RESEARCH ARTICLE

Formulation and Evaluation of Nanosponges-loaded Gel of Lornoxicam for Topical Delivery

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ABSTRACT

Nanosponge loaded gels are novel drug delivery system that combine the advantages of achieving optimum concentration of drug at site of action and reduction in systemic side effects. The objective of the present study was to formulate and evaluate gel loaded with nanosponges of Lornoxicam for topical delivery. Lornoxicam nanosponges were prepared successfully using ethyl cellulose as polymer, polyvinyl alcohol as cross-linking agent and dichloromethane as solvent by emulsion solvent diffusion method, which undergo analysis of drug entrapment efficiency, surface morphology, particle size analysis and zeta potential. Among all 6 different formulations, F5 batch was considered as the best with 89% of drug entrapment efficiency and least particle size. From the SEM analysis it was found that nanosponges are spherical, discrete with smooth surface. The nanosponge of the best formulation F5 was loaded into the Carbopol 394P gel which was evaluated for viscosity, spreadability, pH, drug content, *in vitro* drug diffusion study, release kinetics and stability studies. From the study it was found that the prepared Lornoxicam nanosponge topical gel shows promised drug release and good stability.

Keywords: Ethylcellulose, Lornoxicam, Nanosponges, Polyvinyl alcohol, Topical gel.

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INTRODUCTION

An efficient and impactful drug delivery system resembles optimum drug concentration at the target site for a designated duration to reduce local and systemic side effects. For favourable therapeutic response, the suitable concentration of drug must be made available at the action site with further controlled drug input rate.[1,2]

Development of notechnology has helped in founding many dosage forms like nanoparticles, nanosuspensions, nanocrystals, nano capsules, nano-erythosomes etc. There have been some major issues with targeted drug delivery but because of various problems like localizing the expected drug concentration and controlled release pattern, discrete functionalized particles have been formed, and identified as "Nanosponges". Nanosponges are virus size sponges, consisting of cavities which various drugs can fill. These sponges meet specific target site and initiate the drug release in a controlled manner. Nanosponges are water soluble and easygoing for less aqueous soluble drugs.[3-5]

Lornoxicam is a highly potent nonsteroidal anti-inflammatory drug (NSAID), used for osteoarthritis, rheumatoid arthritis and variety of inflammatory conditions. Like most of the NSAIDs, its oral administration cause side

FORMULATION OF LORNOXICAM NANOSPONGES[10-13]

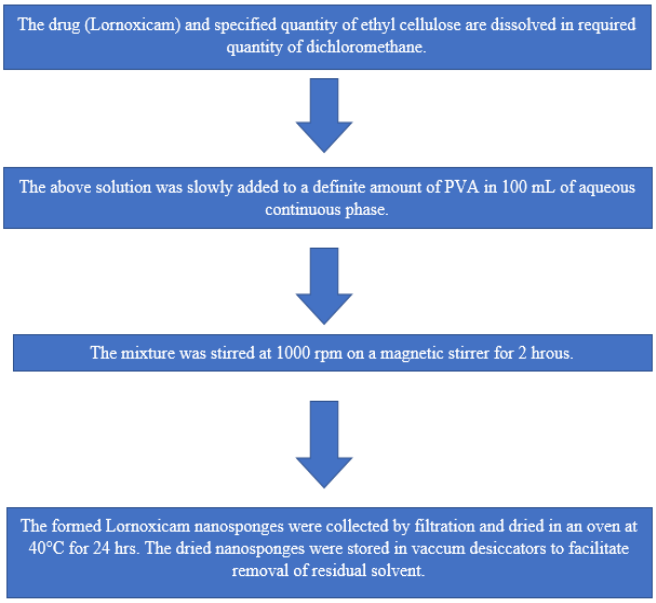

Figure 1: Simple dispersion method to prepare lornoxicam nanosponges.

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effects such as peptic ulcers and gastric irritation. Topical delivery of lornoxicam will not only reduce its systemic side effects but also helps in achieving optimal pain relief by direct targeting to the affected areas.[6-9]

The present study was aimed towards the formulation and evaluation of gel loaded with nanosponges of lornoxicam for topical delivery using ethyl cellulose as polymer by emulsion solvent diffusion method. Based on the characterization, nanopsonges with high entrapment efficiency and least particle size (F5) was selected for hydrogel formulation. Hydrogels were prepared by using Carbopol 934P as gelling agent.

