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RESEARCH ARTICLE

Formulation and Evaluation of Keterolac solid lipid nanoparticles

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ABSTRACT

Transdermal patches of Keterolac 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: Keterolac, Compritol 888 ATO, Precerol ATO 5 and Pluronic F127

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CONTENTS

1. Introduction

The uses of drugs to all the diseases are seen now a days. There are varieties of means by which these drugs are delivered to the human body for therapy. They include tablets, capsules, injections, aerosols, creams, ointments, suppositories, and liquids etc., often named as conventional drug formulations. Treatment with such formulations involves attainment and maintenance of drug concentration in the body within a therapeutically effective range by introduction of fixed doses of a drug, at regular intervals, into the body. After the administration of one dose, the drug concentration rises to high levels, system-wide, atleast initially. With the passage of time, the concentration decreases due to natural metabolic processes and a second dose must be administered to prevent the concentration from reducing the minimum effective level.

The disadvantages of these kinds of therapies are:

(i) Drug concentration in the body follow a peak and trough profile leading to greater chances of undeliterious effects,
(ii) Therapy is inefficient and costly since large amounts of drug are lost in the vicinity of the target organ and close attention is required to monitor therapy to avoid overdosing.

It is observed that continuous intravenous infusion is a superior mode of drug administration as compared to the oral route not only to bypass hepatic "first-pass" metabolism but also to maintain a constant and prolonged drug level in the body. A closely monitored intravenous infusion can provide the dual advantage of direct entry of the drug into the systemic circulation and the control of circulating drug levels. But, such a mode of administration involves certain risks which require hospitalization of the patient for close medical supervision of drug administration. This benefit led to the thought of using the skin as the port of entry of drugs. This is known as transdermal administration and the delivery systems are known as transdermal drug delivery system[1].

1.2 TDDS

The TDDS are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation[1].

1.2.1 ADVANTAGES OF TDDS [2]

The advantages of transdermal delivery over other delivery systems are as follows:

- Transdermal medication releases a steady rate of a drug over a prolonged period of time.
- Adverse effects or therapeutic failures that are frequently associated with intermittent dosing can be avoided.
- Trasndermal delivery can improvise the therapeutic value of many drugs via avoiding major problems associated with the drug e.g. gastro-intestinal irritation, low absorption, decomposition due to 'hepatic first pass' effect, formation of metabolites that cause side effects, short half-life necessitating frequent dosing etc.
- From the above mentioned advantage, it is possible that an equivalent therapeutic effect can be seen via transdermal drug input with a lower daily dose of the drug than it is necessarily required.
- Improved patient compliance by reducing inter and intra-patient variability.
- Patients facing difficulty in swallowing tablets and capsules can be made into TDDS.
- Greater flexibility of dosage in that dosing can be easily terminated by removal of the transdermal drug delivery system.
- Self administration is possible with these systems.
- It is of great advantage in patients who are nauseated or unconscious.

1.3 SKIN AS A TRANSDERMAL ROUTE[3,4]

The skin is one of the most extensive organ of the human body covering an area of approximately 2 m^2 in an average human adult. This multilayered organ receives approximately one-third of all blood circulating through the body. It is a complex organ having a greater variety of cell types than the brain. It has varied functions and properties.

1.3.1 SKIN ANATOMY AND PHYSIOLOGY[5, 6, 7]

There are three major components of the skin

(i) Hypodermis
(ii) Dermis
(iii) Epidermis

Discoveries in drug delivery have not only been successful implementation of pharmaceuticals, but promoted the developments of new medical treatments with existing drugs. The creation of a transdermal drug delivery system (TDDS) has been one of the most important innovations. Nanoparticles are solid colloidal particles in which the active ingredients are dissolved, entrapped [8]. A nanoparticle offers so many benefits in drug delivery because of their small particle size and large surface area. Nanoparticles can be utilized to target the delivery of drugs, to prolong its effect, to enhance bioavailability, to solubilize it for intravascular delivery and to get better its stability against enzymatic degradation [9, 10]. Based on the type of the inactive ingredient used, there are four classes of nanoparticles: Lipid based nanoparticles [11] polymeric nanoparticles [12], metal based nanoparticles [13] and biological nanoparticles. In this study, we have developed solid lipid nanoparticles loaded transdermal film for the controlled delivery of Ketorlac.

