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Original Article

# ETORICOXIB-LOADED SOLID LIPID NANOPARTICLE DOSAGE FORM: FORMULATION, OPTIMIZATION, CHARACTERIZATION, STABILITY STUDYAND *IN-VITRO IN-VIVO* EVALUATION

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**ABSTRACT**

**Objective:** The aim of present research work is to increase the bioavailability of poorly water soluble drug etoricoxib by developing solid lipid nanoparticle (SLN). Due to their unique size dependent properties, lipid nanoparticles offer the possibility to develop new therapeutics and enhance the bioavailability.

**Methods:** An aqueous-based etoricoxib loaded solid lipid nanoparticles were prepared by hot and high speed homogenization technique, using different ratio of stearic acid and tripalmitin as lipid and different amount of pluronic F-68 as emulsifier. Optimization was done by surface response methodology (SRM) technique. The formulations are charecterised by drug content, drug entrapment efficiency, particle size and zea potential determination, SEM etc and evaluated by pharmacokinetic, pharmacodynamic and stability study.

**Results:** Particle size distribution, entrapment efficiency and drug release were found 499.20 nm, 72% and 98.36% simultaneously, for selected optimized formulations. Zeta potential and span of optimized formulation found to be within the range of+34.2±0.9 and 0.29. *in-vivo* studies shows that pain reaction time (PRT) has increased from 6.2±0.42 to 8.45±0.19 second. Pharmacokinetic study shows an increasing remarkable result for $C_{max}$ which one is increased from 6274.290 µg $ml^{-1}$ h to 8558.134 µg $ml^{-1}$ h when compared with the standard formulation and for AUC it has been observed from 94202.963 mg. h. $l^{-1}$ to 124310.201 mg. h. $l^{-1}$

**Conclusion:** Development of SLN formulations could be a better approach to increase the bioavailability of poorly water soluble drug like etoricoxib.

**Keywords:** Etoricoxib, Pluronic F-68, Solid lipid nanoparticles, Surface response methodology.

## INTRODUCTION

Poorly soluble drugs are a general problem in pharmaceutical drug formulation and it is expected to increase because approximately 40% or more of the new chemical entities being generated through drug discovery programmes are poorly water soluble [1]. Lipid-based delivery systems are becoming more prevalent as carriers of drugs [2, 3]. Lipid-based systems have been successful in enhancing the bioavailability of BCS Class II molecules that are poorly water-soluble but highly permeable [4, 5]. Etoricoxib is a non-steroidal anti-inflammatory belonging to BCS Class II [6] rendering a prolonged therapeutic action and a delayed onset of anti-inflammatory and analgesic effect. It is employed to patients with chronic arthropathies and musculoskeletal and dental pain. The nobility of this research was to improve the bioavailability of poorly water soluble drug, etoricoxib, by preparation of solid lipid nanoparticle dosage form. Prepared formulations were optimized by surface response methodology. After in-vitro evaluation, the optimized formulation shows stable and increased bioavailability when compared with marketed products. In-vivo study indicates enhancement in the value of $C_{max}$, $T_{max}$, and for AUC.

## MATERIALS AND METHODS

### Materials

Etoricoxib was obtained as a gift sample from Rantus Pharmaceuticals Hyderabad, A. P. (India). Tripalmitin (99%), PluronicF68 and stearic acid were purchased from Himedia Laboratories Pvt. Ltd, Mumbai (India) and all other chemicals and glass apparatus used were of analytical grade.

### Preparation of solid lipid Nanoparticles

Stearic acid and tripalmitin were melted (heated 5 or 10 °C above the melting point of the lipid) separately in organic solvents at different ratio to form the oil phase. The drug was dispersed in hot oil phase of the same temperature (5-10 °C above the melting point of the solid lipid or lipid blend) with continuous stirring. The aqueous phase was heated above the melting point of lipid and the surfactant, pluronicF-68 at different ratio was added to it. The oil phase was added to the aqueous phase. The obtained emulsion (generally called pre-emulsion) is then sonicated at the same temperature for 15 minutes followed by stirred at high temperature for 1 hr and then passed through a homogenizer, adjusted to the same temperature. The produced hot O/W nanoemulsion was cooled down to room temperature; the lipid recrystallizes and leads to solid lipid nanoparticles.

### Characterization of prepared etoricoxib sln

### Differential scanning calorimetry (DSC) study

Drug-excipients compatibility study was performed by differential scanning calorimetric (DSC). 5 mg, accurately weighed etoricoxib and physical mixture (etoricoxib, lipids and pluronicF-68) were performed by using an automatic thermal analyzer system. (DSC60 Shimadzu Corporation, Japan) sealed and perforated aluminum pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as standard. The entire samples were run at a scanning rate of 10 °C/min from 30-200 °C. DSC study fig. 4, 5 and 6 revealed that all the above excipients and drug are compatible to each other.

### Particle size analysis

Particle size distribution of etoricoxib loaded SLN was studied by Mastersizer 2000 (Malvern Instruments Ltd, Worcestershire, UK). Particle size distribution was evaluated by using the volume distribution (d10%, d50%, d90%). Uniformity of distribution of nanoparticles was evaluated by span, by using the following equation.

SPAN= (D90%-D10%)/D50%

Where d90% is the particle diameter at 90% cumulative sized 10% is the particle diameter at 10% cumulative size and d50% is the particle diameter at 50% cumulative size.

**Measurement of zeta potential of SLN**

Zeta potential of SLNs was measured by Photon Correlation Spectroscopy (PCS) using zetasizer 3000HSA (Malvern, U. K.). Samples were diluted appropriately with the aqueous phase of the formulation for the measurements and the pH of diluted samples ranged from 6.8 to 7.0. Zeta potential measurements were made at 25 °C and the electric field strength was around 23.2 V/cm. The zetasizer measures the zeta potential based on the smoluchowski equation.

**Drug content by HPLC**

The assay was performed by high performance liquid chromatography (HPLC), equipped with a Waters 515 pump, a Waters 2487 dual l absorbance detector, and a C18 Waters symmetry® column (Novapak C 18 250×4.6 mm, packed with 4 µm particle size), flow rate = 1 ml/min). Calculation was done by using em power 2 Software.

