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Research Article

Development, Characterization and Transdermal Delivery of Meloxicam Entrapped in Proniosomal Gel for the Treatment of Osteoarthritis

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Abstract

Objective: Applying Proniosomal Gels(PGs) in transdermal drug delivery system has evoked impressive intrigue in light of their great water-solvency and biocompatibility. The point of present investigation was to get ready and describe proniosomes of Meloxicam(MLX) for osteoarthritis. which may convey these medications to focused site more effectively than and furthermore beat the issues related with oral organization of MLX.

Methodology: Proniosomes were set up by coacervation phase separation technique at that point described for molecule size, capture effectiveness (EE), zeta potential and saturation examines. Vesicular size was controlled by optical microscopy and saw as changed from 05.61 ± 0.04 to 10.30 ± 0.05 µm relying upon the convergences of range.

Results: The normal percent of drug entrapment was in range 67.2 ± 1.44 % to 76.8 ± 0.60 %. It was seen that F3 detailing was having zeta capability of MLX was - 54.6 mV so don't aggregate quickly. The drug release of MLX was 84.21% run from 84.68%. Proniosomal gel was readied read for its discharge and physicochemical qualities.

Conclusion: At last, F3 exhibited better osteoarthritis impact to improve adequacy, steadiness and to lessen symptoms and poisonousness related with the picked drugs so as to treat Osteoarthritis.

Keywords: Meloxicam; Proniosomes; Topical Delivery; Proniosomal Gel; Irritation Studies

The medication conveyance innovation scene has gotten exceptionally serious and quickly developing. An ever increasing number of advancements in conveyance frameworks are being incorporated to advance the adequacy and cost viability of the treatment. Osteoarthritis also known as degenerative arthritis, degenerative joint disease and osteoarthritis. Osteoarthritis is age factor disease, occurs mostly in old days.

Risk is greater in over weight persons. Osteoarthritis can be occurs in spine joints, hip joints, knee joints (most commonly), finger joints and foot joints.

New classes of pharmaceutical, biopharmaceutical (peptides, protein, and DNA-based therapeutics) are powering the quick development tranquilize conveyance innovation. These new medications regularly can't be adequately conveyed by ordinary methods. The benefits from targeted, localized delivery of therapeutic agents are other driving forces to the market [1].

Drug delivery systems(DDS) that can unequivocally control the discharge rates or target medications to a particular body site enormously affect the social health care system. Carrier technology offers an intelligent approach for drug delivery by coupling the drug

to a carrier particle such as microsphere, nanoparticles, liposomes, proniosomes, proniosome etc. which modulated the release and absorption characteristics of the drug. Microsphere is an important part of DDS [2].

To control the delivery rate of active agents to a prearranged site in human body has been one of the largest challenges faced by drug industry. Several systems were developed for Transdermal delivery system (TDS) using the skin portal entry. It has enhanced the usefulness and safety of many drugs. Controlled arrival of medications onto the epidermis with affirmation that the medication remains principally restricted and doesn't enter the fundamental course in huge sums is a territory of examination that just been tended to with progress. No effective vehicles have been created for controlled and restricted conveyance of medications into the layer corneum and basic skin layers and not past the epidermis.

These vehicles require high grouping of dynamic elements for successful treatment on account of their low effectiveness of delivery system, coming about into bothering and unfavorably susceptible response in critical clients other disadvantage of skin detailing are uncontrolled vanishing of dynamic fixings, disagreeable scent and expected inconsistency of medications with vehicle [3].

The fundamental point of the examination is to accomplish successful medication focus at the expected site of activity for an adequate timeframe to inspire the reaction.

Proniosomal gel was prepared with MLX to improve efficiency, stability, bioavailability and to reduce side effects and toxicity of chosen drugs.