MATERIAL AND METHODS

MATERIALS

Lornoxicam was supplied from Yarrow Chem Products, Mumbai. All other excipients and solvents used were of the analytical pharmaceutical grade.

METHODS

Compatibility Studies Using FT-IR Spectroscopy

The pure drug, drug and polymer were prepared and scanned from 4000-400 cm^{-1} in FTIR spectrophotometer. The results are shown in figure 5 and 6.

EVALUATION OF PREPARED LORNOXICAM NANOSPONGES

Drug Entrapment Efficiency[1]

Entrapment efficiency is defined as the percentage amount of drug which is entrapped by the nanosponges and evaluated by measuring the drug concentration in the supernatant, post-centrifugation. For the determination of entrapment efficiency, 10 mg of lornoxicam nanosponges of each batch were selected, powdered in a mortar and pestle and crushed material was dissolved in 10 ml of phosphate buffer pH 7.2 and then the

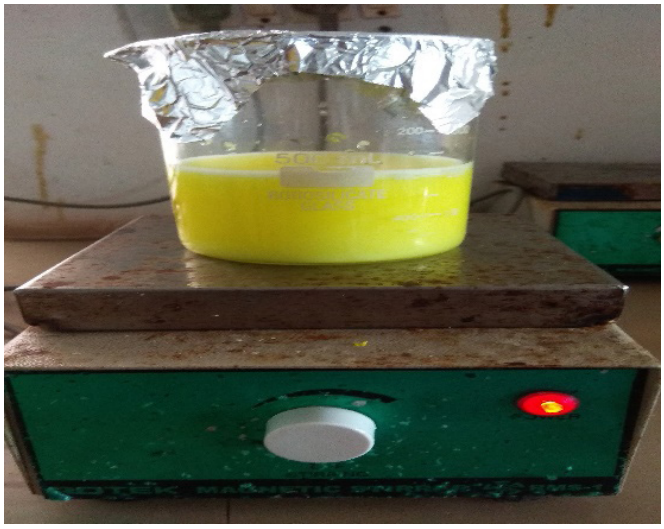

Figure 2: Preparation of Lornoxicam nanosponges

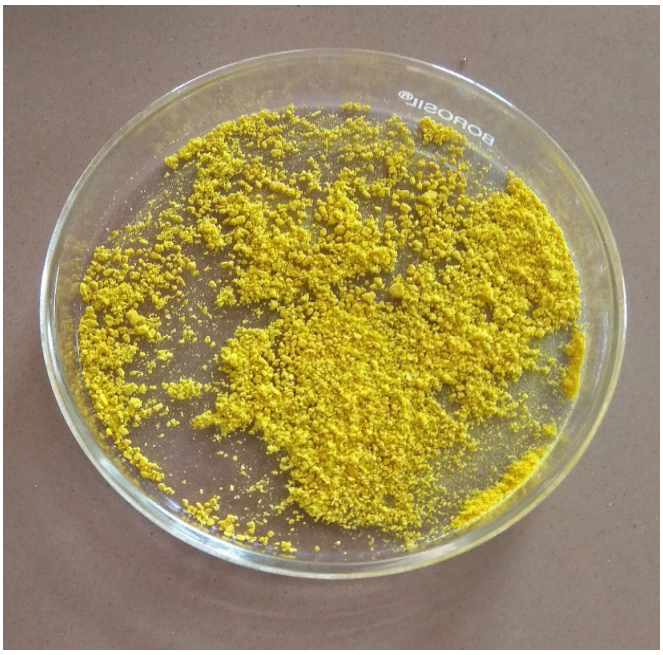

Figure 3: Prepared Lornoxicam nanosponges

FORMULATION OF LORNOXICAM NANOSPONGES LOADED GEL [14, 15]

