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RESEARCH ARTICLE

Preparation and Characterization of Meloxicam Solid Lipid Nanoparticles

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ABSTRACT

The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation into the skin through skin at predetermined rate with minimal inter and intra patient variation. Currently transdermal delivery is one of the most promising methods for drug application. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug caused from temporary over dose and is convenience in transdermal delivered drugs that require only once weakly application. In the present study Meloxicam solid lipid nanoparticles were prepared and evaluated. Stable nanoparticles of SLNs were prepared using high-shear homogenization followed by ultrasonication technique. 3^2 factorial designs were used in the process of optimization. This method was easy to apply, simple, cheap and promising for preparing nanoparticles. To study the interaction between drug and excipients DSC and FT- IR studies were performed and it was found that there was absence of interaction between drug and excipients. The drug release studies that were performed for 24hrs conferred that the drug release was by diffusion through the prepared SLNs. It can be concluded that from the obtained results Keterolac SLNs can be employed for controlled delivery of drug in the treatment as NSAIDs.

Keywords: Meloxicam, Compritol 888 ATO, Precerol ATO 5 and Pluronic F127

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CONTENTS

1. Introduction

Transdermal Drug Delivery System (TDDS)[1] are defined as self contained, discrete dosage forms which are also known as "patches" [2, 3] when patches are applied to the intact skin, deliver the drug through the skin at a controlled rate to the systemic circulation. [4] TDDS are dosage forms designed to

deliver a therapeutically effective amount of drug across a patient's skin.[5]

The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation into the skin through skin at predetermined rate with minimal inter and intra patient variation. Currently transdermal delivery is one of the most promising methods for drug application. [6] It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug caused from temporary over dose and is convenience in transdermal delivered drugs that require only once weakly application.[7]

That will improves bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms.[8] Transdermal delivery not only provides controlled, constant administration of drugs, but also allows continuous input of drugs with short biological half lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Several important advantages of transdermal drug delivery are limitations of hepatic first pass metabolism, enhancement of therapeutic efficacy and maintenance of steady plasma level of drug. The developments of TDDS is a multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an *ex vivo* and *in vivo* model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical, stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important economy.

2. Materials and Methods

Meloxicam procured from Milton Generic Pvt Ltd, **Ethanol and Methanol** procured from Tradewell International Pvt Ltd, **Compritol 888 ATO, Precerol ATO 5** and **Pluronic F127** from Gattefose India Pvt Ltd, **Dynasan 114** from K G Supplier, **Tween 80** and **Span 20** from Mohini Organics Pvt Ltd

Methods:

Standard solutions preparation[9, 10]**:**

Standard solutions of Meloxicam were prepared by dissolving 50 mg of Meloxicam with ethanol, methanol in 50 ml volumetric flasks separately, then diluting up to the mark.

Determination of Absorbance spectrum:

Transfer 1 ml of standard solution into ethanol, methanol in 10 ml volumetric flasks seperately and dilute up to the mark. The resulted 10 µg/ml solution was measured at range (200- 400nm) using ethanol, methanol as blank. It was found that Meloxicam showed the absorbance spectrum λmax at 365nm (Fig 1).

Preparation of Calibration curve: From the sample solution, 100µg/ml resulting solution was prepared. From this 100 µg/ml solution (0.4- 2.0 ml) was transferred to 10ml volumetric flasks and diluted with distilled water up to the mark. The method was determined at different concentration levels ranging (4-20µg/ml) for Meloxicam, the calibration curve was constructed by plotting absorbance versus concentration of Meloxicam (µg/ml) (Table 1) (Fig.2).

