Iraqi Journal of Industrial Research (IJOIR)

Journal homepage: http://ijoir.gov.iq

Transdermal Delivery of Lornoxicam Hybrid Nanogel: Design, Preparation, Characterization, and In-Vitro Diffusion Evaluation

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Article information

Article history:
Received: December, 19, 2022
Accepted: April, 12, 2023
Available online: October, 20, 2023

Keywords:
Lornoxicam,
Hybrid nanogel,
LPHNs

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DOI:
https://doi.org/10.53523/ijoirVol10I2ID289

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Abstract

Lornoxicam was practically water insoluble and a nonsteroidal anti-inflammatory therapeutic agent thus associated with gastrointestinal tract (GIT) side effects. Lipid polymer hybrid nanocarriers (LPHNs)-based transdermal nanogel of lornoxicam was formulated to increase solubility of lornoxicam and sustained lornoxicam release that lead to eliminate GIT related side effect, prolong therapeutic activity and improve patient compliance .The lornoxicam LPHNs formulations (LH1-LH6) were prepared by microwaves based method. The conventional gel of lornoxicam (G) was prepared by solvent diffusion method. The LH1-LH6 was entered to characterization processes that were later used as a base to prepare lornoxicam hybrid nanogel formulations (LN1-LN6). The LN1-LN6 was tested for various evaluations. It was found that all the LH1-LH6 were show nanosize globules, low polydispersity index and acceptable surface charge, entrapment efficiency and drug loading. LH3 was the most optimized LPHNs due had lower particle size and higher lornoxicam release.The evaluation processes indicate stable organoleptic properties, high homogeneity, and acceptable values of pH. The comparability profile of the lornoxicam release from the lornoxicam nanogel formulations (LN1-LN6) and conventional lornoxicam gel (G) was in the following descending order: LN3 > LN2> LN1 > LN6 > LN5 > LN4 > G. The characterization and evaluation processes highly support promise transdermal delivery system to decrease pain and inflammation in musculoskeletal diseases.

1. Introduction

The tremendous development in nanotechnology compels researchers to exploit it in the process of solving various problems, including delivery of therapeutic agents and others related to the patient, leading to the fight against various human diseases. The amazing features in nanocarriers, which are the possibilities of chemical and physical molecular arrangement, lead to encouraging and effective designs in the process of controlling drug transport and release under different environmental and physiological conditions [1]. Lornoxicam is a nonsteroidal anti-inflammatory therapeutic agent that was belong to an oxicam class having great anti-inflammatory and analgesic activity.It inhibit prostaglandin synthesis through the enzymatic cyclooxygenase (COX)inhibition which are COX-one and COX-two that lead to prevent prostaglandin production from arachidonic acid. The great role of prostaglandins in mucosal protection of the gastrointestinal (GI) tract

represented by inhibiting gastric acid secretion, therefore inhibition of prostaglandin synthesis causes GI problems such as ulceration, dyspepsia, and bleeding [2-3]. Lornoxicam practically water insoluble where it belongs to biopharmaceutical classification system (BCS) - class II. It was employed to symptomatic treatment of inflammation and pain associated with osteoarthritis and rheumatoid arthritis, pain of pre-operative and post-operative, bone-related, dental surgeries and gynaecology department. Lornoxicam needs to administer by patients in 2-3 times due to have short duration of action and low elimination half-life [4-5]. The injection and oral dosage forms such as tablet are currently used widely to use in process of pain management. The injection associated with many demerits such as tissue damage, infection and patient discomfort [6]. Oral dosage forms faces many problems such as presence of intestinal- hepatic first pass effect, not suitable for poorly water soluble therapeutic agents and drugs that associated with gastrointestinal side effects [6]. Transdermal delivery system had been used to overcome the GIT related side effect of lornoxicam. In transdermal drug delivery systems, the stratum corneum represent important obstacle in human skin that reduce therapeutic agents passage. In order to weaken the stratum corneum barrier and enhance the skin permeation of drugs, several approaches have been achieved, such as physical and chemical improvement techniques: magnetophoresis, electroporation, iontophoresis, and microneedles, but their applications were limited due to expensive, toxicity, and patient incompliance [2]. The nanoparticulated based gel delivery system such as hybrid nanogel was considered successful method for transdermal lornoxicam delivery. The hybrid nanogel composes of lipid polymer hybrid nanocarriers (LPHNs) and gel base [2]. The LPHNs were shown important features, including biocompatibility, the structural components diversification, controlled drug delivery, ability to loading the hydrophilic and hydrophobic therapeutic agents, ability to higher encapsulation, enhance solubility and permeability of drugs, and improved in-vitro and in-vivo stability [7]. The aim of this research was design and prepares lornoxicam hybrid nanogel (LN) to increase solubility of lornoxicam and sustain drug release that lead to prolong therapeutic activity, eliminate GIT related side effect and improve patient compliance.