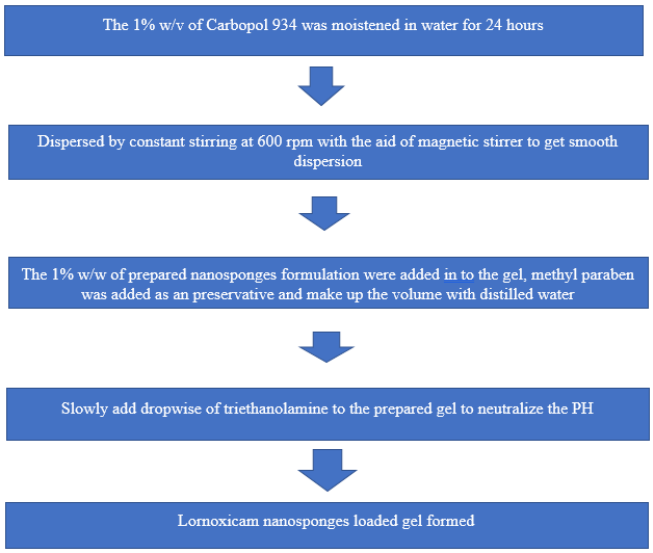

Figure 4: Simple dispersion method to prepare lornoxicam nanosponges loaded gel

Table 1: Composition of Lornoxicam nanosponges by emulsion solvent diffusion method

Ingredients	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*
Drug: Ethylcellulose (mg)	100:100	100:100	100:150	100:150	100:200	100:200
PVA (%w/v)	0.2	0.3	0.2	0.3	0.2	0.3
Dichloromethane (mL)	20	20	20	20	20	20
Distilled water (ml)	100	100	100	100	100	100

dispersion was centrifuged at 1200 rpm for 30 minutes in order to separate entrapped and the unentrapped drug. The free drug concentration in supernatant layer after centrifugation was determined at λ_{max} 375 nm using UV Spectrophotometer. The percentage entrapment efficiency (%EE) was calculated by following formula.

EE%= Total drug - Free drug ÷ Total drug ×100

Percentage Yield[16]

The lornoxicam nanosponges obtained after drying was weighed. Percentage yield value was calculated using the equation below.

Percentage yield=(Weight of nanosponges obtained ×100)/ (Total weight of drug and polymer)

Particle Size Analysis[17]

The particle size (in nano meter) of Lornoxicam nanosponges was measured using a Malvern nano zeta sizer instrument. The samples were suitably diluted with distilled water for every measurement.

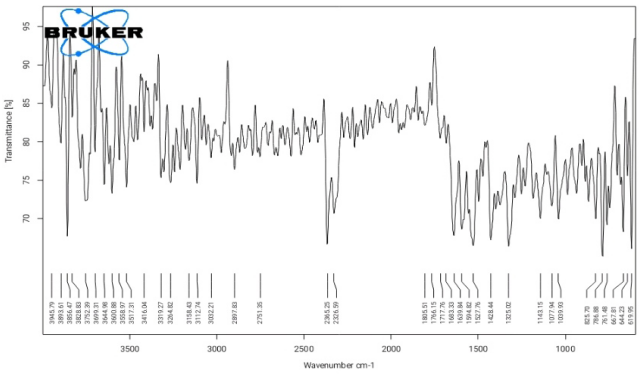

Figure 5: FTIR Spectra of pure drug Lornoxicam

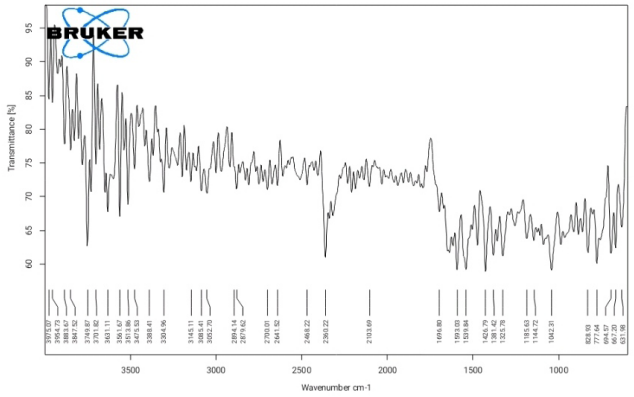

Figure 6: FTIR spectra of drug-polymers

Zeta Potential[15]

Zeta potential can be measured by using instrument zeta sizer, which is the measure of surface charge of Nanosponges.

Scanning Electron Microscopy (SEM)[16]

The surface morphology of nanosponges can be analysed by using scanning electron microscopy. Sample was collected on a glass slide, and kept under vacuum. Then nanosponges were coated with a thin gold/palladium layer using a spulter coater unit. Finally, the morphology and size of the nanosponges observed under the scanning electron microscopy at an accelerated voltage of 20 kV at different magnification.

