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Stability Study and *In-vivo* Evaluation of Lornoxicam Loaded Ethyl Cellulose Microspheres

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ABSTRACT
Sustained release microspheres of Lornoxicam were prepared by emulsion solvent evaporation method using ethyl cellulose as release retarding agent and evaluated for *in-vivo* efficacy and stability study. The anti-inflammatory and analgesic activity of microspheres was evaluated by using the carrageenan-induced hind paw edema and Eddy's hot plate methods, respectively. *In-vivo* study of microspheres demonstrated significant analgesic and anti-inflammatory activities of prepared microspheres for a longer period of time as compared to the standard drug. The microspheres showed minor changes (non significant) in physical appearance, particle size with no appreciable change in drug content in different conditions of stability studies. Results also showed that no remarkable changes in the drug release from microspheres formulation of different storage conditions. From these findings, it is concluded that Lornoxicam significantly increases anti-inflammatory and analgesic effect when oral administration in ethyl cellulose microspheres formulation.

Keywords: Lornoxicam, microspheres, solvent evaporation, analgesic.

INTRODUCTION

Lornoxicam (Lxm) also known as chlortenoxicam, is a member of the oxicam group of non-steroidal anti-inflammatory drugs (NSAIDs). [1-2] Like other NSAIDs, the anti-inflammatory/ analgesic activity of lornoxicam is related to the inhibitory action on prostaglandin synthesis, via inhibition of cyclooxygenase (COX) activity in the COX pathway of arachidonic acid metabolism [3] and also may produce gastrointestinal side effects. However, Lornoxicam usefulness is limited due to its short half-life that ranges from 3 to 5 hours. [1, 4] Hence, it requires repeated dosing which lead to local irritation and ulceration, and hence is the cause of the patient's non-compliance. To reduce the frequency of dosing and improve the patient compliance, controlled/ sustained release formulation is desirable.

In the last few decades, advancements in controlled/sustained drug delivery systems has lead to attainment of more effective therapy, i.e. delivery of drug over a long period of time, avoiding the large fluctuations and reducing the need of several administrations. [5] Over the past few decades, Microspheres are one of the microparticulate delivery systems which are widely accepted to achieve oral controlled drug delivery. Microspheres can be defined as solid, approximately spherical particles ranging from 1 to 1000μm, containing dispersed drug in either solution (or) microcrystalline form. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance. [6-7] A number of different polymers, both biodegradable and non-biodegradable nature has been investigated for preparation of polymeric microspheres. [8] Among them, ethyl cellulose (EC) is a water insoluble, biocompatible and nontoxic cellulose polymer, widely used in the formulation of pharmaceutical products. [9-10] It is also studied extensively as encapsulating material for sustained release of various drugs. [9, 11-12] The aim of the present study was to prepare ethyl cellulose microspheres of Lxm by emulsion-solvent evaporation technique and to investigate its analgesic and anti-inflammatory efficacy.

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MATERIALS AND METHODS

Materials

The drug, Lornoxicam was obtained as a gift sample from Zydus Cadila Healthcare Limited, India. Ethyl Cellulose (EC), Dichloromethane (DCM) and Tween 80 were purchased from Central Drug House Pvt. Ltd., New Delhi,

India. Carrageenan was obtained from HiMedia Ltd., Mumbai, India. All other chemicals used were of analytical grade.

Preparation of Lxm Loaded Ethyl Cellulose Microspheres

The Lxm loaded ethyl cellulose microspheres (LECM) were prepared by emulsion solvent evaporation method with some modification. [13-14] Weighed amount of ethyl cellulose (600 mg) and Lxm (200 mg) in the ratio of drug: polymer (1:3) was dissolved in 10 ml of dichloromethane as the internal phase. The prepared organic phase was then added drop wise to the water (100 ml), containing 1.0 % tween-80 (surfactant), which acts as external (continuous) phase. The mixture was stirred with mechanical stirrer at controlled stirring speed of 1000 RPM. The formed oil-in-water (o/w) emulsion was stirred continuously at room temperature until complete evaporation of dichloromethane and formation of solid microspheres. The prepared microspheres were filtered washed with excess of distilled water and dried in a desiccator under vacuum at room temperature.

***In-vivo* Evaluation**

Test Animals

Albino mice weighing 20-25 g and albino rats (150-200 g) of both sexes were used. The animals were housed in standard well-spaced ventilated cages in a controlled environment (temperature 25±2°C and 12 h dark/light cycle) with standard laboratory diet and water *ad libitum*. Food was withdrawn 12 h before and during the experiment. The mice were used for analgesic evaluation; while the rats were used for the anti-inflammatory evaluation. The Animal Ethical Committee of the Institute approved all the protocols of the study.