2. Experimental Procedure

2.1. Materials

All solvents and reagents that had been used in the research were of experimental grade. Lornoxicam was purchased from Nanjing Duly Biotech Co., Ltd China. Myrtle oil, chitosan, polyacrylic acid (PAA)-940, Tween 80 and PEG laurate purchased from Beijing Yibai Biotechnology Co., Ltd. China. Potassium chloride, disodium hydrogen phosphate, sodium hydroxide and potassium dihydrogen phosphate, methanol and ethanol from grin land chemical comp, United Kingdom.

2.2. Method

The microwaves-based technique [7] was applied to formulate six lornoxicam LPHNs formulations (N1-N6). The hydrophobic phase was prepared by dissolving lornoxicam, lauric acid and chitosan in a myrtle oil using a magnetic stirrer device at 1000 rpm for 5 minutes. The hydrophilic phase that contains PEG-laurate, tween 80 and distilled water was prepared under a magnetic stirrer at 1000 rpm for 5 minutes. Then mixing hydrophobic and hydrophilic phases according to the concentrations that described in Table (1). The mixture was inserted in microwave instrument for 10 seconds, then subjected to magnetic stirring of 1000 rpm until the associated colloidal system of lornoxicam LPHNs was formed. The gel base was formulated by Carbopol 940 dissolving in distilled water with continuously stirring using electric homogenizer. Few drops of triethanolamine were added until pH about (6.2-7.4) was obtained. The lornoxicam LPHNs was added to the newly prepared gel in 1:1 ratio using electric homogeniser to get clear dispersion system of lornoxicam nanogel (N). The lornoxicam nanogel (N1-N6) formulations were stored in a tightly closed container at 25 OC temperatures for evaluation [8]. The conventional lornoxicam gel [9-10] was prepared by solvent diffusion method by dissolving two grams of the drug in 5ml of ethanol then incorporates to carbopol 940 base gel to create lornoxicam gel that was kept the container open for 24 hours to get conventional gel of lornoxicam (N).

3. Characterization of Lornoxicam LPHNs Formulations (LH1-LH6)

3.1. Measurement of Globule Size, Polydispersity Index (PDI), and Zeta Potential (ZP)

The experimental technique that had been exploited to measure size of dispersed vesicles, polydispersity index (PDI) and surface charge was photon correlation spectroscopy (PCS) using Horiba instrument, Ltd. Kyoto, Japan. Three trials of experiments were performed [7].

3.2. Entrapment Efficiency (EE) and Drug Loading (DL)

The EE expressed in percentage (%) is an important factor that gave information about process of lornoxicam encapsulation. The indirect method was achieved to determine EE by calculating free lornoxicam molecules in supernatant layer after process of the centrifugation. It was determine by equation 1:

$$\text{EE (\%)} = [(\text{Total lornoxicam quantity} - \text{Free lornoxicam quantity}/\ \text{Total lornoxicam quantity})] \times 100$$

Drug loading (DL) parameter expressed in percentage (%) is the lornoxicam amount that can be found in the nanoparticles divided by the total lipid quantity. It was calculated by equation 2:

$$\text{DL (\%)} = [(\text{Total lornoxicam quantity} - \text{Free lornoxicam quantity} / \text{Total lipid amount})] \times 100$$

The study was achieved in triplicate for EE and DL [7].