***In vitro* drug release studies**

*In vitro* release of etoricoxib from solid lipid nanoparticle was evaluated by dissolution method. The release study of etoricoxib nanoparticle was performed in 7.4 pH phosphate buffer. The aqueous nanoparticulate dispersion equivalent to 60 mg etoricoxib was placed in dissolution apparatus containing 900 ml dissolution medium, which is stirred at 50 rpm and maintained at 37.2 °C. Samples were withdrawn at regular time intervals and the same volume was replaced by fresh dissolution medium. The samples were analyzed using UV-Visible spectrophotometer (Shimadzu) at 233 nm. All experiments were repeated thrice and the average values were to taken.

**Drug entrapment efficiency (EE)**

The total drug entrapment efficiency was determined by the use of ultrasonicator and the loading capacity is generally expressed in percent related to lipid phase (lipid+drug).

Entrapment efficiency (%) = total weight of drugs-weight of free drugs/total weight of drugs ×100

**Scanning electron microscopic (SEM) analysis**

The etoricoxib loaded SLN suspension was centrifuged at 4000 rpm. The supernatant was discarded and the sediment was dried to get the powdered etoricoxib loaded SLN. The powdered antiparticle was sputter-coated with gold–palladium, placed in a sample holder and viewed in a JSM5200 SEM (JEOL, Japan) with an accelerating voltage of 17 kV.

**Pharmacodynamic study-tail flick method**

Tail flick method is used to investigate the analgesic activities of the etoricoxib drug loaded solid lipid nanoparticles. The experiment was carried out by measuring tail withdrawal time with hot water.30 mice were randomly subdivided into five groups (1-5) of 6 mice per group and fasted for 12 hours. The mice (Group 1) were pretreated 1 hour before the experiment with 10 ml/kg normal saline. Group 2, (positive control) was given 400 mg/kg acetylsalicylic acid was administered to 150 gm rat Group 3, 4 and 5 (treatment group) was treated by formulation number F1, F2 and F3 by 100 mg/kg body weight. About 3-5 cm of the tail of each mouse was dipped into a water bath containing warm water maintained at the temperature of 50 °±1 °C and the time taken for the mouse to flick the tail known as the pain reaction time (PRT) was recorded for all the mice.

**Pharmacokinetic study**

Male Wistar rats (body weight 110–120 gm) were housed in cages for a minimum of at least 3 days prior to begin of the study and had free access to food and water. Food was withdrawn 12 h prior to the beginning of the study. Each study group consisted of six animals and received F1, F2, F3, Standard (Nucoxia) and control (Saline water) drugs. Oral formulations were administered at a dose of 100 mg/kg weight. Thus 2.49 ml formulation was administered to a 150g rats. Blood (200 µl) was sampled by retrobulbary puncture and puncture of the tail vein at the following time points: 1, 2, 3, 10, 15, 20, 25, 30, 35, 40, 50, 60h (12samples) because half-life of the drug is about 22h. Serum was obtained from whole blood. The serum samples were frozen at 20 °C until sample analysis by HPLC.

**Stability study**

Short term stability study was performed according to ICH guidelines and all the prepared etoricoxib loaded solid lipid nanoparticle formulations were found physically stable. Few parameters have been studied for the stability like particle size, drug entrapment efficiency, drug release, drug content and zeta potential.

**RESULTS AND DISCUSSION**

**Optimization of solid lipid nanoparticles using response surface methodology**

Response surface methodology (RSM) is a widely practiced approach in the development and optimization of drug delivery devices [7-12] based on the principal of design of experiments (DoE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations, and mapping of the response over the experimental domain to determine the optimum formulations [13-17]. The current study aims at developing and optimizing an oral SLN drug delivery system of etoricoxib using RSM. Computer aided optimization. The ratio of stearic acid and tripalmitin (X1) and amount of Pluronic F 68 (X2) was selected as the factors, studied at 3 levels each. The central point (0, 0) was studied in quintuplicate. All the formulation and processing variables were kept invariant throughout the study. Table 1 shows the composition of different SLN formulations prepared by hot homogenization technique. Table 2 summarizes an account of the 13 experimental runs studied, their factor combinations and the translations of the coded levels of the experimental units employed during the study.

**Table 1: Composition of different SLN**

| Ingredients | Amount(mg) |
|---|---|
| Etoricoxib | 600 |
| Stearic acid | 1300-1700 |
| Tripalmitin | 100 |
| Pluronic F 68 | 200-300 |

**Table 2: Factor combinations**

| TRAIL | $X_1$ | $X_2$ |
|---|---|---|
| I | -1 | -1 |
| II | 0 | 0 |
| III | 1 | 1 |
| IV | 0 | -1 |
| V | -1 | 0 |
| VI | 0 | 1 |
| VII | 1 | -1 |
| VIII | 1 | 0 |
| IX | -1 | 1 |
| X | 0 | 0 |
| XI | 0 | 0 |
| XII | 0 | 0 |
| XIII | 0 | 0 |

The ratio of stearic acid and tripalmitin (X1) and amount of pluronic F-68 (X2) was selected as the factors, studied at 3 levels each. The central point (0, 0) was studied in quadruplicate. All the formulation and processing variables were kept invariant throughout the study. Table 2 summarizes an account of the 13 experimental runs studied, their factor combinations and the translations of the coded levels to the experimental units employed during the study. Amount of

release in1h (Q1), particle size (n) and entrapment efficiency (e) were taken as the response variables.

**Optimization data analysis**

Various RSM computations for the current optimization study were performed employing Design Expert software (version 8.0.1. Stat-Ease Inc, and Minneapolis. MN). Polynomial models including interaction and quadratic terms were generated for all the response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented as,

Equation 1. $Y= \beta_0+\beta_1X_1+\beta_2X_2+\beta_3X_1X_2+\beta_4X^2_1+\beta_5X^2_2+\beta_6X_1X^2_2+\beta_7X^1_2X_2$

Where, ß0 is the intercept representing the arithmetic average of all quantitative outcomes of 13 runs; ß1to ß7 are the coefficients computed from the observed experimental values of Y; and X1and X2 are the coded levels of the independent variable, the terms $X_1X_2$ and Xi2 (i = 1 to 2) represent the interaction and quadratic terms, respectively. 3-D response surface graphs and 2-D contour plots were constructed in MS-Excel environment using the output files generated by the Design Expert software.