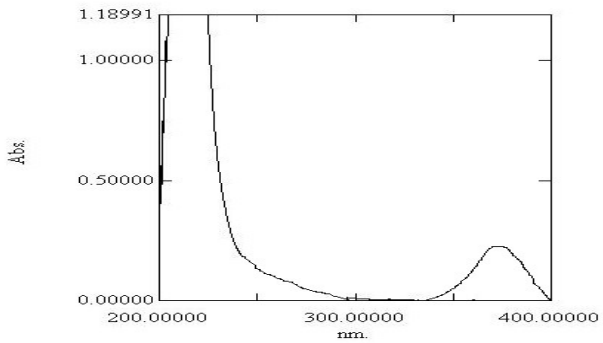

Fig 1: λmax of Meloxicam

Table 1: Standard plot for Meloxicam

Conc(ng/ml)	Absorbance(nm)
0	0
4	0.174±0.32
8	0.349±0.14
12	0.524±0.68
16	0.699±0.47
20	0.876±0.11

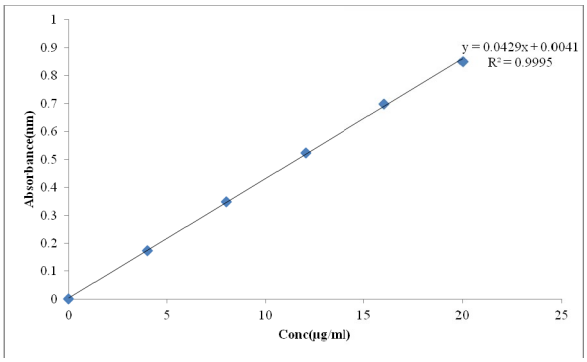

Fig 2: Standard plot of Meloxicam

Preformulation studies:

The pre formulation studies were executed for drug and excipients by fourier transforms infrared spectroscopy and differential scanning calorimetry.

Preparation of Meloxicam SLNs[11]

Meloxicam SLNs were prepared by using Dynasan 114 and heating above 45^0c. Slowly dissolve 15 mg of drug so that drug lipid mixture was obtained. An aqueous phase was prepared by dissolving Pluronic F 127 in distilled water and heated up to the same temperature as lipid phase. Now add the lipid phase in to the aqueous phase and homogenization was carried out at 25000 rpm for 5 min using a Heidolph homogenizer (Heidolph Instruments, Schwabach, Germany). The resultant mixture was sonicated for 30 min (Digital Sonicator; MTI, Michigan, USA). Meloxicam-loaded SLNs were finally obtained by allowing the hot

nanoemulsion to cool to room temperature (Table 2). Blank SLNs were prepared using the same procedure but excluding the drug.

Experimental Design [12, 13, 14]

In order to optimize the best formulation, Design-Expert 10.0 version software (Stat-Ease Inc., USA) was employed. Nine experiments were conducted at all promising combinations since 2 factors at 3 levels were used (Table 3). The amount of Lipid (X_1) and the amount of surfactant(X_2) were chosen as independent variables, where as particle size (Y_1), entrapment efficiency (Y_2) and % drug release (Y_3) were selected as dependent variables (responses) in order to optimize the response data.

Data analysis, optimization and cross validation of model[15,16,17]

6.1 Data analysis:

Responses were used for statistical analysis and optimization. Responses obtained from the nine runs for each drug were simultaneously fitted to linear, interactive and quadratic models using the Design Expert software.

Optimization:

A multi-criteria decision approach, numerical optimization technique (desirability) and graphical optimization technique (overlay plots) were employed to optimize the formulations with the desired responses (responses from theoretical profile values). Optimization for Meloxicam were performed with constraints of Y_1, Y_2 and Y_3. For finalizing the optimum formulation, targets were set for these constraints for getting respective desirability function response and overlay plots.

6.3 Cross-validation of model:

The chosen experimental design was validated by preparing the optimized formulation using predicted optimal independent values. Optimized formulations were also further studied.

The experimental values of the responses were determined from the *in vitro* dissolution data of the optimized formulation.

Characterization of Nanoparticles

1. Size measurement and Polydispersity index (PDI): The studies were performed at room temperature. All the samples were analyzed in triplicate.