2. Materials and Methods

Ketorolac14, 15 is used for the short-term treatment of moderate to severe pain. It is usually used before or after medical procedures or after surgery. Reducing pain helps you recover more comfortably so that you can return to your normal daily activities. This medication is a nonsteroidal anti-inflammatory drug (NSAID). It works by blocking your body's production of certain natural substances that cause inflammation. This effect helps to decrease swelling, pain, or fever.

a**Keterolac** 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

2.1 Methods:

2.1.1 Standard solutions preparation[16, 17]**:**

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

2.1.2 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 Keterolac showed λmax at 320nm (Fig 1).

3.0 Preparation of Calibration curve[18]**:** From the sample solution, 100µg/ml resulting solution was prepared. In case of Keterolac 0.5-2.5 ml was transferred to 10ml volumetric flasks and diluted with distilled water up to the mark (5-25 µg/ml). Calibration curve was shown in (Table 1) and Fig 2.

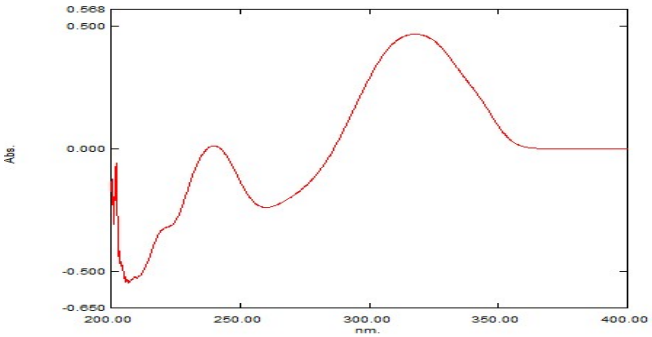


Fig 1: λmax of Ketorolac

Table 1: Standard plot for Keterolac

Conc(ng/ml)	Absorbance(nm)
0	0
5	0.149±0.66
10	0.299±0.27
15	0.450±0.39
20	0.598±0.30
25	0.751±0.47

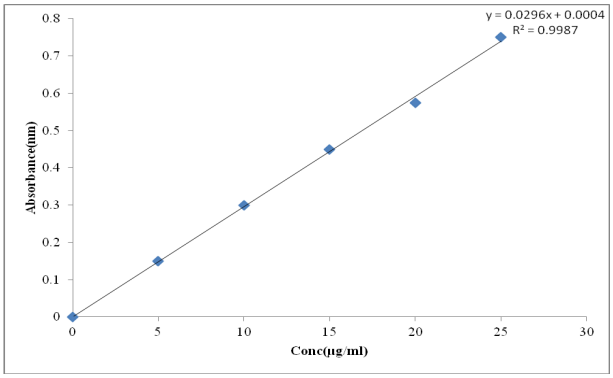


Fig 2: Standard plot of Keterolac

4.0 Preformulation studies[19]**:**

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

4.1 Preparation of Keterolac SLNs[20]

Keterolac SLNs were prepared by using high-shear homogenization followed by ultrasonication technique. Different Lipids namely Compritol 888 ATO, Dynasan 114, Precerol ATO 5 and Surfactants namely Pluronic F127, Tween 80, Span 20 were considered during this study. Different trails were performed in order to suit the best combination of lipid and surfactant. In case of Keterolac Compritol 888 ATO as lipid, Tween 80 as surfactant. In order to optimize the best ratio of Lipid and surfactant, commercially available Design Expert software was used. A randomized, 3^2 full factorial designs with 2 factors at 3 levels were used to study the formulation of SLNs.

5.0 Experimental Design

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. 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.

6.0 Data analysis, optimization and cross-validation of model

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.

6.2Optimization: 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 Keterolac was 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.

7.0 Characterization of Nanoparticles

i. Scanning electron microscopy (SEM): The scanning was performed at a voltage of 15 KV and the images were observed for surface characters.

ii. Size measurement and Polydispersity index (PDI):

The studies were performed at room temperature. All the samples were analyzed in triplicate.

8.0 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.