4. Evaluation of Lornoxicam Hybrid Nanogel Formulations (LN1-LN6)

4.1. Organoleptic Measurement

It was performed by notice of the shape, colour, and odour that can occurs in lornoxicam nanogel formulations (LN1-LN6) at 0, 7, 14, 21 and 28 days. The experiments were done in three trials [11-12].

4.2. Homogeneity Test

It was achieved by application 0.5g of lornoxicam nanogel formulations (LN1-LN6) to transparent material such as glass piece [11-12].

4.3. Measurement of pH

It was performed by employ a digital pH meter. The samples were taken from lornoxicam nanogel formulations (LN1-LN6) are 10 g. The optimum pH value of skin in the range of 4.5 - 6.5. The experiment was achieved in triplicate [11-12].

4.4. In-Vitro Diffusion Studies

Franz diffusion cell is a technique that had been used to measure diffusional behaviour of lornoxicam molecules. The samples of lornoxicam hybrid nanogel formulations (LN1-LN6) and conventional lornoxicam gel (G) were applied onto the dialysis membrane surface that inserted between donor and receptor compartment. The volume of phosphate buffer solution pH 7.4 was 200 mL, fills the receptor part in presence of magnetic beads at 25°C. Samples of 0.1 gram from receptor compartment were taken at predetermined intervals of time (0, 0.25, 0.3, 1, 2, 4, 6, 8 and 12, 24 hr.) with adding of same volume of fresh of diffusion solution to obtain constant diffusional volume. The content of lornoxicam in each sample was determined by ultraviolet-visible spectrophotometer at 376nm [12-14].

5. Statistical Analysis

The excel program was used to performed study. The experimental data was obtained as the mean of three trials in presence of standard deviation (SD). The one-way analysis of variance (ANOVA) was statistical test, where the level at ($P \leq 0.05$) was kept as significant while ($P > 0.05$) was kept as no significant [7].

6. Results and Discussion

6.1. Measurement of Globule Size, Polydispersity Index (PDI), and Zeta Potential (ZP)

The formulation process of lornoxicam LPHNs formulations (LH1-LH6) which are LH1, LH2, LH3, LH4, LH5, and LH6 that had been used as to prepare lornoxicam hybrid nanogel formulations (LN1-LN6) were achieved under high experimental discipline according to the concentrations of the components present in Table (1). The results of globule size of lornoxicam LPHNs formulations (LH1-LH6) were LH1 (106.3nm); LH2 (94 nm); LH3 (77.6nm); LH4 (164 nm); LH5 (143 nm) and LH6 (135 nm) as shown in Table (2). LH3 had lower particle size as shown in Figure (1) while that LH4 had larger particle size as shown in Figure (2). The outcomes indicate that all dispersed particles had nanosized diameter and presence of associated colloids [15]. PDI is a parameter that explains colloidal system homogeneity. It is dimensionless value from 0 to 1. The smaller values indicate a more

homogenous system, while the homogeneity of colloidal system decreases as the PDI increase. The outcome shows that PDI was from (0.26 to 0.62) as shown in Table (2) that indicates lornoxicam LPHNs homogeneity [15]. The zeta potential parameter was related to the physical stability of nano globules. The results of absolute value of zeta potential were (14.63 to 25.13 mV) as shown in Table (2).In spite of low value of zeta potential, there was high physical stability of lornoxicam LPHNs due to the stabilization process was achieved by hydration forces and steric forces which are non DLVO molecular forces [16]. The ANOVA showed there was a significant relationship between dependent factors which are particle size, PDI and zeta potential, and the independent factors which are myrtle oil/lauric acid oil, chitosan and PEG laurate/tween 80 at the level ($p \leq 0.05$).