Evaluation of Nanoparticles

Drug loading:

The drug content of obtained nanoparticles was calculated using below equation:

$$Drug\ content\ (\%) = \frac{weight\ of\ drug\ in\ nanoparticles}{Total\ weight\ of\ nanoparticles} \times 100$$

Determination of entrapment efficiency: The entrapment efficiency (%) was determined using the below equation.

$$Entrapment\ Efficiency\ (EE\ \%) = \frac{Weight\ of\ Drug\ in\ nanoparticles}{Total\ Weight\ of\ Drug\ taken} \times 100$$

***In vitro* drug release studies:** The amounts of drug present in the Meloxicam SLNs were studied using USP XXIV dissolution rate test apparatus employing the paddle (Apparatus-II). 900 ml of distilled water was used as dissolution medium maintained at a temperature of 37±0.5º C and the paddle was rotated at 50 rpm. 5 ml of samples were withdrawn with a syringe fitted with a pre filter at predetermined time intervals and immediately replaced with 5 ml of fresh medium maintained at 37±0.5º C.

Table 2: Formulation of Meloxicam Solid lipid Nanoparticles

Ingredients	MLS1	MLS2	MLS3	MLS4	MLS5	MLS6	MLS7	MLS8	MLS9
Meloxicam(mg)	15	15	15	15	15	15	15	15	15
Dynasan 114 (%w/w)	1	0.5	1	0.5	0.5	1.5	1.5	1	1.5
Pluronic F 127(%w/w)	0.03	0.03	0.02	0.04	0.02	0.03	0.04	0.04	0.02

Table 3: Experimental range and levels of the independent variables in a 32 full factorial design Actual values (Meloxicam)

Coded values	Amount of Lipid (%w/w)	Amount of Surfactant (%w/w)
-1	0.5	0.02
0	1	0.03
+1	1.5	0.04

3. Results and Discussion

FTIR Studies

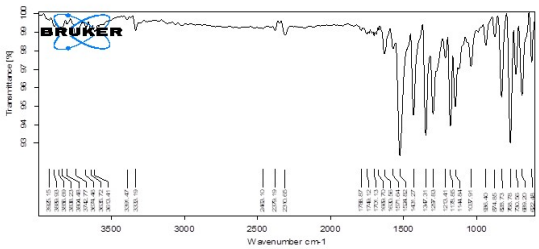

Figure 3: FTIR of Meloxicam Pure drug

-OH	3613.41
-NH	3333.19
S=O	1037.9
C=O	1669.70
C=C	1630.56
-N-H	3391.47

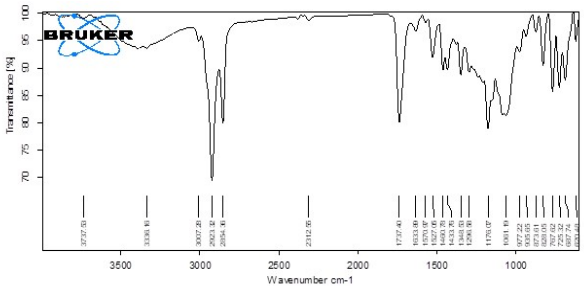

Figure 4: FTIR of Meloxicam Optimized formulation

-OH	3737.53
-NH	3356.16
S=O	1061.1
C=O	1737.40
=C-H	3007.28
C=C	1633.89
-C-H	2933.32

DSC

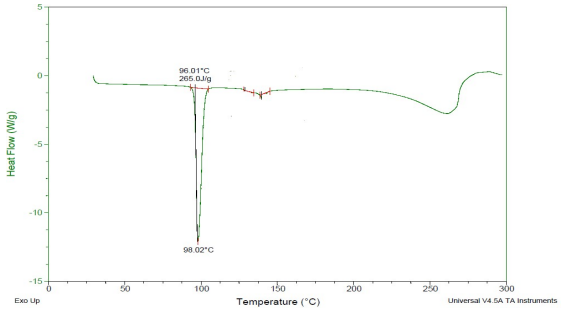

Figure 5: DSC of pure drug MELOXICAM

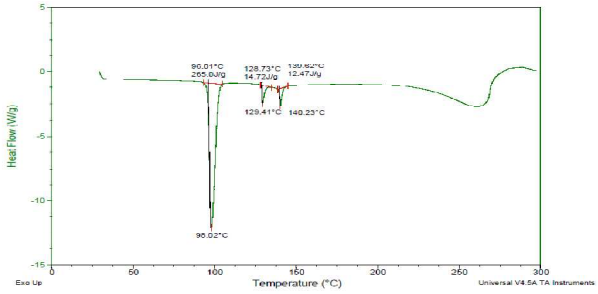

Figure 6: DSC of Optimized formulation of Meloxicam

Determination of Particle size, Zeta potential and Polydispersity index

Table 5: Particle size, Zeta Potential and Polydispersibility index of Meloxicam SLNs