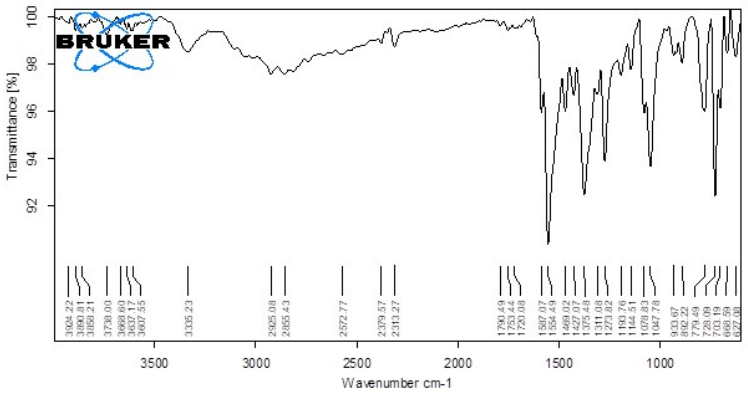
$$Entrapment\ Efficiency\ (EE\ \%) = \frac{Weight\ of\ Drug\ in\ nanoparticles}{Total\ Weight\ of\ Drug\ taken} \times 100$$

***In vitro* drug release studies:** The amounts of drug present in the Ketorolac 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±0.5ºC.

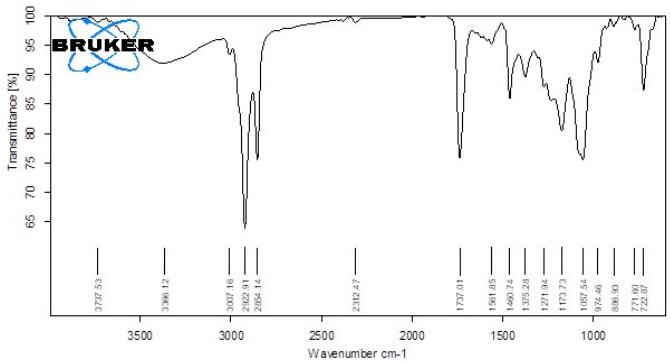
3. Results and Discussion

FT-IR Studies



-C=O(acid)	**1720.08**
C=O	**1790.4**
C=C	**1587.7**
Acid OH	**2572.7**

Figure 3: FTIR of Keterolac Pure drug



-C=O(acid)	1720.08
=C-H	3007.16
C=C	1561.8
Acid OH	2572.7
S=O	1057.54
Ester C=O	1737.01
-OH	3366.1