**RSM optimization results**

Mathematical relationships generated using MLRA for the studied response variables are expressed as equations 1 to 3.

Q 1 h =96.70+3.97A+0.21B+3.42AB-7.92A²-7.16B²…….. (1)

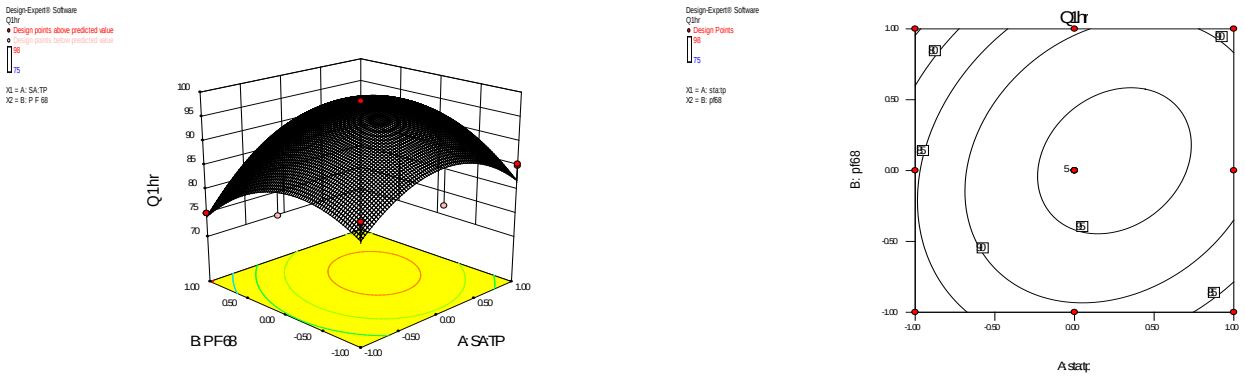
Particle size nm =32.53+0.52A-0.040B-1.97AB+3.92A²-2.40B²…… (2)

Entrapment efficiency = 72.21-0.50A+1.33B+0.00AB-1.22A²-0.72B²... (3)

All the quadratic equations were found to be statistically significant (P<0.01), using ANOVA. Fig. 1A to 3A portray the 3-dimensional response surface plots, while fig. 1B to 3B are the corresponding contour plots for the studied response proper-ties like release in 1 hour, particle size and Entrapment efficiency. The fig 1A and 1B shows a region of maximum with the value 95 for release rate at 1 hour and higher values of A and B shows the trend of linearity. Fig. 2A and 2B depict in a non-linearity manner, but in an ascending pattern with an increase in the ratio of stearic acid and tripalmitin as well as also for the amount of pluronicF-68. From the 3D response curve, it can be observed that if the ratio of lipids increased then the tendency of particle size of the formulation is also in increasing pattern. Fig. 3A and 3B show that at the lower level of mixing the linearity is found. The general trend of the curve shows a descending pattern. pluronic F-68 has a greater effect on the entrapment efficiency. The higher values show the tendency of maximum entrapment.

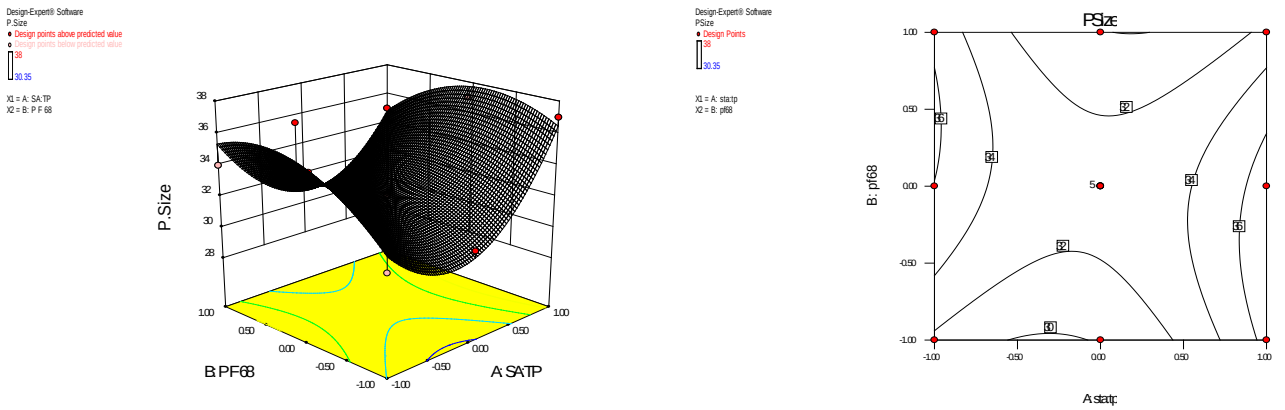
**Selection of optimized formulation**

From table 3, the selection of 3 best formulations was done from the above trial batches, based on satisfactory results of, dissolution release profile, particle size distribution and entrapment efficiency. Trial batch no I, II and III have been selected for further study to get the optimized formula.