Formulation code	Particle size (nm)	Zeta Potential (mV)	Polydispersibility Index
MLS1	355±5	+39.5±3.2	0.404±0.06
MLS2	334±3	+35.1±3.0	0.564±0.03
MLS3	394±7	+36.3±2.7	0.663±0.01
MLS4	244±5	+41.5±2.5	0.567±0.04
MLS5	386±7	+35.9±3.1	0.573±0.02
MLS6	361±8	+36.2±2.4	0.744±0.07
MLS7	311±9	+35.4±2.6	0.786±0.06
MLS8	212±6	+35.1±2.1	0.695±0.04
MLS9	404±4	+34.9±2.3	0.453±0.01

* mean ± SD, n=3

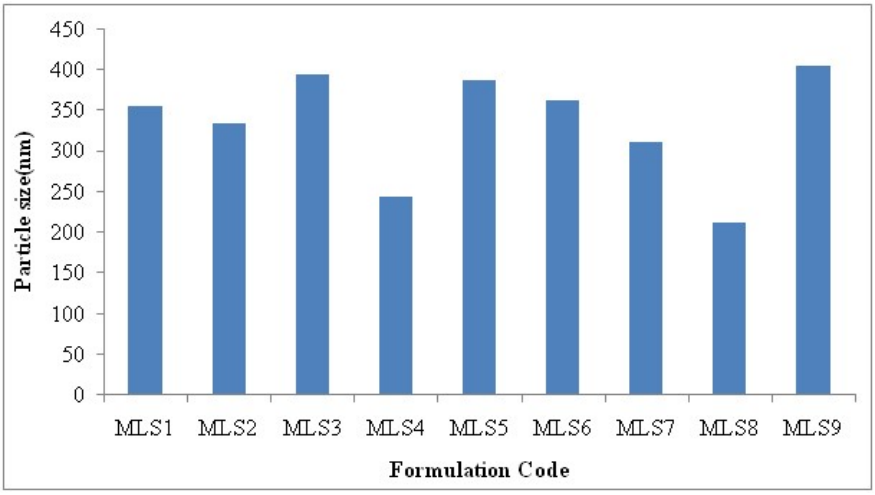

Fig 7: Average particle size of SLNs of Meloxicam

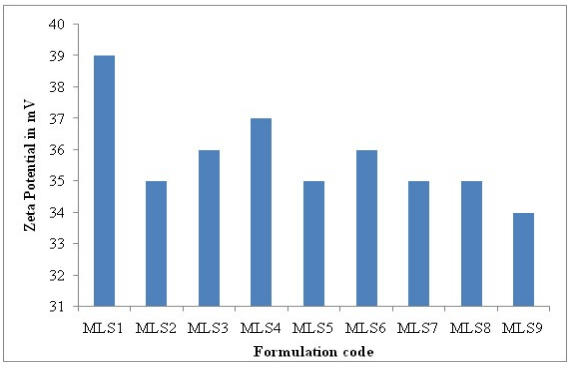

Fig 8: Zeta Potential of SLNs of Meloxicam

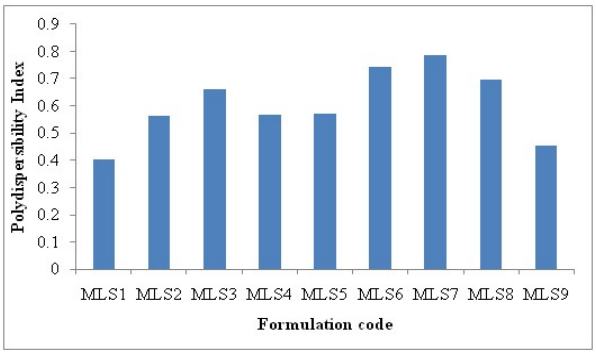

Fig 9: Polydispersibility Index of SLNs of Meloxicam

Determination of drug loading & entrapment efficiency

Table 6: Drug Loading and Entrapment Efficiency of Meloxicam

Formulation code	Meloxicam	
	Drug Loading (%)	Entrapment Efficiency (%)
MLS1	19.1±1.2	46.4±0.02
MLS2	19.3±0.99	47.3±0.33