Figure 4: FTIR of Keterolac Optimized formulation

DSC

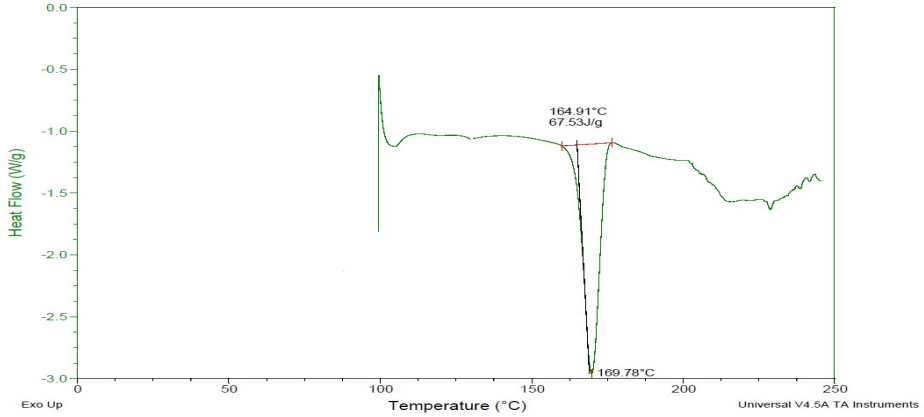


Figure 5: DSC of pure drug Keterolac

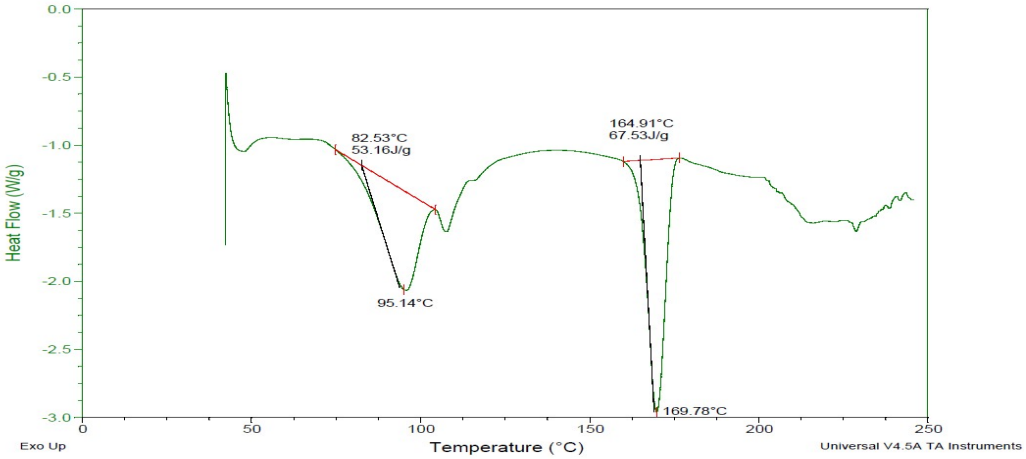


Figure 6: DSC of Optimized formulation of Keterolac

Determination of Particle size, Zeta potential and Polydispersity index

Table 4: Particle size, Zeta Potential and Polydispersibility index of Keterolac SLNs

Formulation code	Particle size (nm)	Zeta Potential (mV)	Polydispersibility Index
KTS1	351±10	+41.1±1.1	0.396±0.02
KTS2	330±9	+36.3±2.6	0.561±0.05
KTS3	390±14	+36.5±2.3	0.662±0.08
KTS4	240±11	+41.7±1.7	0.562±0.11
KTS5	382±15	+36.1±1.1	0.575±0.35
KTS6	357±12	+36.4±1.5	0.745±0.02
KTS7	367±15	+35.7±1.2	0.788±0.05
KTS8	208±16	+35.6±1.9	0.697±0.07
KTS9	400±23	+34.5±3.3	0.455±0.09