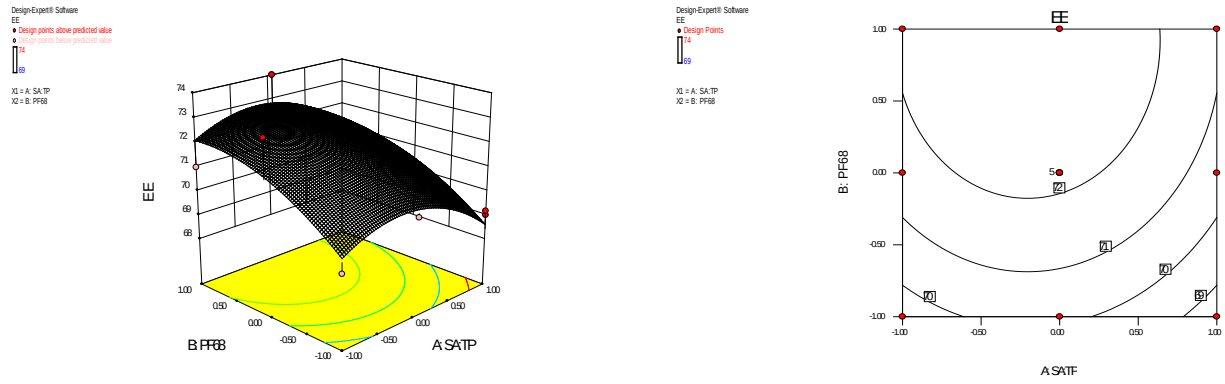

**(A)** **(B)**

**Fig. 1: (A) Response surface plot showing the influence of stearic acid: tripalmitin and the amount of pluronic F-68 on drug release in 1 hour and (B) corresponding contour plot showing the relationship between various levels of lipid ratio and amount of surfactant**




**(A)** **(B)**

**Fig. 2: (A) Response surface plot showing the influence of stearic acid: tripalmitin and the amount of pluronic F-68 on particle size and (B) corresponding contour plot showing the relationship between various levels of lipid ratio and amount of surfactant**




**(A)** **(B)**

**Fig. 3: (A) Response surface plot showing the influence of stearic acid: tripalmitin and the amount of pluronic F-68 on entrapment efficiency and (B) corresponding contour plot showing the relationship between various levels of lipid ratio and amount of surfactant**

**Table 3: Release parameters, entrapment efficiency and particle size of various SLN formulations prepared as per the experimental design, X1: stearic Acid: tripalmitin, X2: pluronic F-68**

| Trial No | Factor $X_1$ (mg) | Factor $X_2$(mg) | Release till 1h (Qrel, 1h,%) | Particle Size(nm) distribution | Entrapment Efficiency (%) |
|---|---|---|---|---|---|
| 1. | 13:1 | 0.20 | 84.45 | 776.00 | 69 |
| 2. | 15:1 | 0.25 | 80.32 | 867.45 | 73 |
| 3. | 17:1 | 0.30 | 98.36 | 499.20 | 72 |
| 4. | 15:1 | 0.20 | 82.46 | 971.35 | 70 |
| 5. | 13:1 | 0.25 | 88.36 | 947.26 | 70 |
| 6. | 15:1 | 0.30 | 85.23 | 987.78 | 69 |
| 7. | 17:1 | 0.20 | 88.29 | 982.23 | 70 |
| 8. | 17:1 | 0.25 | 75.31 | 984.56 | 71 |
| 9. | 13:1 | 0.30 | 88.92 | 867.45 | 73 |
| 10. | 15:1 | 0.25 | 80.32 | 867.45 | 73 |
| 11. | 15:1 | 0.25 | 80.32 | 867.45 | 73 |
| 12. | 15:1 | 0.25 | 80.32 | 867.45 | 73 |
| 13. | 15:1 | 0.25 | 80.32 | 867.45 | 73 |

**Differential scanning calorimetry**

Fig. 4 shows the result of DSC analysis of etoricoxib, the onset of the curve was started at 127.47 °C and the curve ends with 140.45 °C. For etoricoxib the endothermic peak was obtained at 137.4 °C. Fig. 5 shows the curve of physical mixture of tripalmitin, stearic acid and pluronic-F-68 and the peak was found at about 60.5 °C, 66.21 °C and 57.3 °C which are nearer about to their melting points that is respectively 65-68 °C, 69.6 °C and 52 °C.

From the Fig.6 it shows that four peaks were obtained at 57.3 °C, 66.21 °C, 60.5 °C and 136.81 °C consecutively for pluronic F-68, Stearic acid, tripalmitinand etoricoxib and there is no significant shifting.

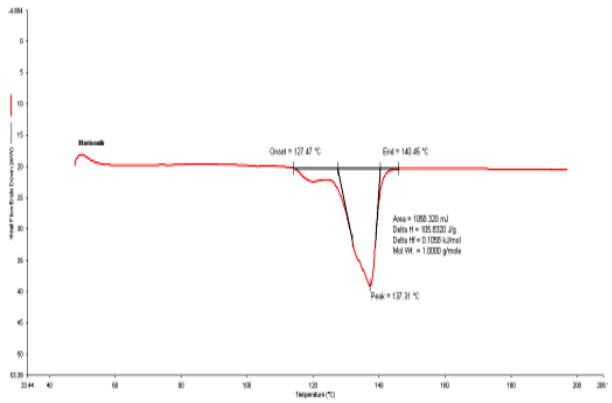


**Fig. 4: DSC of pure drug**

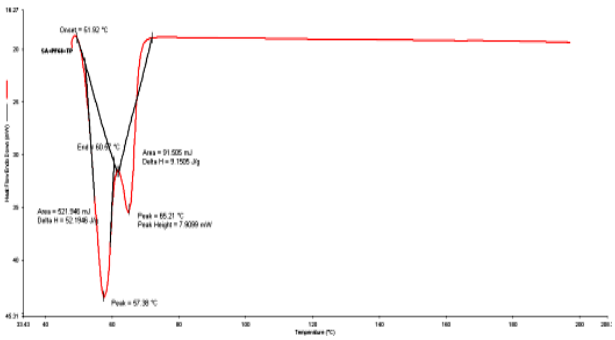


**Fig. 5: DSC of stearic acid, pluronic F 68 and tripalmitin**

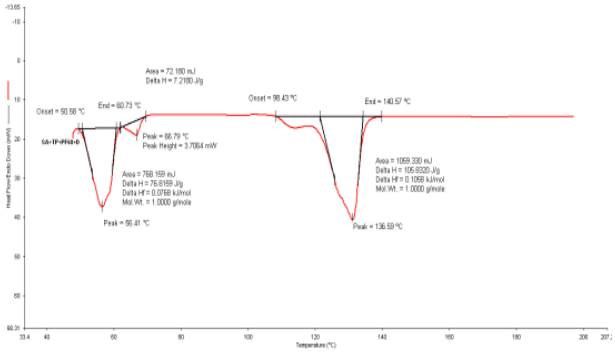


**Fig. 6: DSC for stearic acid, tripalmitin, pluronic-F-68 and etoricoxib**

**Particle size analysis**

The SLN dispersion was successfully prepared by high speed homogenization method. Particle size distribution, zeta potential and span value of SLN were shown in table 4. Stearic acid induced positive charges to the etoricoxib solid lipid nanoparticles. Positively charged nanoparticles repulse with adjacent nanoparticles there by coalescence is minimized and the particles obtained were smaller. The greater the ratio of stearic acid: tripalmitin and concentration of pluronic F-68, the mean size of formulations was found smaller. The mean value of SLN F1, SLN F2 and SLN F3 has been found 776.20, 947.34 and 499.02 nm. fig. 7, fig. 8 and fig. 9 show the particle distribution curve obtained by Mastersizer.