MLS3	21.2±0.32	43.1±0.14
MLS4	23.6±0.34	51.6±0.25
MLS5	23.3±0.11	45.2±0.21
MLS6	22.1±0.51	40.9±0.37
MLS7	21.4±0.32	43.2±0.66
MLS8	17.9±0.47	54.2±0.41
MLS9	19.25±0.61	39.8±0.37

*mean ± SD, n=3

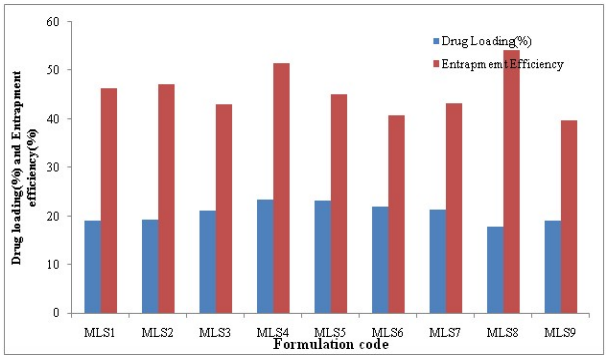

Fig 10: Drug loading (%) and Entrapment Efficiency (%) of Meloxicam SLN s

Table 7: Observed response in 3^2 factorial design for Meloxicam SLNs

Formulation code	% of Lipid	% of Surfactant	Particle size(nm)	Entrapment Efficiency (%)	Percentage drug release in first one hour (%)
MLS1	1	0.03	224±10	46.2±0.84	13.2±0.33
MLS2	0.5	0.03	398±11	44.1±0.18	17.2±0.14
MLS3	1	0.02	367±14	48.9±3.1	14.6±0.32
MLS4	0.5	0.04	256±12	58.2±0.47	24.4±0.22
MLS5	0.5	0.02	346±12	55.6±0.28	15.2±0.47
MLS6	1.5	0.03	323±13	51.3±0.74	11.08±0.61
MLS7	1.5	0.04	374±10	50.1±0.39	10.47±0.32
MLS8	1	0.04	405±10	43.2±0.81	16.03±0.24
MLS9	1.5	0.02	410±15	47.1±0.66	15.68±0.21