Materials and Methods

MLX were kindly provided by *Taj Pharma group (API), Ankleshwar, Gujarat, India*. Soy Lecithin was purchased from Central drug house, New Delhi. Cholesterol crystalline was purchased from Sisco research laboratories ltd. Bombay. Span 20/Span 40/Span 60/ Span 80 were purchased from Qualikems fine Chemical Pvt. Ltd. Vadodara, (Gujarat). Ethanol was purchased from Glxy Laboratories (India) and Glycerol was purchased from Fisher Scientific (India).

Preparation of blank and drug loaded proniosomes

- **Step 1:** First of all ethanol (1 mL) was taken in a clean and dry glass bottle and added accurately weighted 360 mg of surfactant, 30 mg drug (MLX), cholesterol and soya lecithin.
- **Step 2:** Warmed on water bath at 60-70^{0}C till 5 minutes, all ingredients mixed well with glass rod and then covered with a lid to prevent loss of solvent.
- **Step 3:** Than the 2 mL of aqueous phase (PBS-pH 7.4) was added in to it, after the appearance of homogeneous solution.
- **Step 4:** Further Warmed on the water bath till a clear solution was not obtained.
- **Step 5:** It was stored all night for cooling.

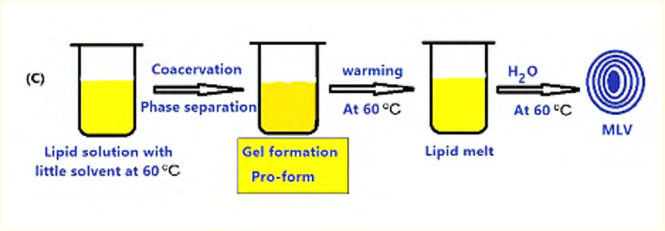

Figure 1: Preparation of Blank and Drug Loaded Proniosomes.

Characterization of prepared proniosomal gel

pH determination

The pH of gel formulations was determined by using digital pH meter. 1gram of gel was dissolved in 100 ml of distilled water and stored for 2 hours. The measurement of pH of each formulation was done and average values were calculated [22].

Drug entrapment efficiency

Proniosomal gel, was transferred into a centrifuge tube and centrifuged for 1 h at 4000 rpm. Sediment was diluted using methanol and filtered through filter paper. The drug conc. was measured in both the sediment and supernatant to determine the entrapment efficiency by the following equation [17].

% Entrapment Efficiency= AS/AD ×100

Where, AS= Amount of drug in sediment, AD= Amount of drug added.

Compressibility or spreadability

24 hr stored gels was placed between two horizontal plates of 20 cm^2, and on the upper one weighted 46.36 gm and 200gm

Formulation Code	Surfactant (mg)				Drug (mg)	Cholesterol (mg)	Soya Lecithin (mg)	Ethanol (mL)	Carbopol (mg)	PBS/ pH 7.4 (mL)
	Span 20	Span 40	Span 60	Span 80						
F1	360	-	-	-	30	40	560	4	10	2
F2	-	360	-	-	30	80	520	4	10	2
F3	-	-	360	-	30	120	480	4	10	2
F4	-	-	-	360	30	160	440	4	10	2

Table 1: Formulation Design.

weight was placed over it at room temperature. A circle of 5 mm in diameter was made and the distance across of gel was estimated following 5 minutes.

Presence of different functional group: To recognize the presence of functional groups in the ready proniosomal formulations, FTIR study was done. The IR Spectra of all ready formulations were obtained with FTIR Spectrophotometer, Systronics India Ltd.

Vesicle size and shape

Vesicle size and shape for every formulation was done by optical microscope. 2 gm of every formulation was spread equivalently on glass slide and observed under optical microscope for vesicular size and shape [8,22].

Zeta potential

Zeta potential is measured stability of formulation. Its measurement brings detailed insight into the causes of dispersion, flocculation and can be applied to advance the formulation of proniosomes. In general, particles could be dispersed stable when the absolute value of zeta potential is above 30 mV. Moreover, the zeta potential below 20mV is of limited stability and that below 5mV show rapid aggregation. However, several studies have reported that the zeta potentials of proniosome formulations ranged between -10 to -20 mV. Zeta potential of proniosomal formulation was determined using Zeta Sizer (Nano-ZS, Malvern, U.K.) at 250 C [30].

