

Design and characterization of micro sponge loaded controlled release epicutaneous gel of lornoxicam

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ABSTRACT

Aim: Transdermal delivery, a successful novel approach aimed at achieving systematically active level of drug. The work involves the drug lornoxicam is a non-steroidal anti-inflammatory drug bearing analgesic, anti-inflammatory, and antipyretic property. The micro sponge technology used to facilitate the controlled release of active drug into the skin in order to reduce the systematic exposure and minimize local cutaneous reactions of active drugs. The main objective of this work was to design and evaluate the gel formation of micro sponge entrapped lornoxicam to increase the effectiveness of the treatment. **Materials and Methods:** The microsponges were prepared by quasi emulsion solvent diffusion method. The internal phase consisting eudragit RS-100 and ethyl cellulose dissolved in dichloromethane and ethyl alcohol, drug is slowly added to polymer solution with continuous stirring for 4 h, and then mixture was filtered to separate the microsponges. Microsponges was characterized by parameters like scanning electron microscopy, drug content, particle size analysis, compatibility studies using differential scanning calorimetry. Microsponge-loaded gel was characterized by physical parameters of gel, measurement of PH, viscosity study, Drug content study, *in-vitro* release studies using first order kinetics, Higuchi Model, Peppas release Model. **Results:** The different kinetics models showed that the release data followed Higuchi matrix and the release mechanism from microsponges was diffusion. **Conclusion:** From the results, it can be concluded that LMF3 formulation shows drug release in a controlled manner.

KEY WORDS: Epicutaneous gel, lornoxicam, microsponges

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INTRODUCTION

The word topical is derived from the ancient greek topos (plural: topoi), meaning "place" or "location." Although skin is a large and logical target for drug delivery. Topical medications are used to produce local action. Topical route avoided the issues related to the oral route such as hepatic first-pass metabolism, gastric serum variability. Topical analgesics or anesthetic systems including liquids, semisolid (gel, cream, emulsion), and solid (powders) containing an analgesic or anesthetic agent applied on or around the painful site.

Microsponge consists of macroporous particulate systems having diameter in between 10 and 25 μ , while applied to the skin, it releases active medicament in a controlled manner. Microsponge can entrap a wide variety of substances and can be incorporated into different semisolid and solid dosage forms. The outer surface of microsponge is usually porous, allowing sustained release of substances. Microsponge delivery system can provide increased efficacy and safety for topically active agents [1-3].

A topical gel, often contains the active ingredient, is applied to the skin or the mucus membranes. The USP defines gels as a semisolid system consisting the dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid [4,5].

Lornoxicam is used for the treatment of various types of pain, especially of the joints, osteoarthritis, and sciatica. It associated with various side effects including salicylate sensitivity, gastrointestinal bleeding, and liver or kidney function after oral administration. It cannot recommend during pregnancy and breastfeeding and is contraindicated during the last third of pregnancy [6-10].

The present research work aims at developing and characterizing of microsponge-loaded topical gel of lornoxicam for the treatment of arthritis and low back pain to achieve following object:

- To overcome potential systemic side effect of the drug and enhance their therapeutic effectiveness
- To develop formulation with prominent targeting potential of the drug to local inflamed tissues of the skin and increase

residence time as well as compare to other conventional topical delivery system.

MATERIALS AND METHODS

Drug Used

Lornoxicam (chlortenoxicam), It is a new nonsteroidal anti-inflammatory drug of the oxicam class with analgesic, anti-inflammatory, and antipyretic properties.

Polymer Used

1. Eudragit®: Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters in varying ratios.
2. Ethyl cellulose: Ethyl cellulose is a derivative of cellulose in which some of the hydroxyl groups on the repeating glucose units are converted into ethyl ether groups.
3. Carbopol 940: Carbopol 940 is a polyvinyl carboxy polymer used as a viscosity enhancer, gelling agent, or suspension agent. Carbopol 940 is cross-linked with ethers of pentaerythritol. It is used in systems where sparkling clarity or a sharp viscosity response is required.
4. Polyvinyl alcohol (PVA): Odorless, translucent, white or cream-colored granular powder. Soluble in water, sparingly soluble in ethanol. Uses as coating, binder, sealing agent, and surface-finishing agent.
5. Triethyl citrate: Triethyl citrate is used in pharmaceutical coatings and plastics.

The microsponges were prepared by quasi emulsion solvent diffusion method.