EVALUATION OF LORNOXICAM NANOSPONGES LOADED GEL

Determination of Viscosity[18]

The viscosity of the prepared gel was measured by Brookfield viscometer with the reading at 100 rpm using spindle no. 6.

Determination of Spreadability[18]

The spreadability of the gel formulation was determined by taking two glass slides (14.5 cm) of equal length. On one glass slide, 1 gm gel was applied. To the other slide, weights (125 g) were added, and the time taken for the second glass slide to slip off from the first glass slide was determined. A shorter interval indicates better spreadability. Spreadability was calculated by using the formula.

$$S = (M. l)/t$$

Value "S" is Spreadability, M is the weight tied to the upper slides, "l" is the length of glass slide, and "t" is the time taken to slip off the slides completely from each other.

Determination of pH[19-21]

2.5 g of gel was accurately weighed and dispersed in 25 mL of distilled water. The dispersion pH was measured by using a digital pH meter.

Determination of Drug Content of Gel[19]

1-gm of the gel was dissolved in 100 mL of phosphate buffer of pH 7.2. The volumetric flask having gel solution was shaken for 2 hours on a mechanical shaker to allow the drug to dissolve completely. The solution was filtered, and drug content determined spectrophotometrically at 375 nm using phosphate buffer (pH 7.2) as blank.

In vitro Diffusion Study[22,23]

In vitro release study of Lornoxicam nanosponges loaded gel was carried out by using Franz- diffusion cell. 1-g of the formulation was spread uniformly on the cellophane

Table 2: FTIR Interpretations

			Observed frequency (cm^{-1})	
Sl. No.	*Functionalgroups*	*Reported frequency(cm^{-1})*	*Drug*	*Physical mixture of drug and polymer*
1	OH stretch	2500–3500	2365.25	2360.22
2	N-H stretch	3200–3600	3264.82	3513.86
3	C-H stretch	2850–3300	3112.74	3085.41
4	C-C stretch	1600–1585	1594.82	1593.03

membrane. The cellophane membrane was clamped between donor and receptor compartment of diffusion cell which is in contact with the receptor medium. The receptor compartment filled with phosphate buffer (pH 7.2). The whole assembly was placed on magnetic stirrer with continuous stirring (50 rpm) and the temperature of the medium was maintained at 37 ± 0.5°C. At specific intervals, 5 ml of sample was withdrawn from the receptor compartment through the sampling port and replaced with same volume of fresh buffer. Then the samples were analyzed for drug content by using UV- visible spectrophotometer at 375 nm.

In vitro Drug Release Kinetics[22,24,25]

To analyze the mechanism of drug release from the topical gel, the results obtained from *in vitro* release studies were attempted to be fitted into various mathematical models as follows:

- Cumulative percent drug released vs. Time (Zero order kinetics)
- Log cumulative percent drug retained vs. Time (First order kinetics)

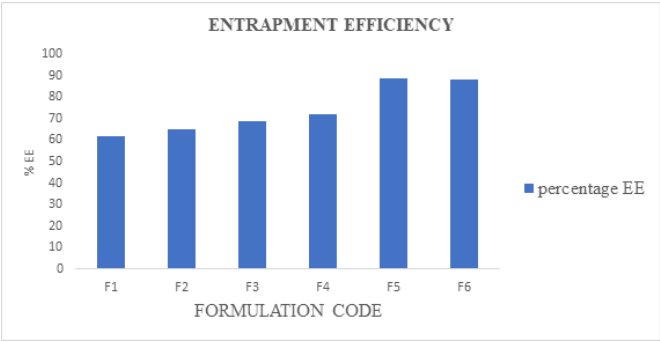

Figure 7: Bar chart for %drug entrapment efficiency

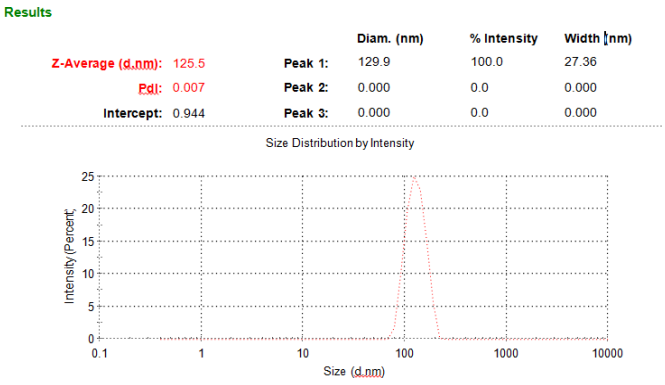

Figure 8: Particle size of optimized formulation F5

Table 3: Drug Entrapment Efficiency (% EE) of Lornoxicam Nanosponges.