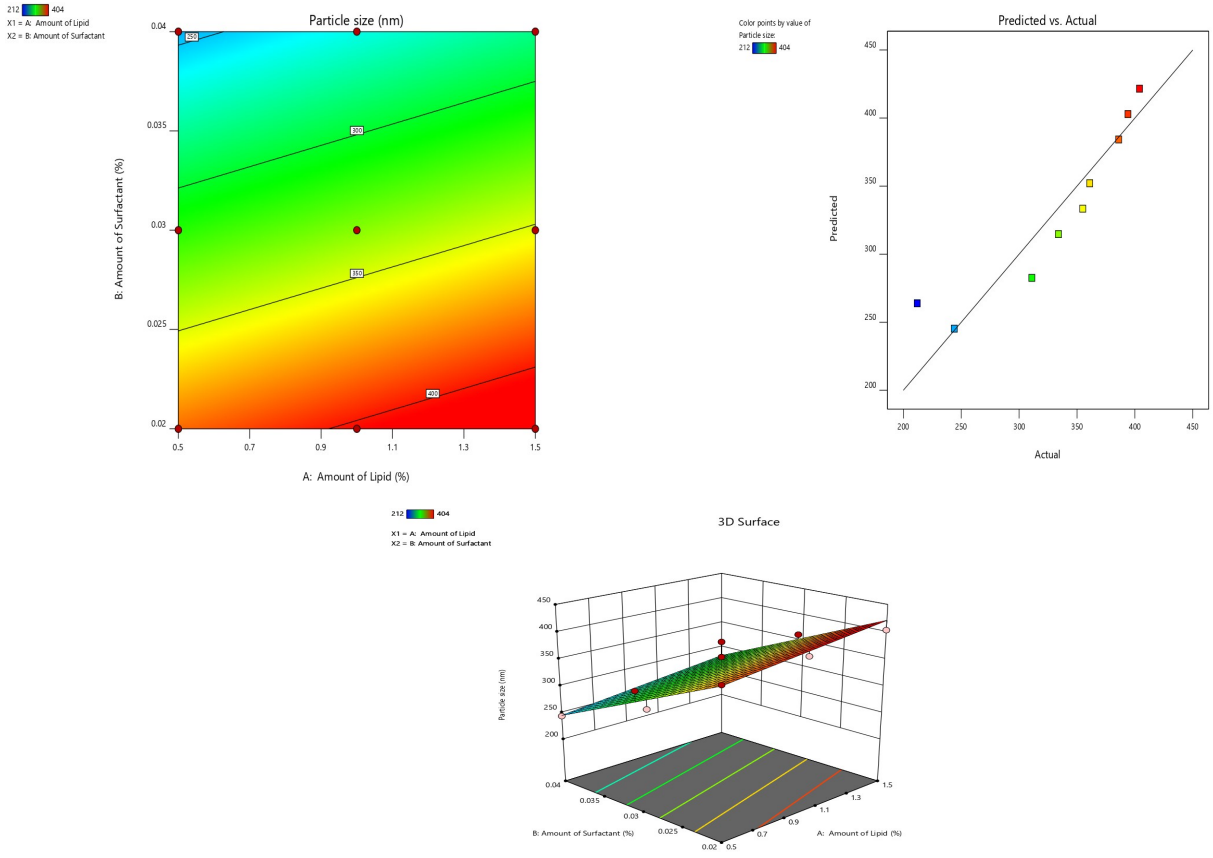

Fig 11: Particle size-Contour plot, Actual VS Predicted and 3D Plot of Meloxicam SLNs

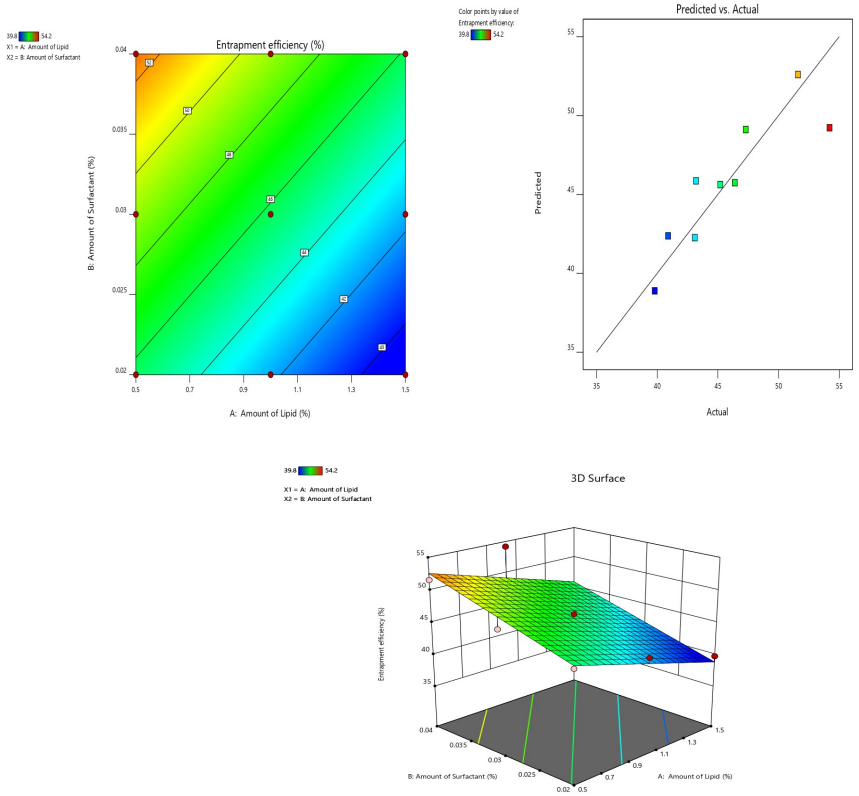

Fig 12: Entrapment Efficiency-Contour plot, Actual VS Predicted and 3D Plot of Meloxicam SLNs