**Drug entrapment efficiency (EE)**

Entrapment efficiency is found for optimized formulation is more than 72%.

**Scanning electron microscopic (SEM) analysis**

Micrographs prove a great morphological difference between the pure drug (A&C) and between the surfaces of prepared SLN (B&D).

Fig. 10 shows a prominent difference between the surface morphology of both.

**Table 4: Particle size, span value and zeta potential of prepared SLNs**

| Formulation | Particle size (nm) | Span value | Zeta potential (mv) |
|---|---|---|---|
| F1 | 776.20 | 1.43 | +31.2±0.1 |
| F2 | 947.34 | 1.40 | +33.2±0.6 |
| F3 | 499.02 | 0.29 | +34.2±0.9 |

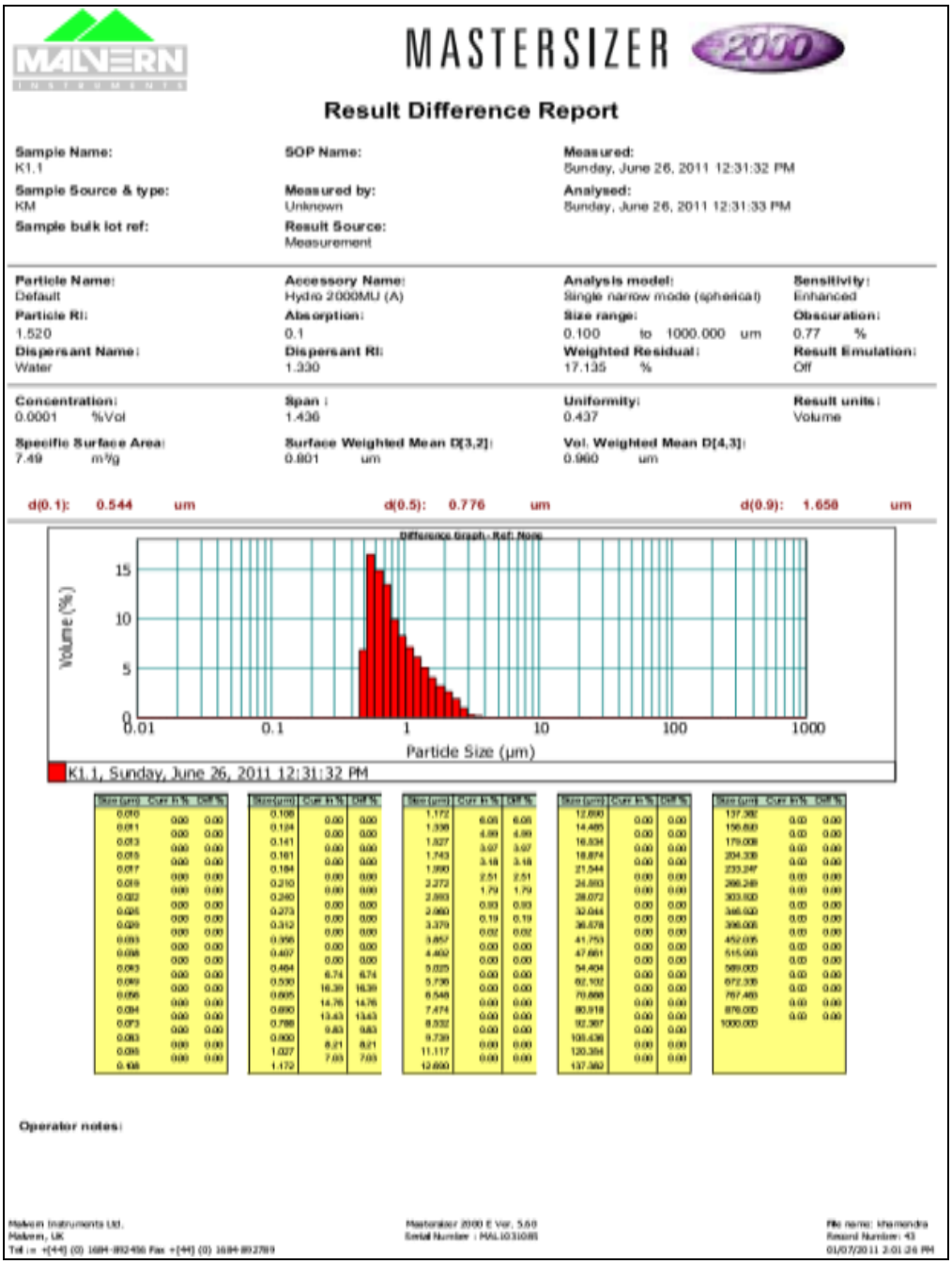



**Fig. 7: Particle size distribution of F1**

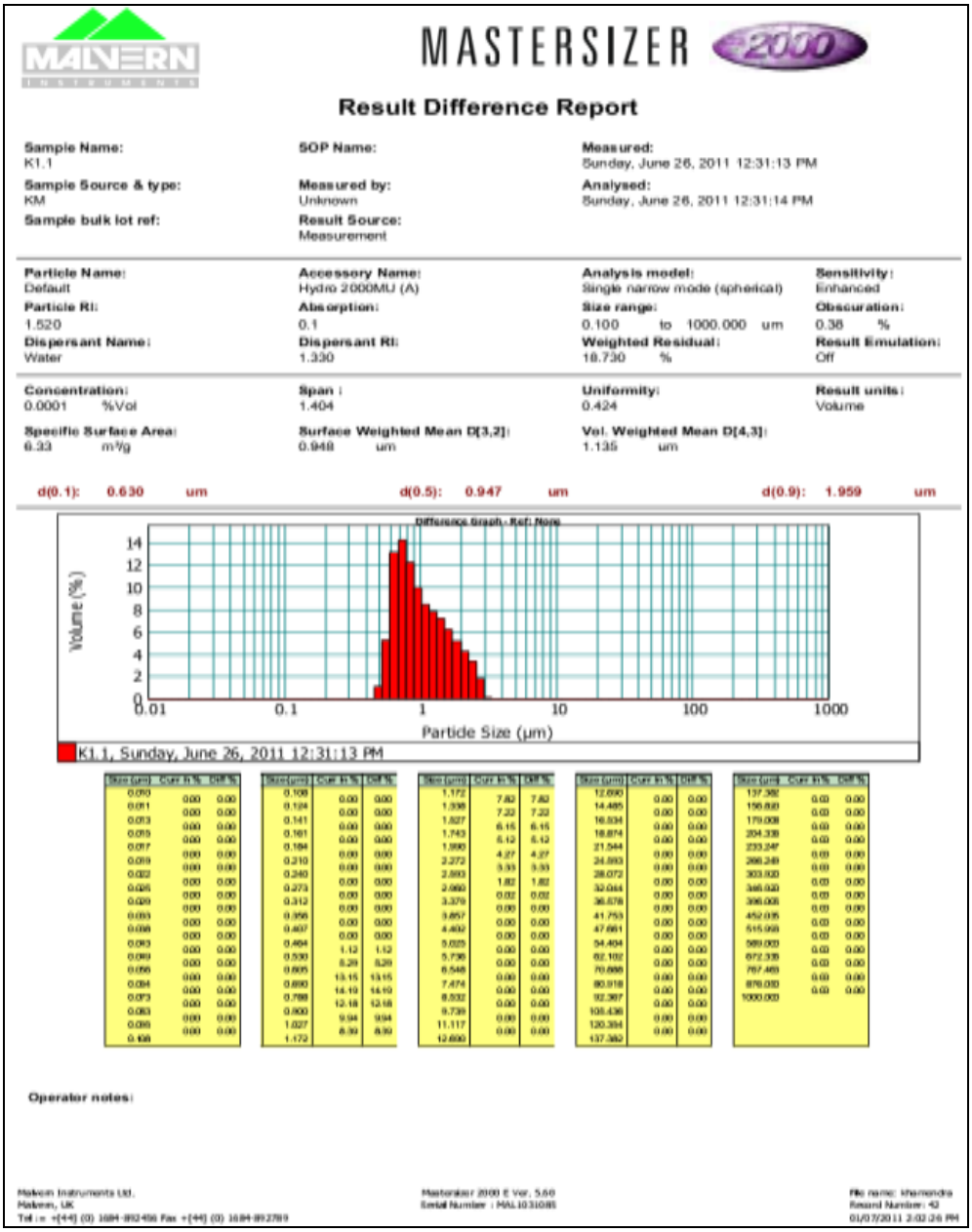



**Fig. 8: Particle size distribution of F2**

**Drug content by HPLC**

The assay was performed by high performance liquid chromatography (HPLC). Calculation was done by using Empower 2 software. The total drug content was found to be 101.8% of the labelled amount. From fig. 11 the retention time was noted 1.357 min.

***In vitro* drug release studies**

In-vitro release of etoricoxib was evaluated by dissolution method. After one hour study the release was found to be 98.36% and it was found higher when compares between two marketed products. fig. 12 shows the release curve of optimized formulation (SLN F3) and between two marketed products.