*** mean ± SD, n=3**

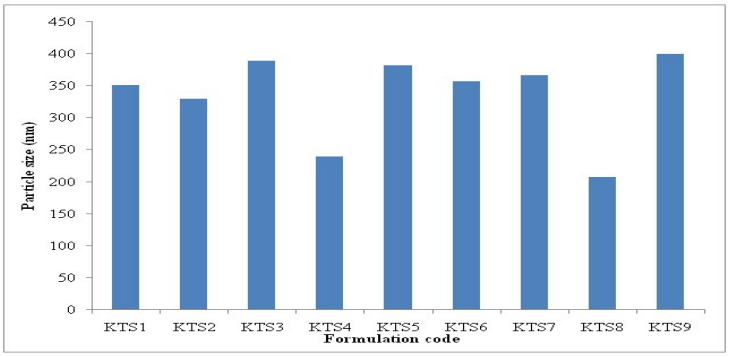


Fig 7: Average particle size of SLNs of Keterolac

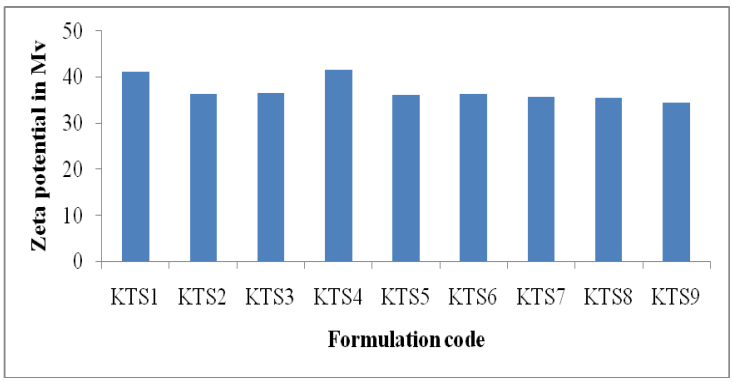


Fig 8: Zeta Potential of SLNs of Keterolac

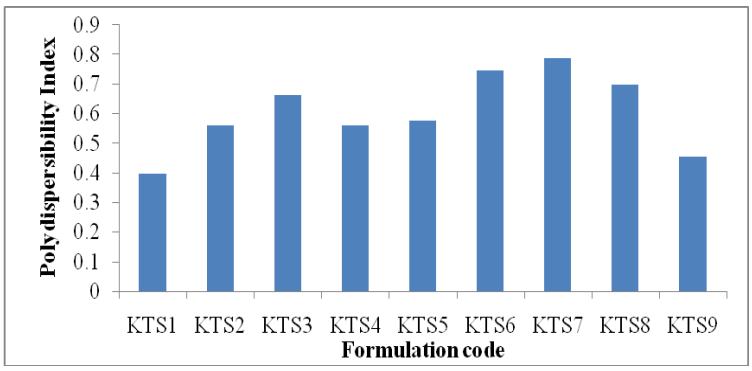


Fig 9: Polydispersibility Index of SLNs of Keterolac

Determination of drug loading & entrapment efficiency

Table 5: Drug Loading and Entrapment Efficiency of Keterolac

Formulation code	Keterolac	
	Drug Loading	Entrapment Efficiency
KTS1	18.5±0.32	46.0±0.44
KTS2	19.2±0.14	46.9±0.65
KTS3	21.0±0.25	41.6±0.91
KTS4	23.0±0.91	51.2±0.74
KTS5	23.5±0.67	44.8±0.32
KTS6	22.4±0.31	40.5±0.44
KTS7	21.1±0.49	42.8±0.69
KTS8	17.4±0.53	53.8±0.73
KTS9	19.1±0.44	39.4±0.12

***mean ± SD, n=3**

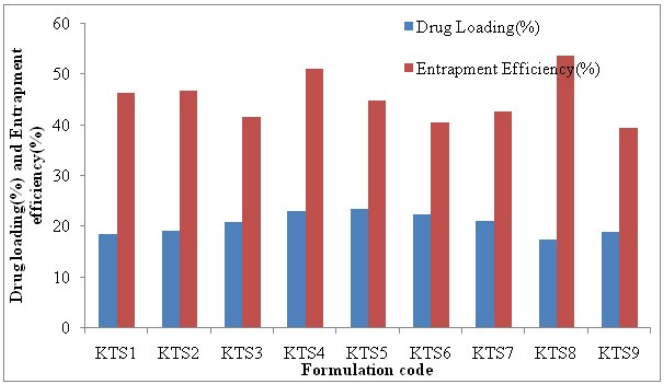


Fig 10: Drug loading (%) and Entrapment Efficiency (%) of Keterolac SLNs

Table 6: Observed response in 3^2 factorial design for Keterolac SLNs

Formulation code	% of Lipid	% of Surfactant	Particle size (nm)	Entrapment Efficiency (%)	Percentage drug release in first one hour (%)
KTS1	1.2	0.03	351±10	46.0±0.44	12.9±0.14
KTS2	0.6	0.03	330±9	46.9±0.65	16.5±0.41
KTS3	1.2	0.05	390±14	41.6±0.91	15.7±0.35
KTS4	0.6	0.04	240±11	51.2±0.74	23.5±0.39
KTS5	0.6	0.04	382±15	44.8±0.32	14.8±0.33
KTS6	1.8	0.05	357±12	40.5±0.44	12.32±0.57
KTS7	1.8	0.04	367±15	42.8±0.69	11.58±0.63
KTS8	1.2	0.03	208±16	53.8±0.73	17.33±0.14
KTS9	1.8	0.05	400±23	39.4±0.12	16.58±0.29