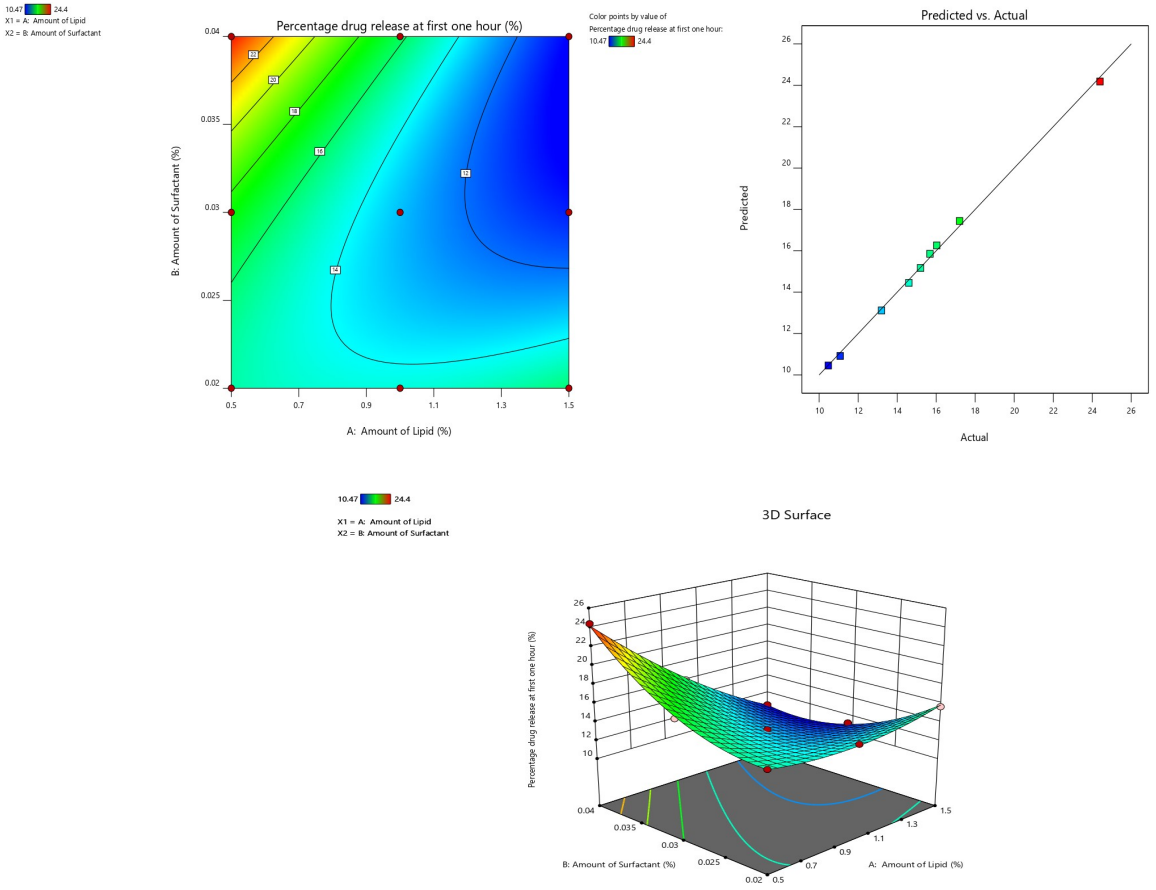

Fig 13: Drug release-Contour plot, Actual VS Predicted and 3D Plot of Meloxicam SLNs