From table 5, It was found that the in-vitro drug release of three optimized batch was best explained by zero order as the plots showed the highest linearity for F1 (r2=0.9987), F2 (r2=0.9978) and for F3 (r2=0.9998) followed by hixson crowell model and others. Drug release was found to be close to zero-order kinetics, drug release was independent of concentration.

**Table 5: Results of model fitting of batch F1, F2 and F3.**

| Formulation | Order of release | Value of $R^2$ |
|---|---|---|
| F1 | Zero order plot | 0.9987 |
| | First order plot | 0.9678 |
| | Higuchi model | 0.901 |
| | Korsmeyer-peppas model | 0.9583 |
| | Hixson Crowell model | 0.9696 |

| Formulation | Order of release | Value of $R^2$ |
|---|---|---|
| F2 | Zero order plot | 0.9978 |
| | First order plot | 0.9568 |
| | Higuchi model | 0.923 |
| | Korsmeyer-peppas model | 0.9585 |
| | Hixson Crowell model | 0.9656 |

| Formulation | Order of release | Value of $R^2$ |
|---|---|---|
| F3 | Zero order plot | 0.9998 |
| | First order plot | 0.9378 |
| | Higuchi model | 0.941 |
| | Korsmeyer-peppas model | 0.9583 |
| | Hixson Crowell model | 0.9636 |

