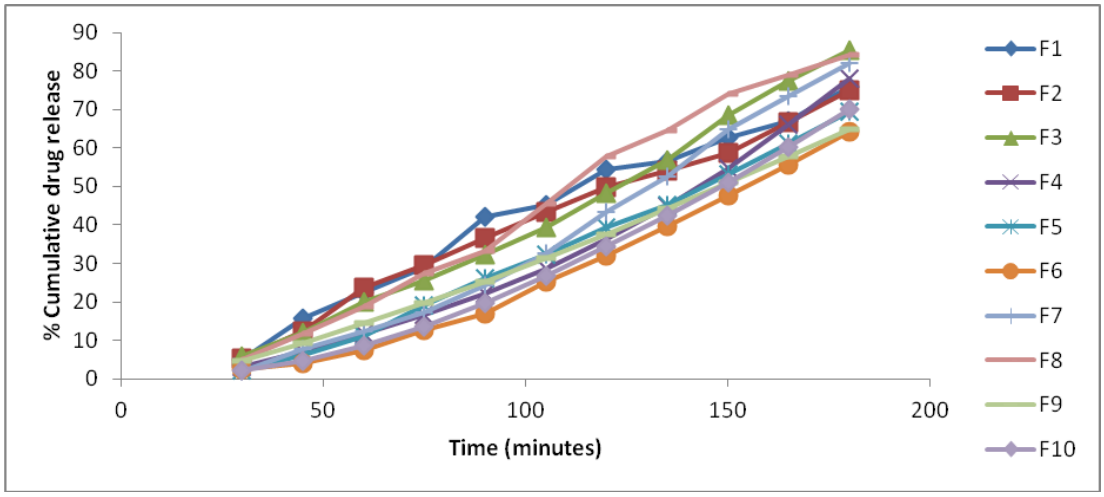

Fig. 4: Dissolution profile of F_1 to F_{10}

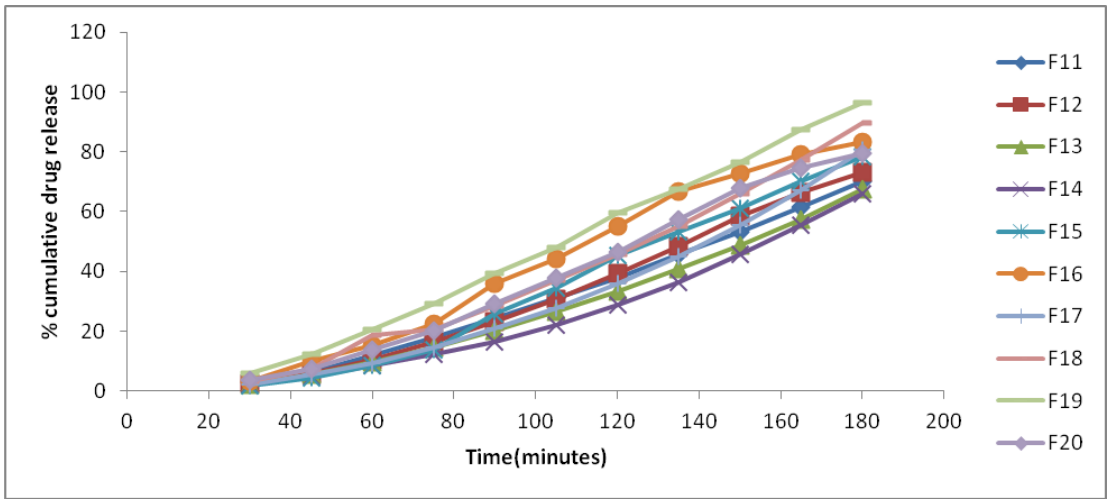

Fig. 5: Dissolution profile of F_{11} to F_{20}

Optimization Results

Based on the desirability approach for optimization one solution was suggested which indicated that a formulation with Sun flower oil concentration at +0.85 level, concentration of Tween 80 at +0.81 level and concentration of PEG 400 at -0.83 level should yield self emulsification time of 1.57 minutes and 89.15 % drug release in 3 hrs.

Cube plots for easier visualization of effect of three independent variables on response were generated. Cube plots for effect of the three independent variables on the selected two responses are shown in Figure 6& 7 for self emulsification time and % drug release in 3 hrs.