Data analysis, optimization and cross-validation of model for SLNs of Keterolac

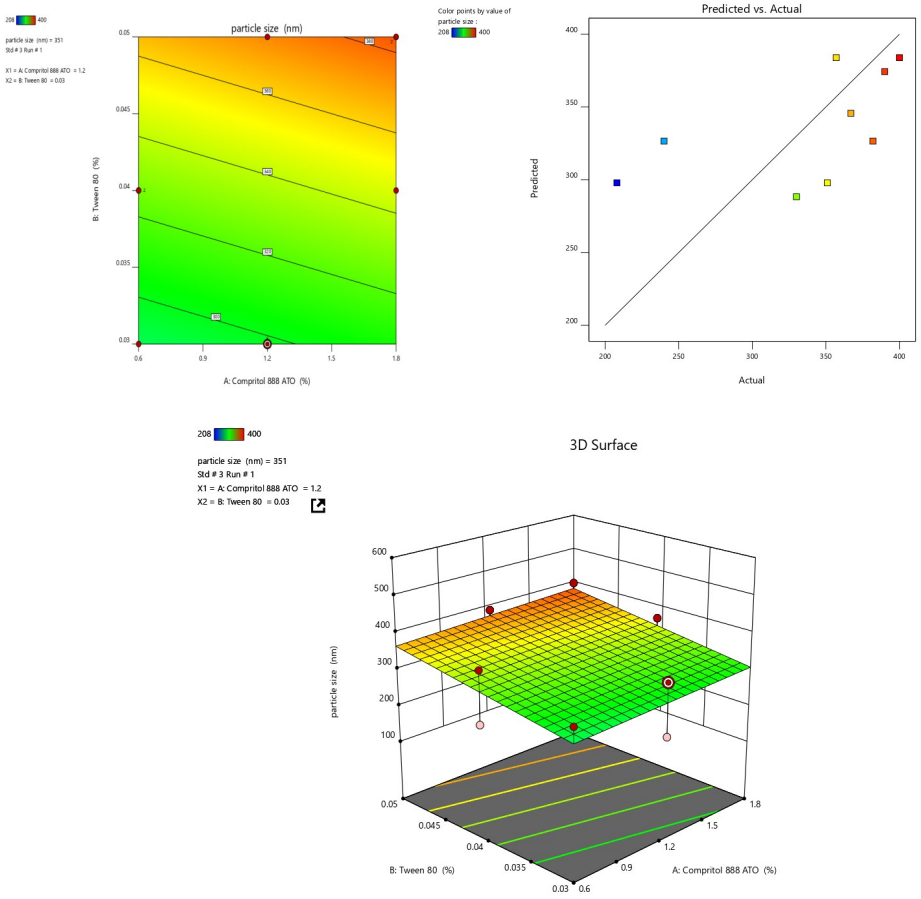


Fig 11: Particle size-Contour plot, Actual VS Predicted and 3D Plot of Keterolac SLNs