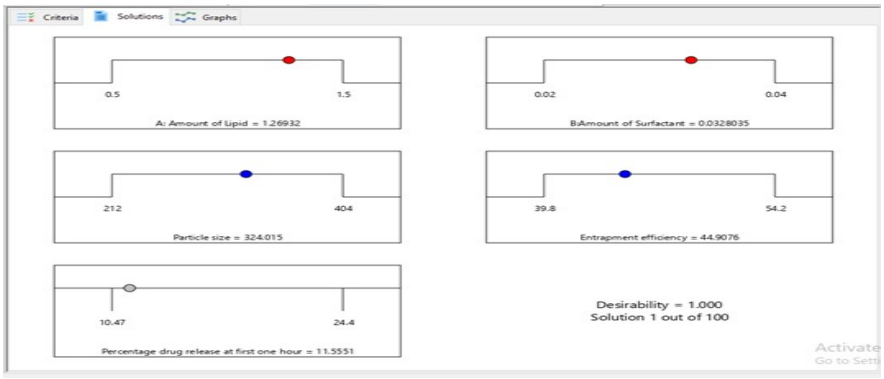

Fig 14: Desirability ramp for process parameter and formulation variables for Meloxicam SLNs

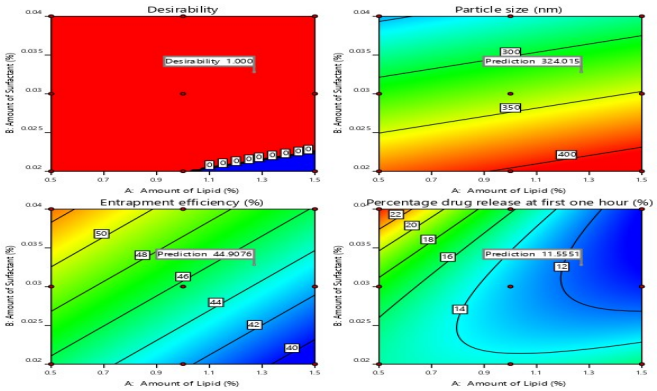

Fig 15: Desirability plot of Meloxicam SLN s

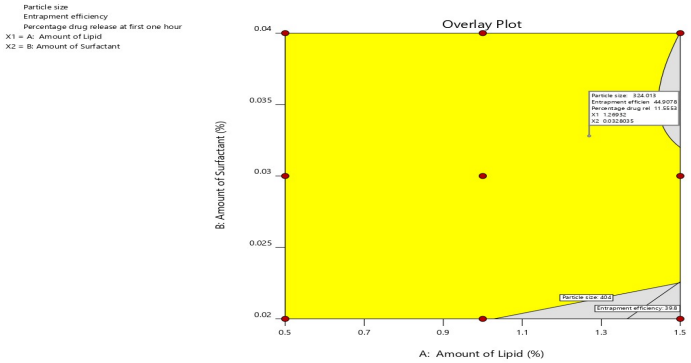

Fig 16: Overlay plot of Meloxicam SLNs

Table 8: Checking point analysis of Meloxicam SLNs

Value	% lipid	% Surfactant	Particle size(nm)	Entrapment Efficiency	Cumulative % drug release
Predicted	1.26	0.032	324.778	44.9	11.8
Observed	1.26	0.032	325	45	12.3
Relative Error	-	-	**0.3**	**0.1**	**0.5**

4. Conclusion

In the present study Meloxicam solid lipid nanoparticles were prepared and evaluated. Stable nanoparticles of SLNs were prepared using high-shear homogenization followed by ultrasonication technique. 3^2 factorial designs were used in the process of optimization. This method was easy to apply, simple, cheap and promising for preparing nanoparticles. To study the interaction between drug and excipients DSC and FT- IR studies were performed and it was found that there was absence of interaction between drug and excipients. The drug release studies that were performed for 24hrs conferred that the drug release was by diffusion through the prepared SLNs. It can be concluded that from the obtained results Keterolac SLNs can be employed for controlled delivery of drug in the treatment as NSAIDs.

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