Assessment of Anti-inflammatory Effect

The anti-inflammatory activity of Lxm loaded ethyl cellulose microspheres (LECM) formulations were evaluated by the carrageenan-induced hind paw oedema method developed by Winter *et al*. [15] Paw oedema was induced by injecting 0.1 ml of the 1 % w/v homogenous suspension of carrageenan in saline into the left hind paw by inserting the needle into the central part of the paw. Albino rats of similar weight were randomly selected and were divided equally into 3 groups of 6 animals each:

Group I (Control Group): Carrageenan (Injected) + No treatment

Group II (Standard Group): Carrageenan (Injected) + Treated with Lxm 1.3 mg/kg (Orally)

Group III (Test Group): Carrageenan (Injected) + Treated with LECM 1.3 mg/kg (Orally)

The first group served as control. The second group received plain lornoxicam 1.3 mg/kg [16-17] (dose calculated as per the body weight of the animals). Animals of the third group were given microspheres formulation containing Lxm equivalent to 1.3 mg/kg dose. The inflammatory response was determined by measuring the paw volumes (ml) using a Plethysmometer at time intervals of 0.5, 1, 2, 4, 6, 8, 10 and 12 hours. The percentage inhibition of the oedema was calculated for each group with respect to its vehicle-treated control group using the following formula: [18]

$$\% \text{ inhibition of oedema} = C_o\text{-}C_t/C_o \times 100$$

Where, C_o is the average increase in paw volume (average inflammation) of the control group at a given time; and C_t is the average inflammation of the drug treated group at the same time.

Evaluation of Analgesic Activity

Analgesic activity of Lxm loaded ethyl cellulose microspheres (LECM) was studied by Eddy's hot plate (thermal) analgesic test method. [18-19] Mice of either sex weighing between 20-25 g showing cut-off time below 15 sec were selected for test and divided randomly into three groups; each group consists of six mice. Group I was used as a control, which received normal saline, group II as a standard received 1.3 mg/kg of lornoxicam (Lxm), and group III received Lxm loaded ethyl cellulose microspheres (LECM) formulation containing Lxm equivalent to 1.3 mg/kg dose. The mice were placed on hot plate analgesiometer adjusted to temperature 55 ± 1°C, where the surface is hot enough to cause discomfort without tissue damage. A cut-off time of 15 seconds was maintained to avoid damage to paw or tissue injury. The time taken in seconds till the mice begin to jump or licking of paw was determined and this time was called the reaction time. The reaction time for the analgesic effect was measured at 0.5, 1, 2, 4, 6, 8, 10, and 12 h. The percentage thermal pain relief or protection against thermal pain was calculated by applying the formula [18], where T_a and T_b is the mean reaction time of treated and control, respectively:

$$\% \text{ protection against thermal pain} = \frac{T_a - T_b}{T_b} \times 100$$

Statistical Analysis

The statistical analysis of data for anti-inflammatory effects and analgesic activity were analysed by one-way ANOVA followed by Tukey's comparison test, using GraphPad PRISM (version 5.00) software. Tukey's comparison test was applied for comparison of formulation (LECM) with control and standard group. An effect was determined to be significant if the *P* value was less than 0.05.

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The Lxm loaded ethyl cellulose microspheres formulation (LECM) was filled in tightly closed glass vials and subjected to stability testing according to the International Conference on Harmonization (ICH) guidelines for zone III and IV. The packed containers of microspheres were kept at refrigeration condition (5±3°C), room temperature (25±2°C) and under accelerated condition (40±2°C/75±5% RH) in a stability chamber for a period of six months. The samples (n=3) were analyzed at intervals of 0, 1, 2, 3 and 6 months and evaluated for physical appearance, particle size, drug content, entrapment efficiency and drug release studies. [20]

The physical appearance (changes in color) of stored formulation was evaluated by visual observations. Particle size of stored formulation was evaluated by an optical microscopic method. [21] For the determination of drug content and entrapment efficiency, stored microspheres (50 mg) were accurately weighed and crushed were suspended in 50 ml of phosphate buffer solution (PBS, pH 6.8) and the resulting mixture was kept shaking on mechanical shaker, filtered, diluted appropriately and analyzed for drug content spectrophotometrically (n=3) at 376 nm (Shimadzu 1700, Japan). Entrapment efficiency was calculated using the following equation. [22-23]

$$\text{Entrapment efficiency (\%)} = (A/T) \times 100$$

Table 1: Anti inflammatory activity of Lxm loaded ethyl cellulose microspheres (LECM) formulation on carrageenan induced paw oedema in rats

S. No.	Treatment	Paw volume in ml (Mean ± SEM) (% inhibition of oedema)							
		0.5 h	1 h	2 h	4 h	6 h	8 h	10 h	12 h
1.	Control	0.32±0.005	0.35±0.016	0.42±0.012	0.58±0.020	0.53±0.021	0.45±0.020	0.43±0.018	0.39±0.017
2.	Standard (Lxm)	0.22±0.011[a] (31.25)	0.20±0.006[a] (42.85)	0.18±0.005[a] (57.14)	0.08±0.003[a] (86.20)	0.18±0.017[a] (66.03)	0.26±0.018[a] (42.22)	0.34±0.012[a] (20.93)	0.36±0.013[a] (7.69)
3.	LECM	0.26±0.005[a,b] (18.75)	0.24±0.003[a] (31.42)	0.23±0.003[a,b] (45.23)	0.21±0.010[a,b] (63.79)	0.15±0.010[a] (71.69)	0.07±0.008[a,b] (84.44)	0.05±0.003[a,b] (88.37)	0.04±0.003[a,b] (89.74)