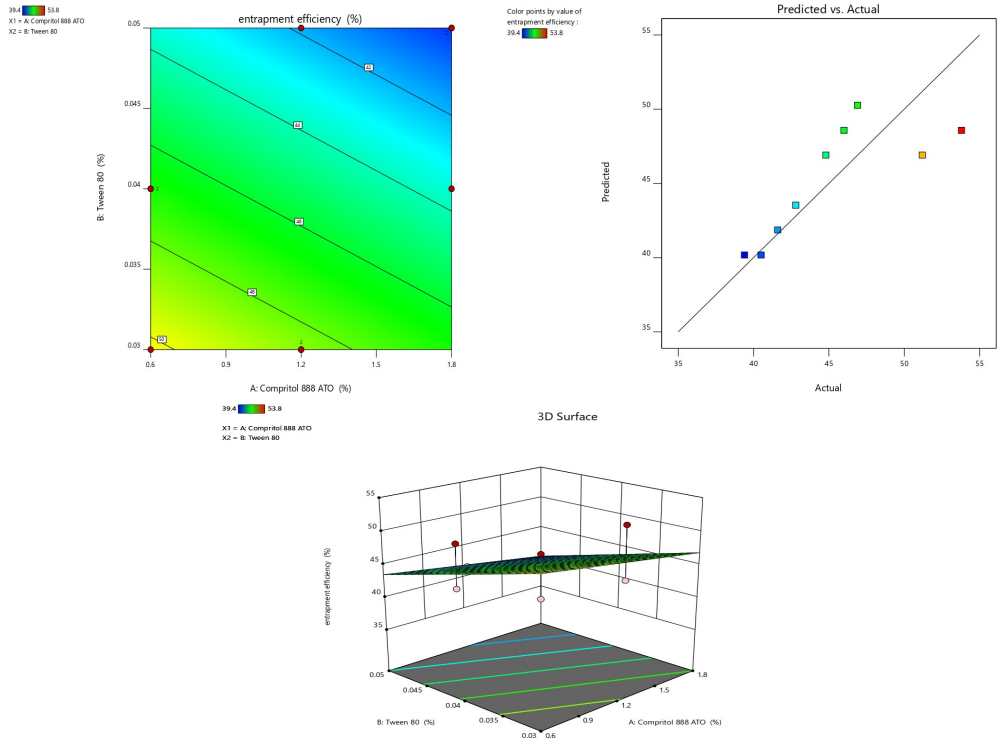


Fig 12: Entrapment Efficiency-Contour plot, Actual VS Predicted and 3D Plot of Keterolac SLNs

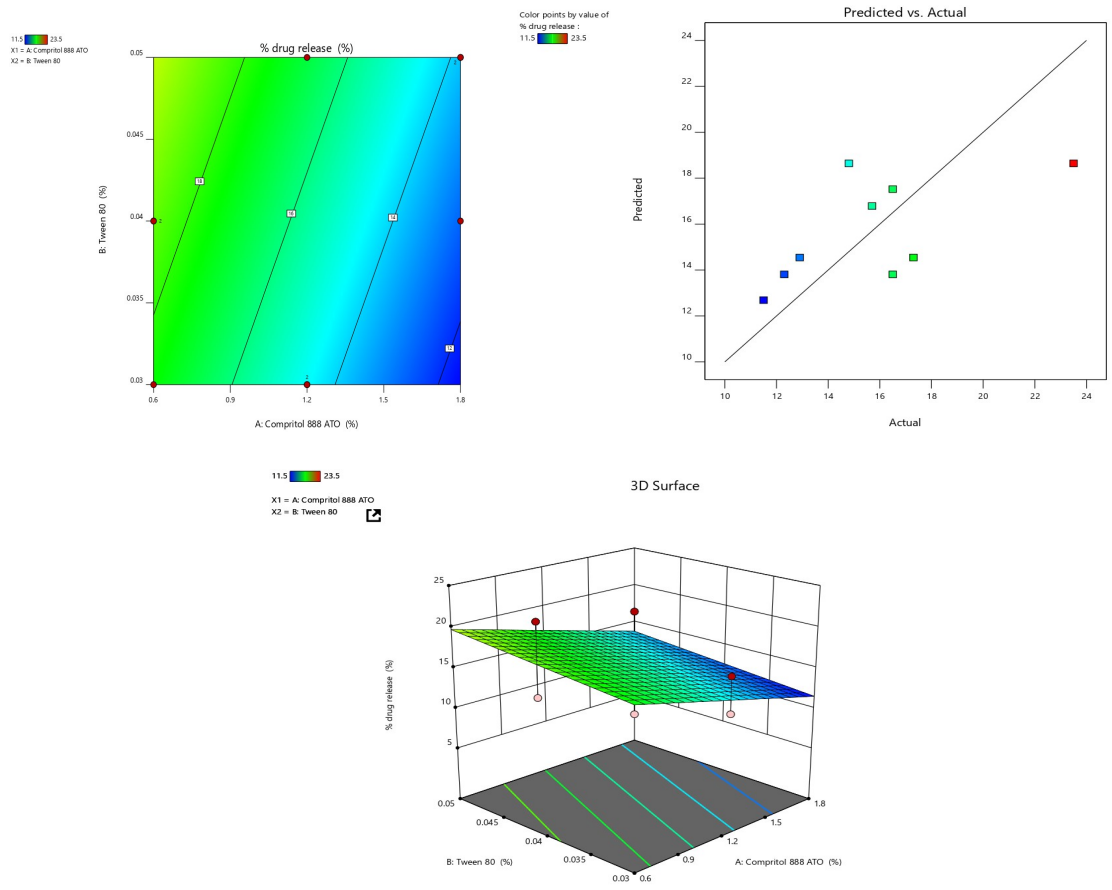


Fig 13: Drug release-Contour plot, Actual VS Predicted and 3D Plot of Keterolac SLNs