Formulation and Optimization of Microsponge

The microsponges drug delivery system was prepared using quasi emulsion solvent diffusion method. The internal part of the system consisted of eudragit RS-100 and ethyl cellulose dissolved in 5 ml dichloromethane and ethanol. The drug was added to this with gradual stirring (500 rpm). The internal phase was then poured into 0.5% w/v PVA, molecular weight 30,000-70,000 solution in water, the external phase. After 4 h of stirring, the microsponges were formed due to removal of dichloromethane from the system. The formulation was filtered and dried at 40°C for 12 h [Table 1].

Table 1: Composition of microsponges

Components	Formulation code			
	F1	F2	F3	F4
Drug (Lornoxicam) (mg)	400	400	400	400
Eudragit RS 100 (mg)	300	300	400	400
Ethyl cellulose (mg)	100	200	100	200
Dichloromethane+ethanol (ml)	5	5	5	5
Triethyl citrate (%v/v)	1	1	1	1
PVA (%w/v)	0.5	0.5	0.5	0.5

PVA: Polyvinyl alcohol

Method of Preparation

Quasi-emulsion solvent diffusion

Microsponges were prepared by a quasi-emulsion solvent diffusion method (two-step process) using an internal phase containing polymer eudragit Rs 100 which is dissolved in dichloromethane and ethyl alcohol. Then, the drug is slowly added to the polymer solution and dissolved; plasticizer was added in for plasticity. The inner part is then poured into external phase containing PVA and distilled water with continuous stirring for 4 h. Then, the mixture was filtered to separate the microsponges. The product (microsponges) was washed and dried in air heated oven at 40°C for 12 h. Method of preparation is shown in Figure 1 [1].

Parameters for Process Optimization of Microsponge

- Optimization of polymer concentration
- Optimization of stirring speed

Formulation of Lornoxicam Microsponge-Loaded Gel

Gels of lornoxicam microsponges are prepared using following formula shown in Table 2

Procedure

A clear dispersion of Carbopol was prepared in water using moderate agitation. Lornoxicam-loaded microsponges were dispersed in propylene glycol and methanol. Various ingredients viz. parabens, sodium metabisulphite, and

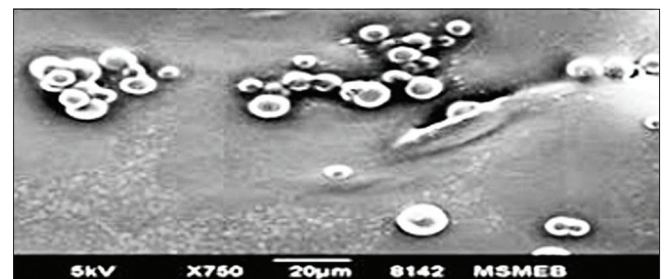


Figure 1: Scanning electron microscopy

Table 2: Composition of the lornoxicam microsponge gel

Ingredients	Quantities (% w/w)		
	LMF1	LMF2	LMF3
Lornoxicam microsponge	1.5	1.5	1.5
Propylene glycol	40	40	40
Methanol	8.0	8.0	8.0
Menthol	0.04	0.04	0.04
Methyl parabens	0.18	0.18	0.18
Propyl parabens	0.02	0.02	0.02
Sodium metabisulfite	0.10	0.10	0.10
Disodium edetate	0.10	0.10	0.10
Carbopol 940	0.5	1	1.5
Triethanolamine	qs	qs	qs
Purified water (qs)	100	100	100

disodium edetate were dissolved in water and added to the drug solvent system. Triethanolamine was used to neutralize, and volume was made with water. Gels prepared were degassed by ultrasonication.

Optimization of Polymer Concentration

Polymer concentration was optimized on the basis of percentage yield and drug content present in the microsponge loaded gel. The formulations LMF1 to LMF3 were prepared and evaluated.

Characterization of Microsponge

Scanning electron microscopy

Morphology details of the specimens were determined using a scanning electron microscope (SEM). Results of SEM analysis are depicted in Figure 1.