Droplet size determination

The average size of droplets formed after emulsification was measured by using Malvern Zetasizer at room temperature which was found to be 461.7 nm with poly dispersity index of 0.9 showing that the particles generated were mono disperse. (Figure 8)

Zeta potential measurement

The zeta potential of optimized batch was found to be -26.8 mV. (figure 9) A high zeta potential above 25(Either positive or negative) indicates that the droplets/particles generated after emulsification, shall repel each other and remain deflocculated and imparts physical stability to the system. Therefore Self emulsifying system of meloxicam appears to be physically stable.

Self emulsification time of optimized batch

The emulsification time of optimized batch was found to be 1.58 minutes i.e. the optimized batch emulsifies quickly. Figure 10 shows the Response Surface indicating the effect of sunflower oil and tween 80 concentration on emulsification time.

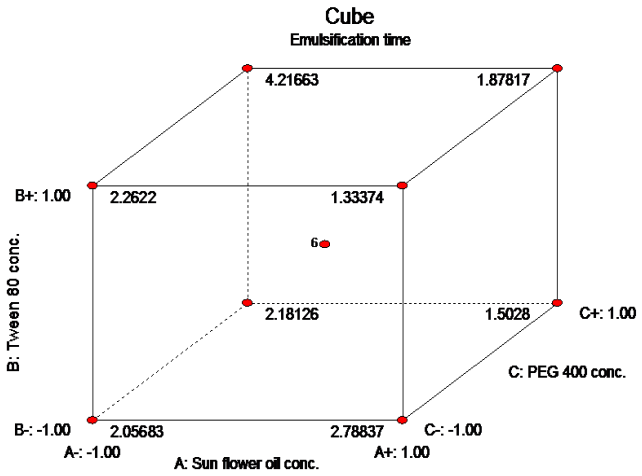

Fig. 6: Cube plot of self emulsification time and conc of all three variables

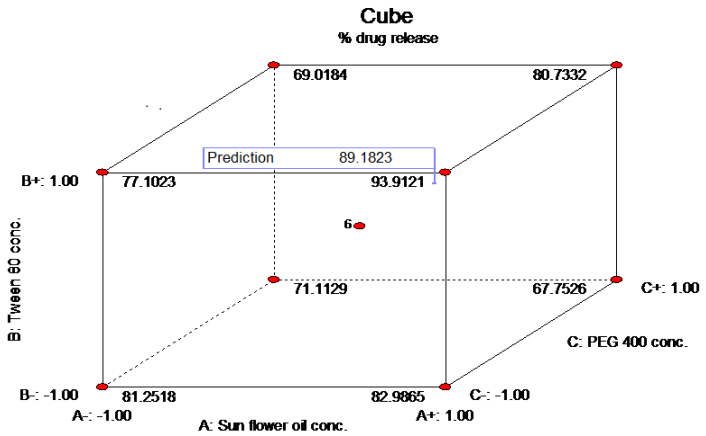

Fig. 7: Cube plot of % drug release and conc of all three variables

Temperature (°C):	25.0	**Duration Used (s):**	50
Count Rate (kcps):	233.3	**Measurement Position (mm):**	4.65
Cell Description:	Disposable sizing cuvette	**Attenuator:**	10

			Diam. (nm)	**% Intensity**	**Width (nm)**
Z-Average (d.nm):	1093	**Peak 1:**	461.7	100.0	65.71
PdI:	0.900	**Peak 2:**	0.000	0.0	0.000
Intercept:	0.975	**Peak 3:**	0.000	0.0	0.000

Result quality : Refer to quality report

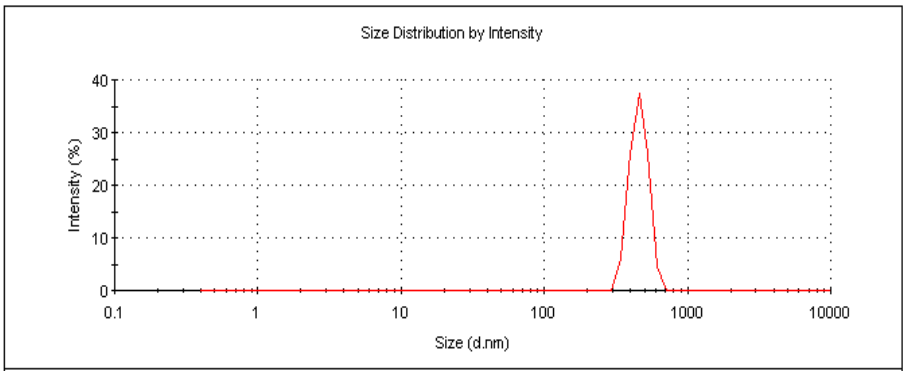

Fig. 8: Droplet size analysis of optimized batch

Temperature (°C):	25.0	**Zeta Runs:**	20
Count Rate (kcps):	222.7	**Measurement Position (mm):**	2.00
Cell Description:	Clear disposable zeta cell	**Attenuator:**	4