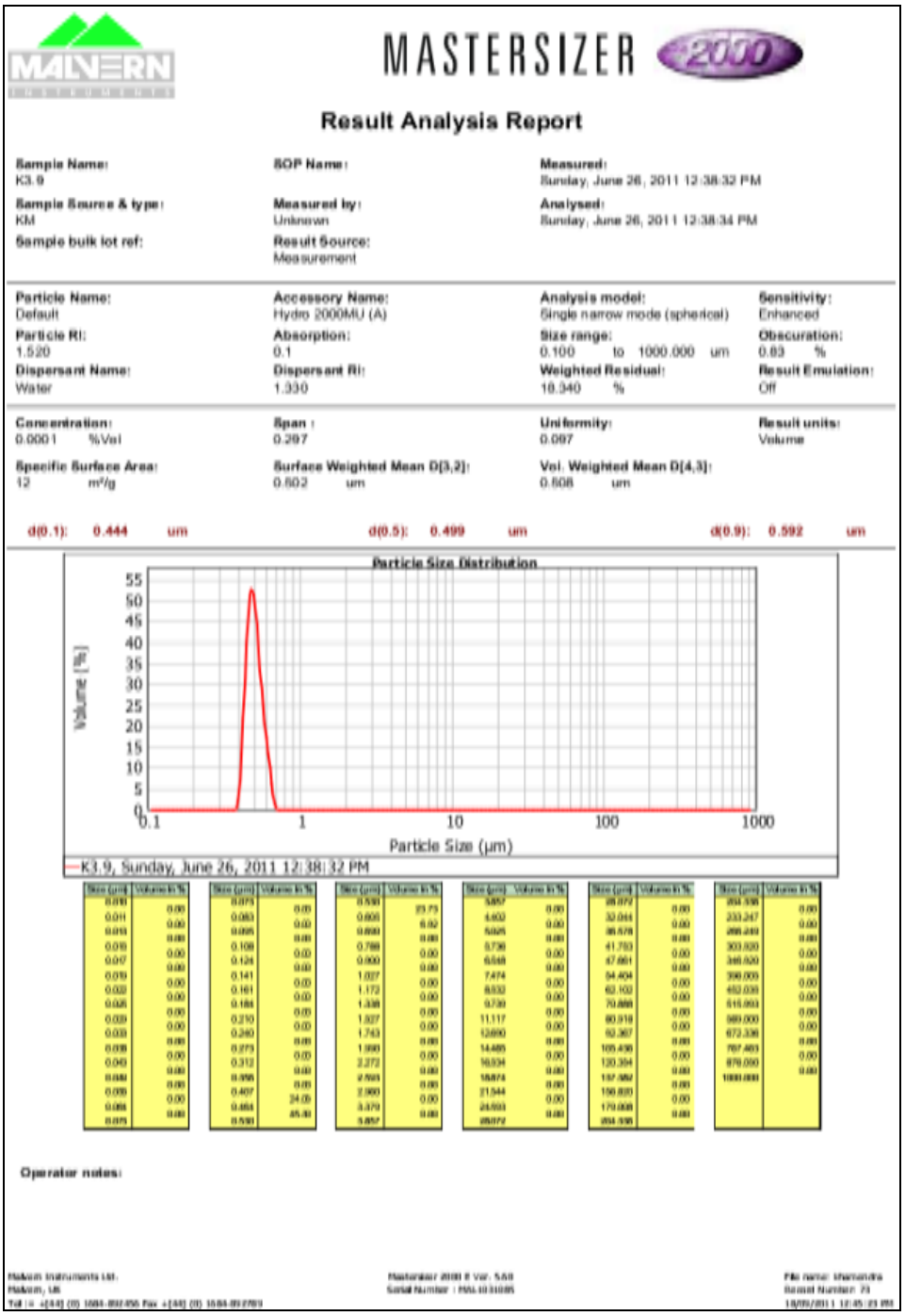



**Fig. 9: Particle size distribution of F3**

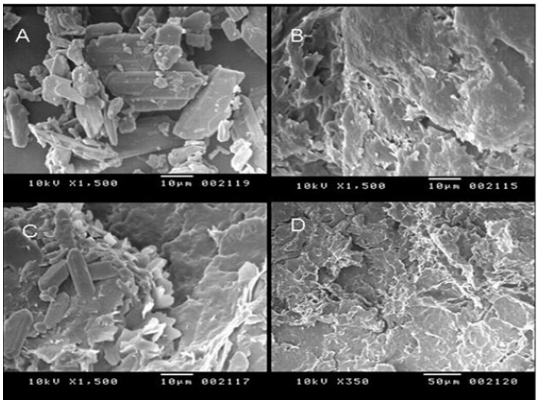



**Fig. 10: SEM photograph of pure etoricoxib drug and drug loaded SLN**

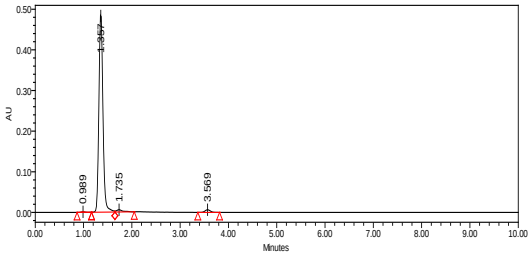



**Fig. 11: Chromatogram spiked with 30µg/ml of the reference standard**

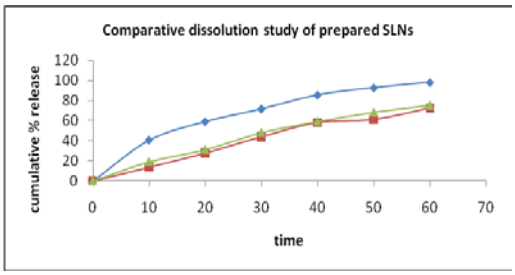



**Fig. 12: Comparative dissolution study of optimized formulation and marketed products**

### *In vivo* study-tail flick method

Table 6 indicates that the tail withdrawal response or tail flick time was significantly ($p<0.0001$) increased from 1.8±0.18 seconds for group 1(10 ml/kg normal saline) to 6.2±0.42 for Group 2, ASA (400 mg/kg) treated group and 7.5±0.21,7.9±0.34 and 8.45±0.19 seconds respectively for Group 3,4 and 5 that were given formulations F1,F2 and F3 (100 mg/kg respectively).

**Table 6: Result of PRT for formulations on tail flick method**

| Group | Treatment (mg/kg, B. O) | Mean PRT (sec) |
|---|---|---|
| 1 | Normal saline 10 ml/kg | 1.8±0.18 |
| 2 | Acetylsalicylic acid 400 | 6.2±0.42 |
| 3 | SLN F1 | 7.5±0.21 |
| 4 | SLN F2 | 7.9±0.34 |
| 5 | SLN F3 | 8.45±0.19 |

### Pharmacokinetic study

After thorough study of pharmacokinetics, it was observed that formulation SLN-F3 have a great enhancement in $C_{max}$ value of 8558.134 when compared with standard 6274.290 and also with respect to other formulation. The value of AUC is found also higher in the case of formulation SLN-F3 (21317.995µg h/ml) than compared to standard (15677.336 µg h/ml). Volume of distribution is also found remarkably higher for formulation SLN-F3 when it compared with other formulations or with standard.