Drug content and percentage yield [11,12]

Determination of percentage yield and percentage entrapment efficiency

Percentage yield can be determined by calculating the initial weight of raw materials and the finally obtained weight of microsponges and calculated using the formula:

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Accurately weighed lornoxicam microsponges were taken in a stoppered test tube and extracted with 5 × 10 ml quantities of phosphate buffer pH 6.8. The extracts were filtered and collected into 100 ml of volumetric flask and made up to the volume with phosphate buffer pH 6.8. The solutions were subsequently diluted suitably with phosphate buffer pH 6.8 and spectrophotometric absorbance was taken at 377 nm to calculate percentage drug entrapment and the percentage entrapment efficiency (PEE) is calculated by the formula is given below.

$$\text{PEE} = \frac{\text{loading drug in microsphere}}{\text{theoretical drug loading}} \times 100$$

The production yield of the microsponges was determined by calculating the initial weight of the raw materials and the final weight of the microsponges obtained. All the experiments were performed in triplicate and the mean of the each value was reported. Similarly, the drug content of all the formulations was determined in phosphate buffer pH 6.8 and results are shown in the Tables 3 and 4 and Figures 2 and 3 (Shwetha et al., 2011).

Table 3: Percentage yield of microsponge in different formulation

Formulation code	Drug content (%)
F1	63.37
F2	72.94
F3	76.45
F4	61.10

3 particle size analysis [11,12]

Particle size and size distribution of microsponge particles were done using optical microscopy. The values were given for the formulations in the form of mean particle size range. This is done by stage micrometer and eye-piece micrometer. Results are shown in Table 5.

Compatibility studies

A proper design and formulation of a dosage form requires consideration of the characteristics of both drug and excipients used in the fabrication of the drug product. Compatibility must be established between the active ingredient and other excipients to produce a stable efficacious, attractive, and safe product. The compatibility studies were performed with the help of differential scanning calorimetry the results are shown as in Figures 4 and 5.

Characterization of Microsponge Loaded Gel

Physical parameters of gels

Three gel formulations of microsponges containing Lornoxicam were characterized for pH using pH meter, spreadability, drug content, and viscosity using a Brookfield digital viscometer are shown in Table 6.

Measurement of pH

The pH of various gel formulations is determined by digital pH meter. 1 g of gel formulation was dissolved in 100 ml distilled water and stored for 2 h. The extent of pH for each formulation is done in triplicate, and average values are calculated.