Evaluation of *in vitro* drug release

In vitro medicate discharge was checked by utilizing a Franz Diffusion cell. The cellophane film was put between the giver and receptor compartment of the diffusion cell. 1 gm of proniosomes were put over the cellophane film and the receptor compartment of the diffusion cell was loaded up with phosphate support 7.4. The entire gathering was fixed on an attractive stirrer and the arrangement in the receptor compartment was constantly mixed utilizing an attractive dot at 50 rpm; the temperature was kept up at 37c. 1 ml test was pulled back at explicit time focuses over a time of 8 hours and equivalent volume of new disintegration medium was utilized to keep up a consistent volume. The aliquot examples were separated and the drug concentration was dictated by ultraviolet (UV) technique at 363nm for MLX individually. The total measure of drug release from proniosomes was plotted against time [17]. To know the component of drug release from these details, the information were treated by first request (log aggregate level of medication remaining versus time), Higuchi's (Cumulative level of drug release versus time) and Korsmeyer's (log combined level of drug release versus log time) condition alongside a zero-request (Cumulative level of drug release versus time) design.

Stability studies

The purpose of the stability study is to provide the quality of a drug substance which varies with time under the environmental factors (temperature, humidity and light). A stability study was checked randomly selected 3 Proniosomal formulations, in which phospholipid, cholesterol and propylene glycol percentage were varied. Proniosomes were stored under static conditions 4C, (room temperature) 25C and at high temperature 60C in glass over a periods of one month.

Result and discussion of Prepared proniosomal Gel

pH Determination: pH of all prepared formulation is under 6 to 6.5 pH range. pH of Span 60 based formulation is 7.1. others formulations pH range is as following table.

pH value of all formulations

S. No.	Formulation code	pH ± S. D
1	F1	06.24 ± 0.05
2	F2	06.93 ± 0.09
3	F3	07.10 ± 0.04
4	F4	06.40 ± 0.05

Table 2: pH value of all formulations.

Drug entrapment efficiency

Drug entrapment efficiency is highest in span 60 based formulation and lowest in span 20 based formulation. Drug entrapment efficiency responsible for capacity of drug entrapment so pharmacological effect of formulation is depend upon the drug entrapment.

Drug entrapment efficiency of all formulations

S. No.	Formulation code	Drug entrapment efficiency (EE%) ± S. D
1	F1	67.2 ± 1.44
2	F2	72.8 ± 1.36
3	F3	76.8 ± 0.60
4	F4	70.6 ± 0.70

Table 3: Drug entrapment efficiency of all formulations.

Viscosity

Viscosity of each formulation determined with Brookfield viscometer. F3 batch viscosity found highest 47889 ± 1.13 centipoise and F2 batch viscosity found 45223 ± 0.92 centipoise. Viscosity play important role in stability and during applying.

Viscosity of all formulations

S.no.	Formulation code	Viscosity (centipoise)
1	F1	46115 ± 1.11
2	F2	45223 ± 0.92
3	F3	47889 ± 1.13
4	F4	45778 ± 0.11

Table 4: Viscosity of all formulations.

Presence of different functional group

To identify the presence of organic functional groups in the prepared Proniosomal formulations FTIR study was performed. We were seen there is no any type of interaction in the drug and excipients.