Chromatographic conditions for all studies were mentioned in table No 7 and chromatogram obtained for the rat plasma blank and then rat plasma with internal standard, shown in fig. 13&14.

**Table 7: Chromatographic condition**

| Column | Hypersil BDS C-18 |
|---|---|
| Mobile phase | methanol: phosphate buffer (ph7.8) (9:1) |
| Flow rate | 1 ml/min |
| Injection volume | 20 µl |
| Run time | 15 min |
| Etoricoxib | 3.480 |
| Internal Standard (IS) | 5.240 |
| Wave length | 235 nm |

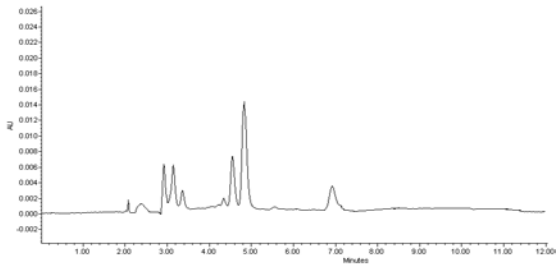


**Fig. 13: Chromatogram of rat plasma blank**

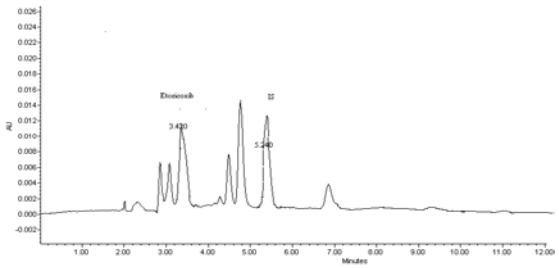


**Fig. 14: Chromatogram of drug along with IS in plasma sample**

Table 8 and fig. 15 shows the plasma drug concentration vs time profile and the calculation did up to 60 hours (nearly 3 half-lives of drugs) to find out the mean drug concentration (ng). The test includes the study of measurements of mean drug concentration after 10, 30 & 40 hrs. Statistical analysis was performed using one way ANOVA test, with $p<0.05$ and it has been found that there are significant differences between F1, F2 and F3. Multiple comparison test between F1-F2, F1-F3, and F2-F3 shows that there is significant differences between each pair of formulations.

**Table 8: Plasma drug concentration vs time profile**

| Time(h) | Mean drug concentration(ng) | | | | |
|---|---|---|---|---|---|
| | SLN F1 | SLN F2 | SLN F3 | STAND | CONT |
| 0 | 0 | 0 | 0 | 0 | 0 |
| T)1 | 2233.11±101.2 | 1925.77±130.4 | 4040.16±110.2 | 1937.64±111.12 | 0 |
| Ti(hr22 | 4061.27±102.3 | 5395.7±140.78 | 5883.58±140.3 | 2729±118.23 | 0 |
| Time 3 (h | 5658.01±108.2 | 6458.6±164.34 | 8558.13±179.9 | 6274.2±140.78 | 0 |
| Time(10r | 6381.51±98.8* | 5940.84±19.9* | 6661±178.23* | 5406.0±140.29 | 0 |
| Time 15 (h | 5469.9±110.32 | 4138.96±134.3 | 3842.4±123.45 | 3481.16±132.23 | 0 |
| Time 20 (h | 4052.47±104.4 | 2863.02±112.9 | 3218.5±178.23 | 1857.27±134.23 | 0 |
| Time(25r | 1438.77±90.23 | 1194.04±98.45 | 1784.0±99.23 | 1442.7±99.90 | 0 |
| Timhr30 | 745.1±70.22* | 740.13±85.34* | 942.23±89.34* | 847.51±64.12 | 0 |
| Time 35 (h | 545.23±63.34 | 577.89±79.90 | 540.65±69.49 | 543.76±75.89 | 0 |
| Time(40hr | 345.12±23.23* | 345.34±36.75* | 346.23±32.12* | 378.98±23.34 | 0 |
| Time(50hr | 145.21±27.76 | 149.13±43.12 | 146.12±33.30 | 160.23±34.12 | 0 |
| Time(60r | 45.12±1.09 | 49.98±1.34 | 46.14±1.90 | 60.99±1.90 | 0 |

mean±SD, n=6,* Significant Difference compared to Time vs MDC ($P<0.05$)

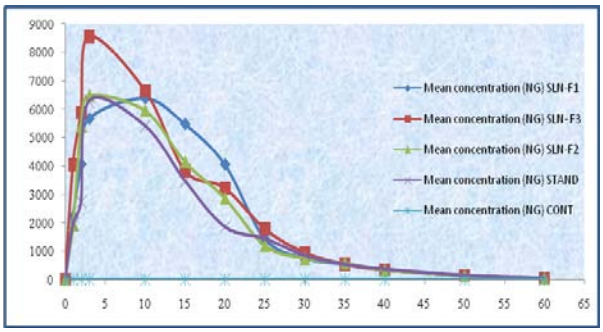



**Fig. 15: Plasma drug concentration vs time profile**

### Stability study

Short term stability study was done for 180days according to the ICH protocol and all the formulation found stable.

## CONCLUSION

Through this research work, an attempt has been undertaken to successfully develop and optimized the formulation by RSM with the use of different ratio of lipid, surfactant and other excipients. The evaluation of the prepared SLN shows a satisfactory result and it also shows that the drug release from the SLN formulation is very significant when we compared with different marketed products. Liquid dosage form is always having better patient compliance than other dosage forms like tablet, capsule and parenteral. Different aged patients can consume liquid dosage forms. It has been observed that through the nano suspension dosage form the bioavailability in terms of dissolution of etoricoxib has increased significantly than the only available etoricoxib tablet dosage form in the market. Pharmacokinetics and pharmacodynamic study proves that the prepared SLN formulation is having better compliance over the standard marketed product when compare the result of $C_{max}$, AUC, or VD. Short term stability study gives an idea of the stability of the product under room temperature and it has been observed a very good stable product.

## CONFLICT OF INTERESTS

Declared None

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