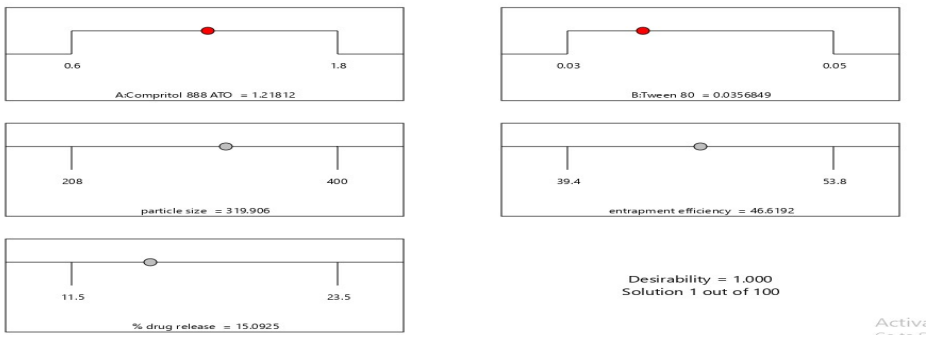


Fig 14: Desirability ramp for process parameter and formulation variables for Keterolac SLNs

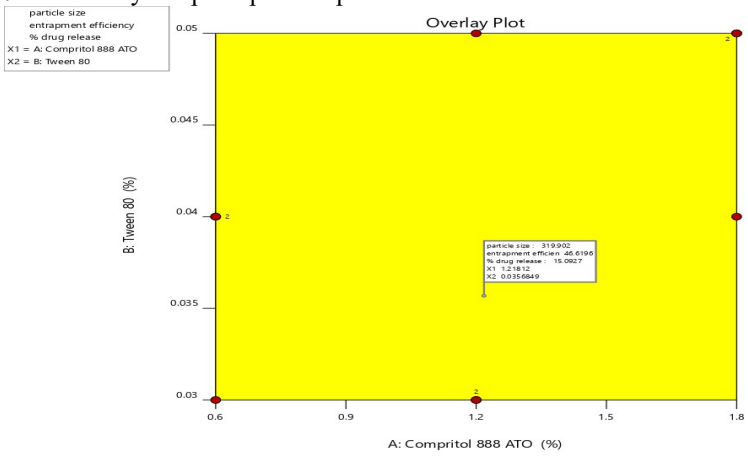


Fig 15: Overlay plot of Keterolac SLNs

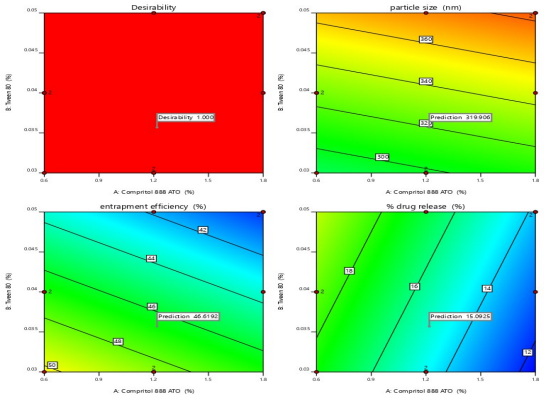


Fig 16: Desirability plot of Keterolac SLNs

Table 7: Checking point analysis of Keterolac SLNs

Value	% lipid	% Surfactant	Particle size(nm)	Entrapment Efficiency	Cumulative% drug release
Predicted	1.21	0.035	319.9	46.6	15.09
Observed	1.21	0.035	320	47	15
Relative Error	-	-	**0.1**	**0.4**	**0.09**

Table 8: Checking point analysis of TP of Keterolac SLNs

Value	Equal Amount of Eudragit RL PO & Eudragit E PO (%w/w)	%Plasticizer	Tensile Strength (n/mm^2)	Cumulative % drug release	Swelling Index
Predicted	1	3.15	9.7	92.3	39.6
Observed	1	3.15	9.7	92.0	39.6
Relative Error	--	--	**--**	0.3	**--**

4. Conclusion

In the present study Keterolac 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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