6.2. Entrapment Efficiency (EE) and Drug Loading (DL)

The ability of lornoxicam encapsulation within LPHNs was determined by the entrapment efficiency and drug loading factors. The results of EE (w/w %) were LH1 (87.4%); LH2 (86.9%); LH3 (81.6%); LH4 (86.8%); LH5 (88.36%) and LH6 (89.1%). While, the results of drug loading (w/w %) were LH1 (21.6%); LH2 (23.16%); LH3 (24.5%); LH4 (17.06%); LH5 (19.5%) and LH6 (23.9%) as shown in Table (2). These data confirm the ability of the lornoxicam LPHNs formulations (LH1-LH6) to encapsulate lornoxicam with high affectivity. It was found that increase in lipid contents which are myrtle oil/ lauric acid leads to an increase in entrapment efficiency and decrease in lornoxicam loading at a constant concentration of PEG laurate/tween 80. This is due to increment in lipid content area that was available for therapeutic agent accommodation7. The analysis of variance was confirmed rejection of null hypothesis and accepted the alternative hypothesis due to there was a significant relationship between dependent variables which are entrapment efficiency and lornoxicam loading, and myrtle oil/lauric acid oil, chitosan and PEG laurate/tween 80 at the level ($p \leq 0.05$).

6.3. Organoleptic Test of Lornoxicam LN1-LN6

It was found that lornoxicam hybrid nanogel formulations (LN1-LN6) show stable physical structure as shown in Table (3) that ascertains acceptable colloidal features [11-12].

6.4. Homogeneity Measurement of LN1-LN6

All the lornoxicam hybrid nanogel formulations (LN1-LN6) had been shown homogeneous and elegance consistency as shown in Table (3) that indicates physical stability of all formulations [11-12].

6.5. Measurement of pH of LN1-LN6

The outcome was indicated that pH value of lornoxicam hybrid nanogel formulations (LN1-LN6) lie in the range (4.6-5.8) as shown in Table (3) that is suitable for topical and transdermal delivery of therapeutic agent [11-12].

6.6. In-Vitro Diffusion Studies of LN1-LN6

The release of lornoxicam forms the lornoxicam hybrid nanogel formulations (LN1-LN6) and conventional lornoxicam gel (G) was studied by Franz diffusion cell method using dialysis bag as diffusion membrane. The diffusion media was phosphate buffer pH 7.4 + 0.3 % polysorbate 80 solutions. According to the experimental data, there is no bust diffusion from all the lornoxicam hybrid nanogel formulations (LN1-LN6) and conventional lornoxicam gel (G). There was a sustained release process over 24 hours from all nano systems. The profile of lornoxicam release was significantly higher (p value <0.05) in dissolution rate for LN3 and was significantly lower (p value < 0.05) in dissolution rate of conventional lornoxicam gel (G) as shown in Figure (3). The comparability profile of the lornoxicam release from the lornoxicam hybrid nanogel formulations (LN1-LN6) and conventional lornoxicam gel (G) was in the following descending order: LN3 > LN2> LN1 > LN6 > LN5 > LN4 > G. It was observed that the conventional lornoxicam gel (G) gave a lower dissolution rate of lornoxicam profile in comparison to all lornoxicam hybrid nanogel formulations (LN1-LN6) due to that LN1-LN6 have nanocarriers which are provide a large surface area in contact to the phosphate buffer pH 7.4 + 0.3 % polysorbate 80 solutions and this was permitted a higher interaction area with the diffusion medium that increases rate of dissolution as shown in Table (3) [12-14]. The ANOVA was confirmed a significant relationship ($p \leq 0.05$) between lornoxicam diffusion and independent variables.