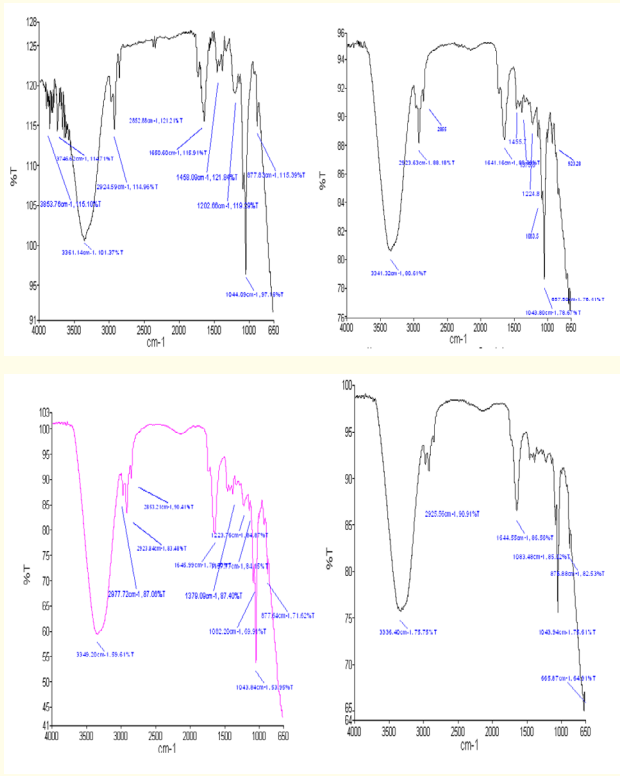

Figure 2: FTIR spectra of Proniosomes prepared with MLX.

Vesicle size and shape

Vesicle size determined and vesicle shape was round with smooth surface. Vesicle size of Span 20 based formulation is largest and Span 60 based formulation is smallest. Vesicle size is important for penetration and drug release factor.

Vesicle size of all formulations

S.no.	Formulation code	Vesicle size (µm) ± S. D
1	F1	10.30 ± 0.05
2	F2	08.50 ± 0.09
3	F3	05.61 ± 0.04
4	F4	07.40 ± 0.05

Table 5: Vesicle size of all formulations.

Zeta potential determination

Zeta potential determined of all formulations at 25^{0}C temperature. Colloidal property of formulation decide physical stability factor. Highest zeta potential is -54.6 (F3) batch and lowest zeta potential is -50.7 (F4) batch.

S.no.	Formulation code	Zeta Potential
1	F1	-51.9
2	F2	-52.8
3	F3	-54.6
4	F4	-50.7

Table 6: Zeta Potential of all formulations.

In-vitro drug diffusion/permeation

Drug permeation is highest in Span 60 based formulation and lowest drug permeation is in Span 20 based formulation. Drug release observed in every 3 hours interval. Drug permeation found as F3 (Span 60)> F2 (Span 40)> F4 (Span 80)> F1 (Span 20). From these data we have found that the prepared proniosomal gel (F3) releases 84.21 % of drug over a period of 18 hrs.

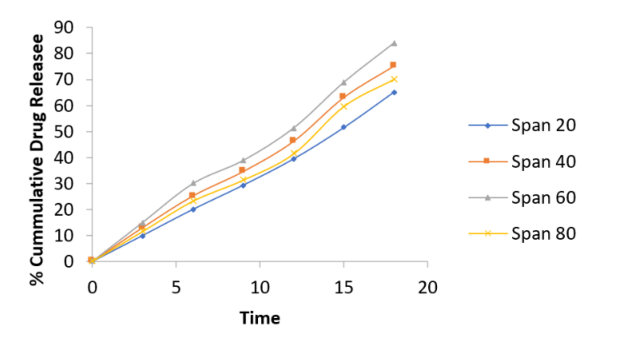

Figure 3: *In vitro* Drug Diffusion of all Formulations.

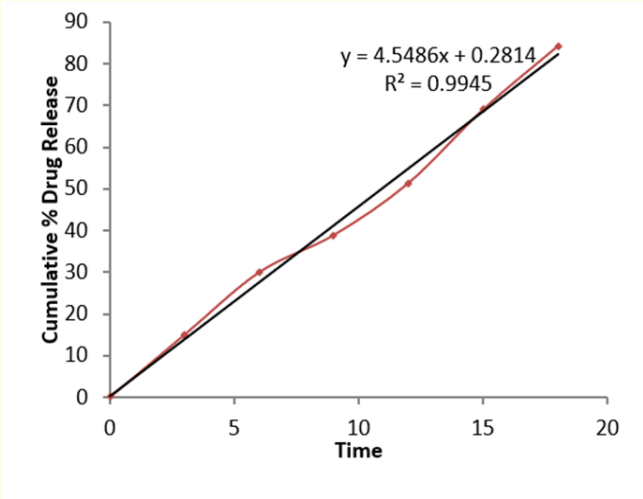

Figure 4: Graph: Cumulative % Drug Release Remaing vs Time (First Order).