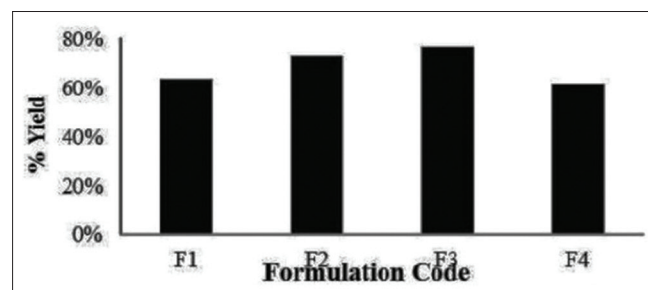


Figure 2: Optimization on the basis of percentage yield

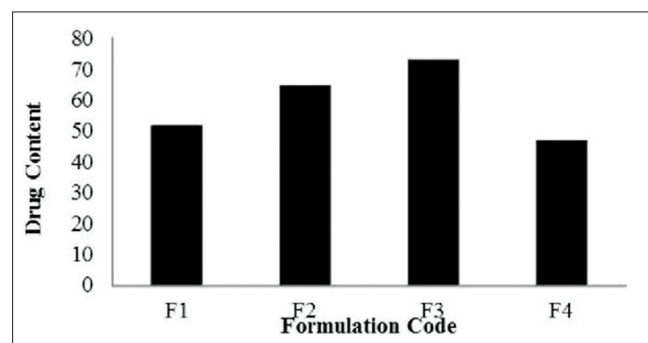


Figure 3: Optimization on the basis of drug content

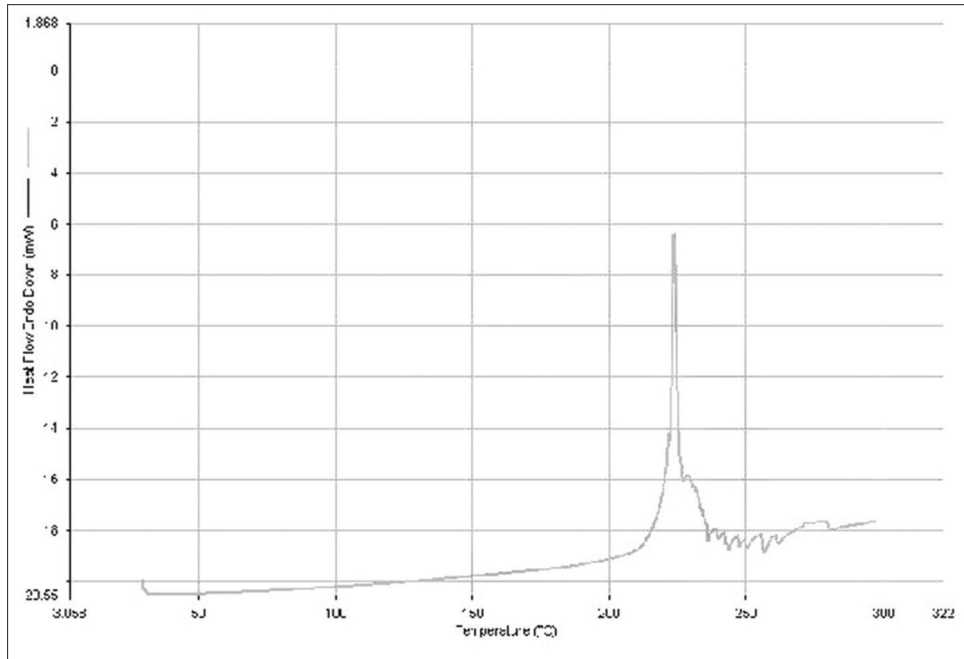


Figure 4: Differential scanning calorimetry of Lornoxicam

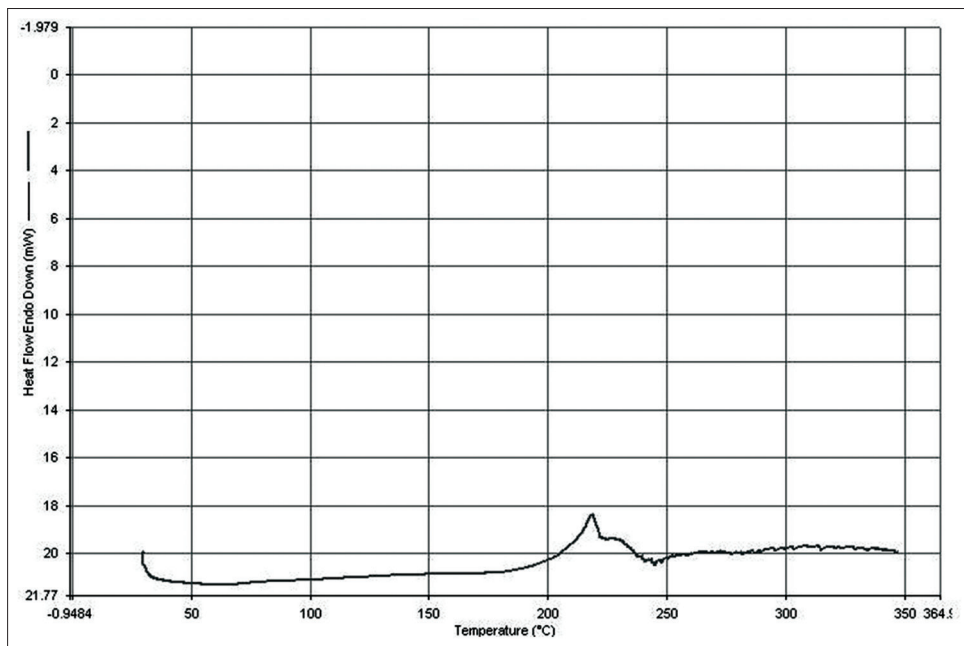


Figure 5: Differential scanning calorimetry of drug and polymers

Viscosity study

The measurement of viscosity of the prepared gel was done by Brookfield Viscometer. The gels are rotated at different rotations speeds, i.e. 0.3, 0.6, and 1.5/min and corresponding dial reading noted. The viscosity of the gel is obtained by multiplication of the dial reading with factor.

Spreadability

One of the criteria for a gel to meet the ideal quantities is that

it should possess good spreadability. It is expressed by denoting the extent of the area to which gel readily spreads on application to the skin. The therapeutic effectiveness of a formulation also depends upon its spreading value. It is calculated using the formula:

$$S = M.L/T$$

Where M = wt. tied to the upper slide
 L = length of glass slides
 T = time taken to separate the slides

Drug content studies

1.0 g of each gel formulations was taken in 100 ml volumetric flask containing 20 ml of phosphate buffer (pH 6.8) and stirred for 30 min and allowed to stand for 24 h in case of microsponge loaded gel formulations. The volume was made up to 100 mL, and 1 mL of the above solution was further diluted to 50 mL with phosphate buffer (pH 6.8). The resultant solution was filtered through membrane filter, and absorbance was measured spectrophotometrically at 377 nm.