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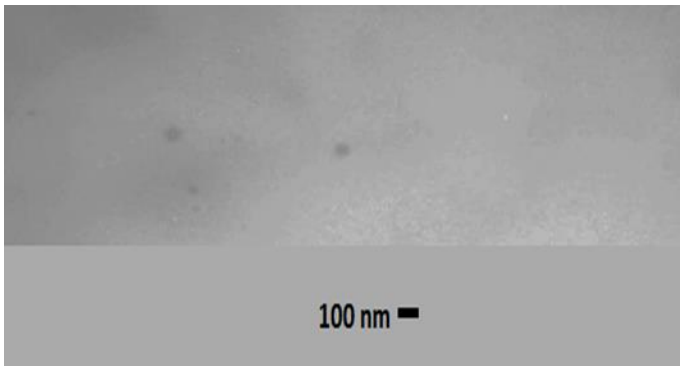

Figure (1). Transmission electron microscopic image of lornoxicam LPHNs (LH3).

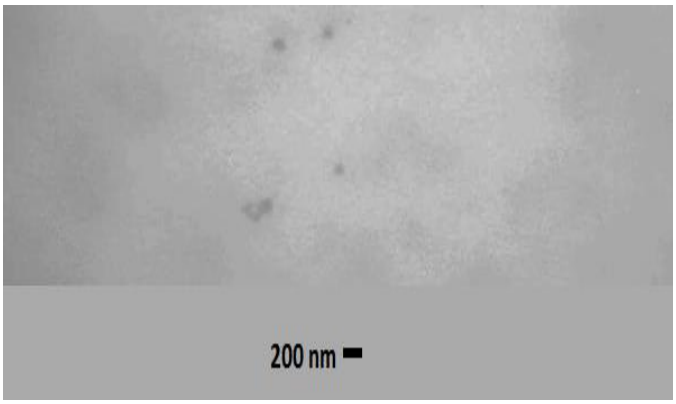

Figure (2). Transmission electron microscopic image of lornoxicam LPHNs (LH4).

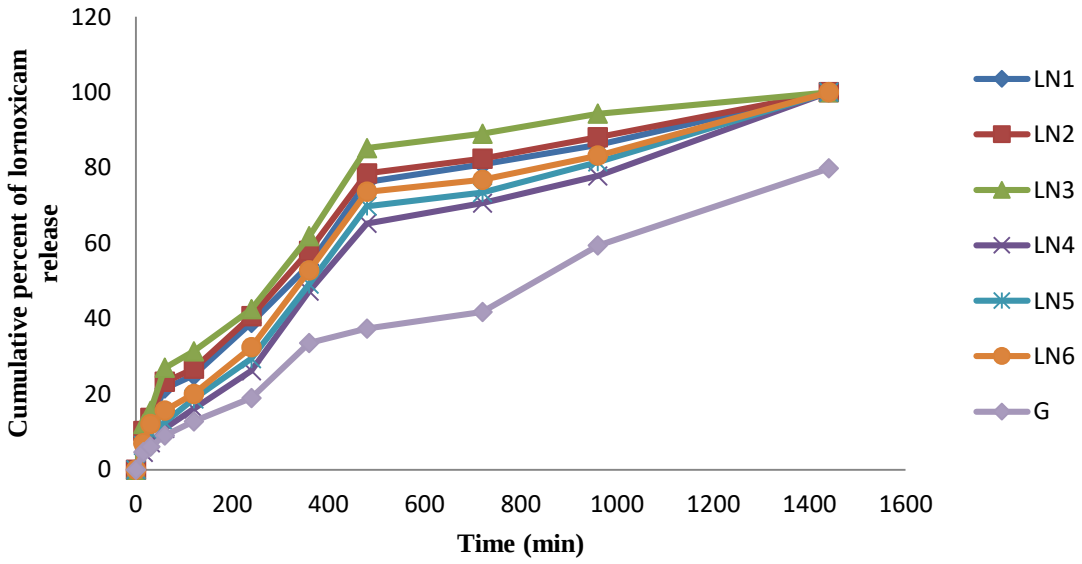

Figure (3). In-vitro release profile of lornoxicam hybrid nanogel formulations (LN1-LN6) and conventional lornoxicam gel (G) at phosphate buffer pH 7.4 + 0.3 % polysorbate 80 solution.