		Mean (mV)	**Area (%)**	**Width (mV)**
Zeta Potential (mV):	-26.8	**Peak 1:** -26.8	100.0	3.86
Zeta Deviation (mV):	3.86	**Peak 2:** 0.00	0.0	0.00
Conductivity (mS/cm):	0.0309	**Peak 3:** 0.00	0.0	0.00

Result quality : Good

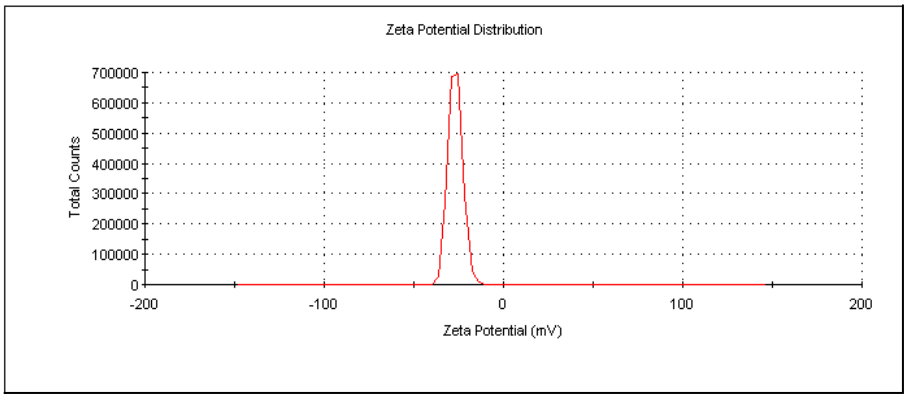

Fig. 9: Zeta potential of optimized batch

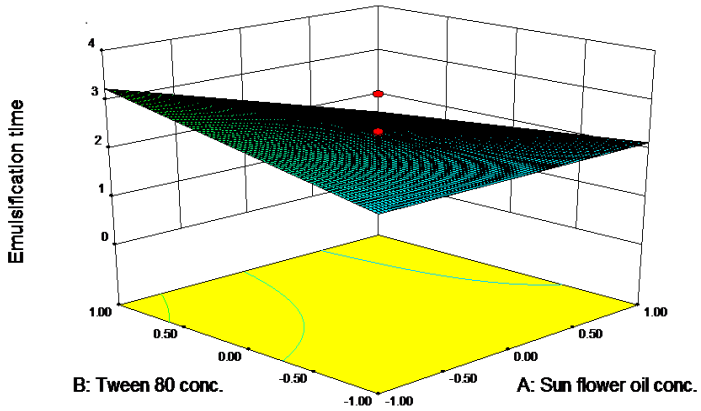

Fig. 10: Contour plot of self emulsification time and conc of 2 variables

Comparison of optimized formulation, marketed formulation and pure drug

Drug release behaviour of optimized formulation, marketed tablet and pure drug was studied in 0.1 N Hydrochloric acid and compared and the comparison of their dissolution profiles are shown in figure 11.