Drug release kinetics

The *in vitro* release of microsponges containing lornoxicam from the gel formulation was studied through cellophane membrane using modified apparatus. Release models of different lornoxicam microsponge gel formulations are presented in Table 7 and shown in Figures 6-8.

SUMMARY AND CONCLUSION

Lornoxicam is used for the relief of pain and inflammation in Rheumatoid Arthritis. Microsponges are porous, polymeric microspheres that are designed to deliver a pharmaceutical active ingredient efficiently at the minimum dose and also to modify drug release from lornoxicam-loaded microsponge gel formulation. Microsponge-based novel delivery system has been

Table 4: Drug content of microsponge in different formulation

Formulation code	Drug content (%)
F1	51.71
F2	64.57
F3	72.97
F4	46.98

Table 5: Mean particle size

Formulation code	Mean particle size in μm
F1	59.88 \pm 0.95
F2	61.77 \pm 6.45
F3	68.82 \pm 2.15
F4	63.55 \pm 5.54

Table 6: Physical parameters of the lornoxicam microsponge gel

Batch no.	pH	Spreadability (g.cm/sec)	Viscosity (cps)	% Drug content
LMF1	6.7	13.1	2772 cps	72.56
LMF2	6.5	14.4	2768 cps	77.10
LMF3	6.9	14.3	2751 cps	81.73

Table 7: Model fitting release profile of the lornoxicam microsponge gel

Formulation code	Mathematical models (kinetics)				Best fit model
	Zero order	First order	Higuchi model	Peppas model	
	R ²	R ²	R ²	n	
LMF1	0.952	0.993	0.994	0.677	Higuchi
LMF2	0.941	0.987	0.997	0.670	Higuchi
LMF3	0.979	0.975	0.980	0.700	Higuchi

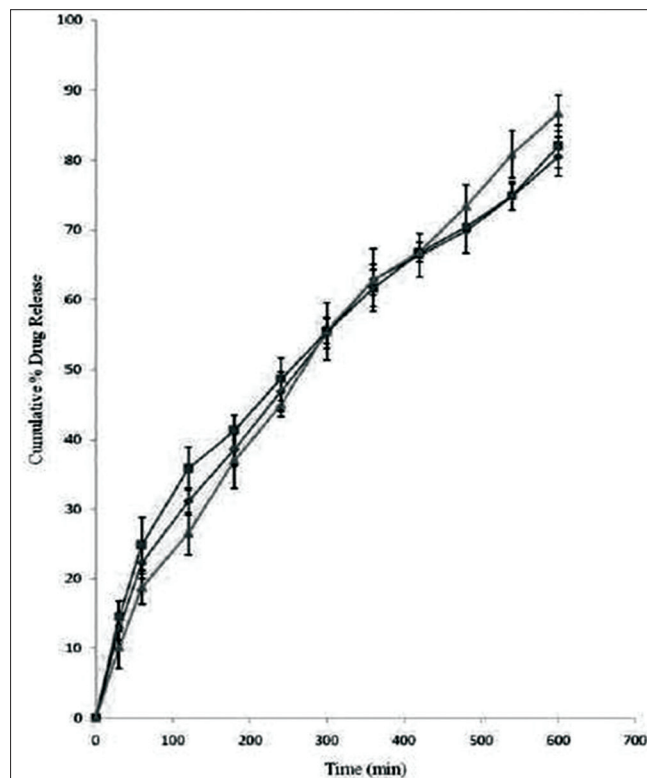


Figure 6: Plot of cumulative % drug release versus time (gel formulation LMF1-LMF3)