Table (1). Lornoxicam LPHNs (LH1-LH6) and lornoxicam hybrid nanogel formulations (LN1-LN6) for optimization.

Formulation code	Lornoxicam % (w/w)	Myrtle oil % (w/w)	Lauric acid % (w/w)	Chitosan % (w/w)	PEG-(400) laurate :Polysorbate 80 % (w/w)	Carbopol 940 %(w/w)	Distilled water % (w/w) up to
LN1	2	3.5	1.5	0.6	17.5:17.5	0.2	100
LN2	2	3.5	1.5	0.6	20:20	0.4	100
LN3	2	3.5	1.5	0.6	22.5:22.5	0.6	100
LN4	2	7	3	0.6	17.5:17.5	0.2	100
LN5	2	7	3	0.6	20:20	0.4	100
LN6	2	7	3	0.6	22.5:22.5	0.6	100
G	2					0.4	100

Table (2). Characterization results of lornoxicam LPHNs formulations (LH1-LH6)

Formulation Code	Globule size (nm)*	PDI*	Zeta potential*	Entrapment efficiency % (w/w)*	Drug loading % (w/w)*
LH1	106.3±4.041	0.413±0.015	23.03±3.564	87.4±1.65	21.6±1.769
LH2	94±3.464	0.356±0.018	19.1±3.567	86.9±1.252	23.16±1.855
LH3	77.6±2.516	0.26±0.024	15.2±2.705	81.6±1.527	24.5±1.345
LH4	164±2.645	0.625±0.021	25.133±3.442	86.8±2.645	17.06±0.986
LH5	143±3.605	0.474±0.014	19.2±1.708	88.36±1.350	19.5±1.705
LH6	135±3	0.385±0.004	14.63±1.517	89.1±0.68	23.9±1.682

*Values are expressed as mean ± SD (n=3).

Table (3). Evaluation results of lornoxicam hybrid nanogel formulations (LN1-LN6)

Formulation code	LN1	LN2	LN3	LN4	LN5	LN6	G
Color	Faint yellowish	Faint yellowish	Faint yellowish	Faint yellowish	Faint yellowish	Faint yellowish	Faint yellowish
Odor	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless	Odorless
Phase separation	No	No	No	No	No	No	No
Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
pH*	5.43±0.416	5.6±0.264	5.8±0.173	4.6±0.264	4.9±0.152	5.1±0.1	5.3±0.05
Release of lornoxicam as cumulative persent in phosphate buffer pH 7.4 + 0.3 % polysorbate 80 solution*	86.5±0.4	88.3±0.251	94.63±0.305	77.54±0.233	81.53±0.351	83.43±0.321	59.46±0.404

*Values are expressed as mean ± SD (n=3).

7. Conclusion

The process of preparation and characterization produced hybrid nanoparticles which are LH1-LH6, with high-quality transport properties and could carry different therapeutic elements for the purpose of transporting them to different parts of the human body and for the purpose of combating various diseases.LH3 was the most optimized LPHNs due had lower particle size and higher lornoxicam release. The evaluation process for lornoxicam hybrid nanogel formulations (LN1-LN6) show acceptable organoleptic features, high homogeneity, optimum pH with sustained lornoxicam liberation that support promise transdermal delivery system to reduce pain and inflammation in musculoskeletal disorders such as osteoarthritis and rheumatoid arthritis, degenerative disc disease, tendonitis and digital neuritis.

Conflict of Interest: The authors declare that there are no conflicts of interest associated with this research project. We have no financial or personal relationships that could potentially bias our work or influence the interpretation of the results.

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