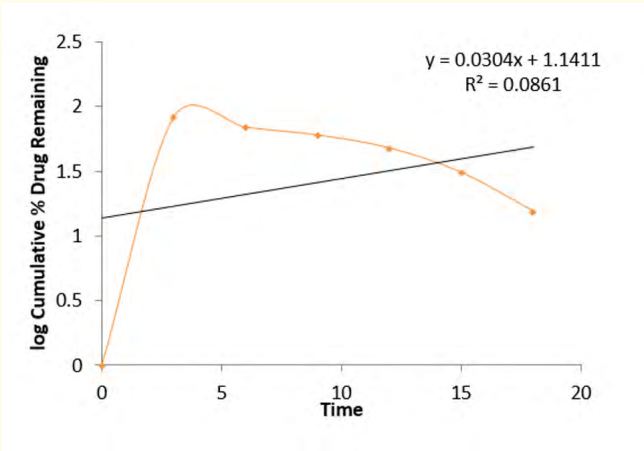

Figure 5: Graph: log Cumulative % Drug vs Time (Zero Order).

Drug Release Kinetics (Span 60)

Drug release is highest in Span 60 based formulation. Drug release of F3 (Span 60) described in Zero order, First order, Higuchi and Peppas.

In vitro drug release data of Optimized proniosomal gel formulation (F3) was utilized for determination of kinetic models such as zero order models. The best fitted line and the highest correlation were observed in order to know the mechanism of drug release. The highest correlation coefficient (R2 =0.9945) was resulted with

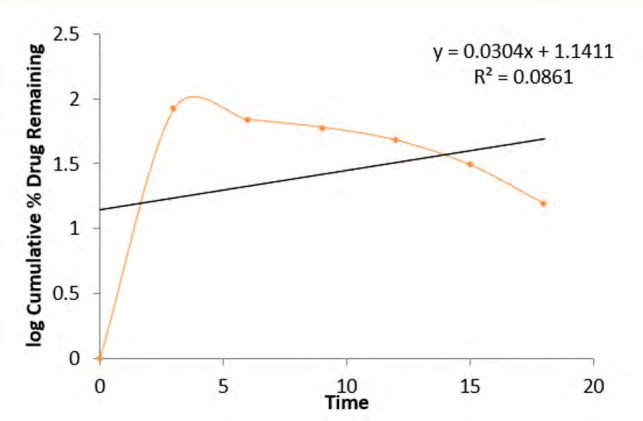

Figure 6: Graph: log Cumulative % Drug Remaing vs Time (First Order).

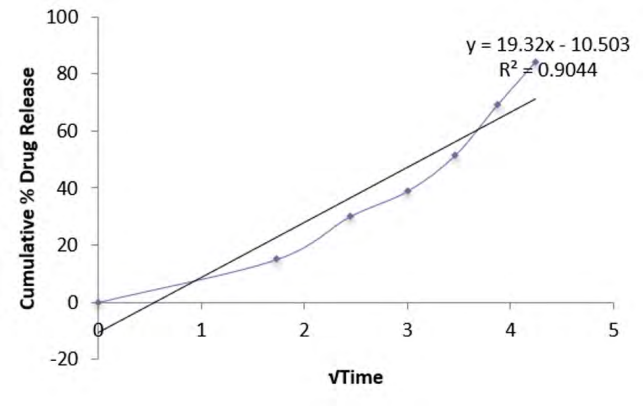

Figure 7: Graph: Cumulative % Drug Release vs √Time (Higuchi Order).

first order kinetic model which indicates that drug release mainly depends on its concentration.