Formulation code	*% Entrapment efficiency**
F1	62 ± 0.55
F2	65 ± 0.76
F3	69 ± 0.12
F4	72 ± 0.54
F5	89 ± 1.23
F6	88 ± 0.22

(Mean ± SD, n=3)

Stability Studies[22,26]

As per the ICH guidelines, the optimized formulation was stored in a tightly closed container in a ICH certified stability chamber at 40 ± 2°C and 75 ± 5% RH for 60 days. Nanosponge gel was evaluated for drug content, pH and *in vitro* drug release studies.

RESULS AND DISCUSSION

Compatibility Studies Using FT-IR Spectroscopy

Compatibility studies of Lornoxicam with different polymers were carried out prior to the formulation of nanosponges.

After the compatibility study of Lornoxicam with excipients, the IR spectra of pure drug and drug-excipient physical mixture were analysed. Figures 5 and 6 show no drug interaction and excipients when compared with spectra of the pure drug due to availability of all functional groups.

EVALUATION OF PREPARED LORNOXICAM NANOSPONGES

Drug Entrapment Efficiency

The EE of all the formulation F1-F6 is in the range of 62 ± 0.5 – 89 ± 1.2 as shown in Table 3. The highest entrapment efficiency was found in the batch F5, consisted of Lornoxicam and ethyl cellulose in the ratio of 1:2 with 20 mL of di-chloromethane. The result shows that the EE increased, as the amount of ethyl cellulose increased.

Percentage Yield

Particle Size and Zeta Potential

Particle size analysis of Lornoxicam Nanosponge (F5) was determined using Malvern zeta sizer instrument. The

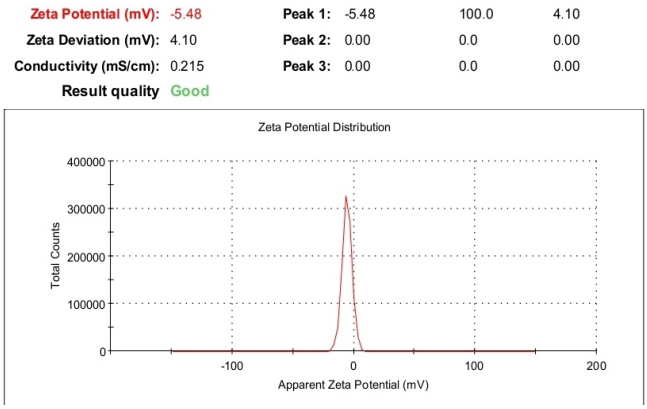

Figure 9: Zeta potential of optimized formulation F5

Table 4: %Yield of lornoxicam nanosponges

Sl. No.	*Formulation code*	*% Yield (w/w)*
1	F1	84.7
2	F2	86.3
3	F3	85.1
4	F4	86.3
5	F5	88.0
6	F6	87.6