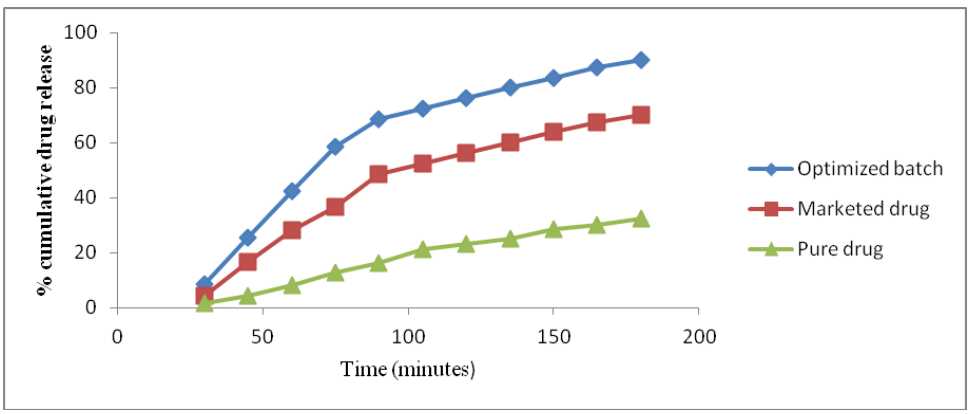

Fig. 11: Dissolution profile of optimized formulation, marketed tablet and pure drug

The dissolution profiles of pure, marketed and optimized batch shows that pure drug released very slowly (32.26%) and marketed tablet released 70.23% where as optimized formulation released 89.95% in 3 hrs. These results indicated that release of meloxicam was significantly enhanced by SEDDS suggesting that meloxicam dispersed perfectly in SEDDS and could be released faster due to small droplet size which permits a faster dissolution of drug into aqueous phase.

Release Kinetics of Optimized Batch

Many models have been proposed to explain the drug dissolution profiles where drug release is a function of time (t) related to the amount of drug dissolved from pharmaceutical dosage form. (Here self emulsifying drug delivery system)

Table 2: Various pharmacokinetic models with their R^2 values

Model	R^2 value
zero order	0.873
First order	0.990
Higuchi's model	0.939
Hixcon Crowell cube root	0.993
Peppas model	0.866

The drug release kinetics followed maximum is in Hixcon Crowell cube root mathematical model (R^2 value is 0.993) suggesting drug release from spherical surface. This model suggests that the dissolution occurs in planes that are parallel to the drug surface if the dosage form dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time (Figure 12). [12]

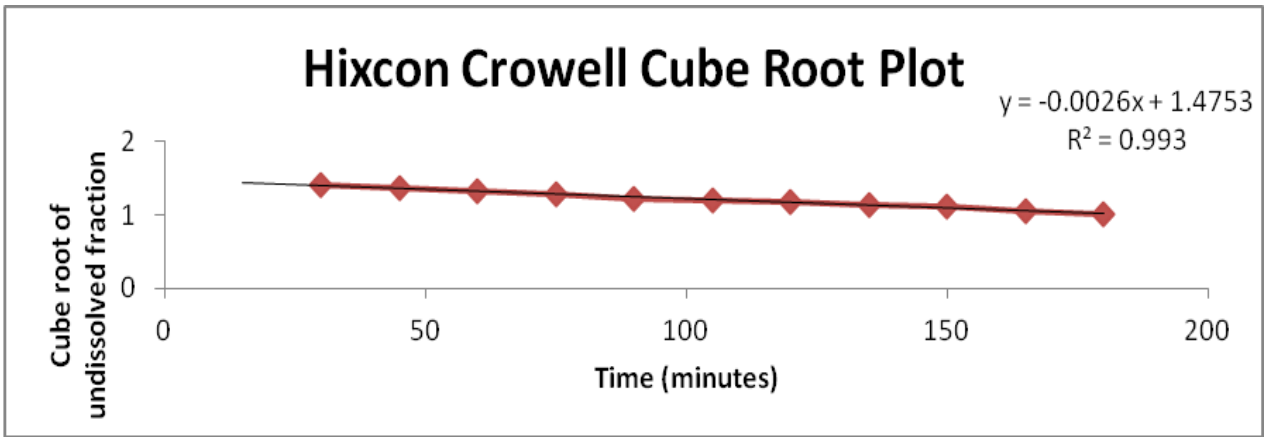

Fig. 12: Best fit model

CONCLUSION

Meloxicam SEDDS was developed using sunflower oil as lipid phase, Tween 80 as surfactant and PEG 400 as co surfactant. *In vitro* drug release study revealed the 89.45% of the drug release which was more than the pure drug as well as marketed formulation. Zeta potential study indicated physical stability of dosage form and droplet size was found to be in nanometer range (461.7 nm). The actual values were found to be closer to the predicted values, suggesting that optimization technique used was good and satisfactory. Future research can be directed towards exploring the pharmacokinetic and pharmacodynamics studies of such formulation. SEDDS can be explored for further dosage form design of drugs suffering from poor aqueous solubility or BCS class-II drugs.

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