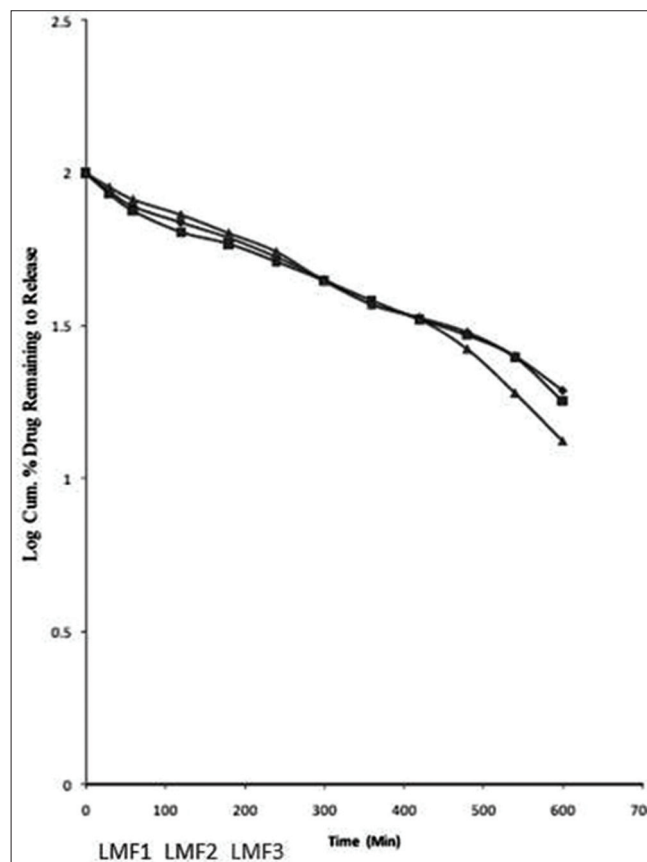


Figure 7: Plot of log cumulative % drug remaining to release versus time (gel formulation LMF1-LMF3)

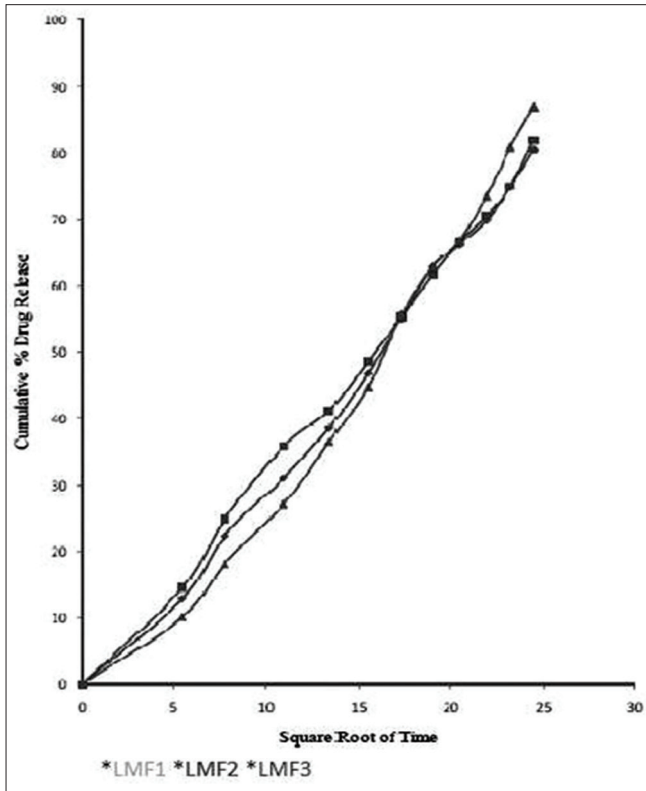


Figure 8: Plot of cumulative % drug release versus square root of time (gel formulation LMF1-LMF3)

developed to provide once a day sustained release medication for topical delivery of lornoxicam. The formulations showed enhanced retention of drug in the skin, indicating better potential of delivery system.

From the study, the following conclusion is obtained. By considering the solubility study of the drug and polymer and the rate of diffusion of the solvent used, the international phase suitable for the preparation of microsponges to be ethanol and the external phase was found to be water. The minimum concentration of an emulsifier PVA required to produce microsponges was found to be 500 mg/100 ml. The particle size range increases as an increase in the amount of polymer in the formulation.

By the drug release studies from the gel formulations LMF1 to LMF3, It can be concluded that the quasi emulsion solvent diffusion method used for the preparation of the microsponges

was simple, reproducible, and rapid. Furthermore, it was observed that as drug/polymer ratio increases, the particle size is decreased. This is probably due to the fact that at higher relative drug content, the amount of polymer available per microsponge to encapsulate the drug becomes less, thus reducing the thickness of the polymer wall and hence, smaller microsponges. Microsponge formulation F3 showed a good physical parameter study and was used for formulating into gel, incorporated in the carbopol. From the results, it can be concluded that LMF3 formulation shows drug release in a controlled fashion.

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