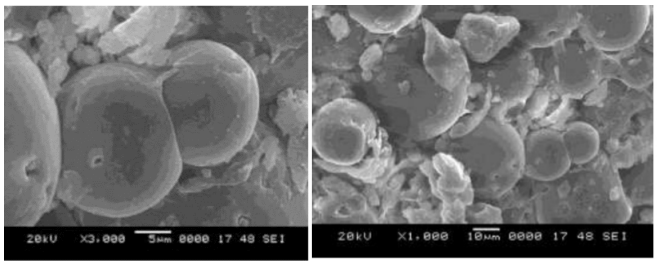

Figure 10: SEM images of F5 formulation of nanosponge

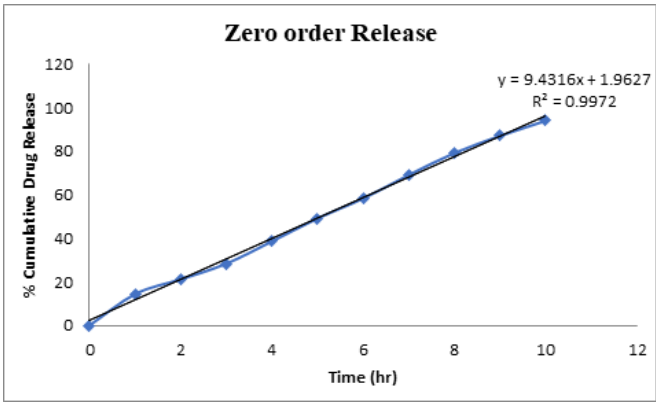

Figure 11: Zero Order Release Kinetics of Gel

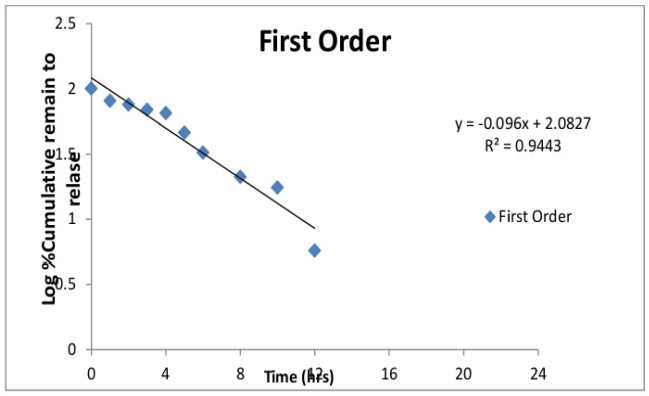

Figure 12: First order Release kinetics of Gel

Table 5: Evaluation parameters of Lornoxicam nanosponge-loaded gel

Evaluation parameters	*Results*
Appearance	Pale yellow
Viscosity (cps)	1245 ± 0.75
Spreadability (gm.cm/sec)	4.1
pH	6.4
% Drug content	95.43 ± 0.89

Figure 8 shows that the particle size of formulation F5 was 125.5 nm.

Zeta potential of the Lornoxicam (F5) was determined by Malvern nano zeta sizer instrument. It was found that zeta potential of formulation was negative i.e., -5.48 mv (Figure 9). Negative potential indicates that the particles have no charge as a whole system is stable.

Table 6: *In vitro* diffusion data of gel

Sl. No	*Time (hours)*	*% Cumulative drug release*
1	0	0
2	1	14.43 ± 0.56
3	2	21.23 ± 0.72
4	3	28.39 ± 0.21
5	4	38.71 ± 0.60
6	5	49.23 ± 0.33
7	6	58.43 ± 0.19
8	7	69.23 ± 0.79
9	8	79.34 ± 0.49
10	9	87.23 ± 0.81
11	10	94.11 ± 0.90

Table 7: Release kinetics data of gel

	Zero- order	*First order*
Formulation	R^2	R^2
Gel	0.9972	0.9443

R^2 =Regression value

Table 8: Evaluation Data of Gel during Stability Studies.

	Time (days) (Accelerated condition at 40 ± 2˚C & 75 ± 5% RH)		
Evaluationparameter	*0*	*30*	*60*
Drug content (%)	95.43	95.06	94.28
pH	6.4	6.4	6.3
%CDR	94.11	93.89	93.47

Scanning Electron Microscopy (SEM)

The shape and surface morphology of the prepared nanosponges were observed by scanning electron microscopy. SEM photograph of formulation F5 revealed that nanosponges were spherical, discrete with smooth surface.

EVALUATION OF LORNOXICAM NANOSPONGES LOADED GEL

In vitro Diffusion Study

In vitro Drug Release Kinetics

The Nanosponge loaded gel formulation followed Zero-order kinetics and their R^2 value was found to be 0.9972 indicating the release to be dose-independent. The Drug release pattern of Lornoxicam loaded Nanosponge follows Zero order release kinetics.

Stability Studies

The results of the stability studies indicated that the gel formulation did not show any changes in the drug content, pH and the percentage cumulative drug release. The % CDR after 60 days showed 93.47% after 10 hours indicating no significant changes. The results obtained were depicted in Table 8.

CONCLUSION

Nanosponges can penetrate through skin. They can bind poorly soluble drugs within the matrix and improve the drug bioavailability. The nanosponges can release drugs in a controlled and expected manner at the target site. Topical nanosponges can be more patient compliant with benefits by lesser doses and side effects.

The present study has been satisfactory attempt to formulate nanosponge topical gel containing Lornoxicam. Based on the observations the optimized formulation was safe and effective for topical use as Lornoxicam nanosponge loaded gel and shows a controlled release effect with reduced side effects.

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