Stability

The capacity of vesicles to hold the medication (Drug Retention Behavior) was surveyed by keeping the figured proniosomal gel at two diverse temperature conditions on the premise portrayal vesicle size and drug content.

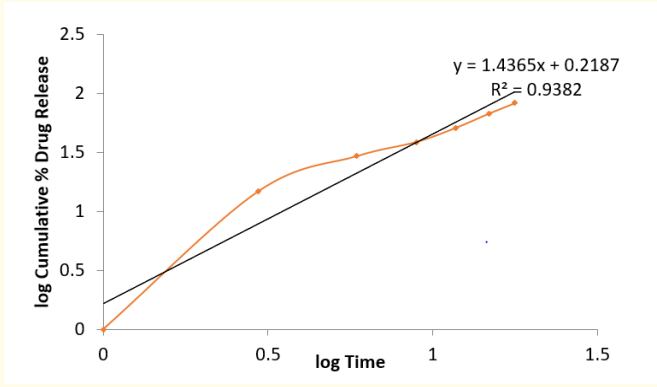

Figure 8: Graph: log Cumulative % Drug Release vs log Time (Peppas Order).

S.no.	Order of Release	R^2 Value
1	Zero Order	0.9945
2	First Order	0.0861
3	Higuchi	0.9044
4	Peppas	0.9382

Table 7: R^2 Value of Drug Release Orders.

Stability parameters of all formulations

Time in Days	Stability Parameter			
	-4 °C to 8 °C		25°C ± 2°C	
	Percentage Drug leakage	Vesicle size	Percentage Drug leakage	Vesicle size
0	-	6.50 ± 1.2	-	6.51 ± 1.6
7	1.12 ± 0.19	6.51 ± 0.5	1.30 ± 0.17	6.55 ± 1.1
15	1.45 ± 0.26	6.87 ± 0.9	2.52 ± 0.45	6.88 ± 0.5
30	2.70 ± 0.74	7.11 ± 0.4	3.32 ± 0.34	7.12 ± 0.4
45	2.90 ± 0.13	7.25 ± 1.2	3.84 ± 0.50	7.26 ± 0.8
60	3.55 ± 0.45	7.32 ± 0.5	7.58 ± 0.80	7.32 ± 0.5

Table 8: Stability parameters of all formulations.

Conclusion

There has been a generous development in transdermal medication conveyance advancements. Proniosomal based drug deliv-

ery system are one of the unic medication delivery system, that are exceptionally ready to furnish therapecutic impact with least symptom. Additionally reasonable for those medication atoms which produce major gastric, cardiovascular, hepatic and renal symptoms on taking other than skin course.

On account of osteoarthritis, patients take a great deal of analgesics and NSAIDs by orally or parenterally for relieving pain and inflammation. So proniosomal gel of MLX can be best treatment with no antagonistic impact.

They are able to enhancing penetration and also known to avoid many of the problems associated with either the aqueous niosome dispersion as problems of physical stability such as aggregation, fusion, and leakage. They give extra comfort of transportation, dissemination, stockpiling and dosing. Because of good dependability character ready to draw out medication activity with keeping up sedate fixation. Proniosomal gel not just offer a promising methods for tranquilize conveyance, yet in addition could improve the recuperation pace of the skin boundary.

Proniosomal gel of MLX will give focusing on based controlled drug delivery system. This definition will likewise expand contact timeframe of medication with successful site.

Proniosomal gel of MLX speak to a promising drug delivery advances and much exploration must be roused in this to sift through all the potential in this transdermal medication conveyance drug delivery system. Defined proniosomal gel of MLX (F3) group upgraded higher saturation rate and follow zero request discharge energy model.

This make proniosmal gel of MLX for the treatment of osteoartritis, a promising mechanical and examination item.

Human and Animal Rights

No humans were involved in the study.

Consent for Publication

Authors are willing to publish the article in your reputed journal.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgement

Declared none.

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