[a]Statistically significant ($p < 0.05$) as compared to control; [b]Statistically significant ($p < 0.05$) as compared to standard;
Values are expressed as Mean ± SEM for 6 animals in each group

Table 2: Analgesic effect of Lxm loaded ethyl cellulose microspheres (LECM) formulation in mice using Eddy's hot plate method

S. No.	Treatment	Reaction time in seconds (Mean ± SEM) (% protection against thermal pain)							
		0.5 h	1 h	2 h	4 h	6 h	8 h	10 h	12 h
1.	Control	4.27±0.017	4.19±0.031	4.15±0.045	4.26±0.039	4.20±0.046	4.41±0.040	4.37±0.063	4.32±0.090
2.	Standard (Lxm)	5.65±0.066[a] (32.23)	6.68±0.028[a] (59.43)	7.18±0.063[a] (70.60)	7.84±0.066[a] (84.03)	6.45±0.063[a] (53.57)	4.88±0.063[a] (10.65)	4.62±0.072[a] (5.72)	4.46±0.065 (3.24)
3.	LECM	5.10±0.046[a,b] (19.43)	5.49±0.045[a,b] (31.02)	6.55±0.076[a,b] (57.83)	7.12±0.058[a,b] (67.13)	7.30±0.121[a,b] (73.80)	8.19±0.110[a,b] (85.71)	7.84±0.090[a,b] (79.40)	7.55±0.092[a,b] (74.76)

[a]Statistically significant ($p < 0.05$) as compared to control; [b]Statistically significant ($p < 0.05$) as compared to standard;
Values are expressed as Mean ± SEM for 6 animals in each group

Table 3: Stability study of Lxm loaded ethyl cellulose microspheres formulation (LECM) at different conditions

Conditions	Time Interval (Months)	Parameters				
		Physical appearance	Particle size (µm)	Drug content (mg)	Entrapment efficiency (%)	Drug release at 12th hr (%)
Refrigeration (5±3°C)	0	-	75.11 ± 1.12	17.90 ± 0.30	71.61 ± 1.20	78.36 ± 1.68
	1	-	75.34 ± 1.02	17.82 ± 0.35	71.28 ± 1.34	78.30 ± 0.76
	2	-	75.62 ± 0.95	17.85 ± 0.46	71.40 ± 1.48	78.14 ± 1.32
	3	-	76.16 ± 1.45	17.75 ± 0.38	71.00 ± 1.40	77.94 ± 1.23
	6	-	76.54 ± 1.30	17.68 ± 0.52	70.72 ± 1.53	77.62 ± 1.43
Room temperature (25±2°C)	0	-	75.11 ± 1.12	17.90 ± 0.30	71.61 ± 1.20	78.36 ± 1.68
	1	-	74.65 ± 1.32	17.80 ± 0.23	71.20 ± 0.92	78.24 ± 1.52
	2	-	74.43 ± 1.95	17.79 ± 0.41	71.16 ± 1.44	78.02 ± 0.79
	3	-	74.15 ± 1.24	17.76 ± 0.37	71.04 ± 1.38	77.76 ± 1.13
	6	+	74.02 ± 1.57	17.69 ± 0.45	70.76 ± 1.46	77.48 ± 0.87
Accelerated (40±2°C/75 ±5% RH)	0	-	75.11 ± 1.12	17.90 ± 0.30	71.76 ± 1.20	78.36 ± 1.68
	1	-	74.90 ± 0.88	17.79 ± 0.43	71.16 ± 1.45	78.12 ± 1.16
	2	-	74.82 ± 1.23	17.77 ± 0.26	71.08 ± 1.14	77.85 ± 1.41
	3	-	74.52 ± 1.06	17.72 ± 0.41	70.88 ± 1.43	77.49 ± 1.16
	6	+	74.36 ± 1.28	17.58 ± 0.49	70.32 ± 1.50	77.04 ± 1.27

– Indicate no change; + Indicate slight change; Values are mean ± S.D. (n =3)

Where, A is actual drug concentration and T is the theoretical drug concentration.

The *in-vitro* drug release of microspheres formulation were studied in simulated gastrointestinal pH conditions, viz, simulated gastric fluid (0.1N HCl, pH 1.2) for the first 2 hours, followed by simulating intestinal fluid (phosphate buffer solution, PBS, pH 6.8) up to 12 h, at 37 ± 0.5°C. Samples (1 ml) were withdrawn at regular time intervals, and replaced with the same volume of test medium to maintain sink conditions. The withdrawn samples were suitably diluted, filtered through a 0.45µ membrane filter and analyzed spectrophotometrically.

RESULTS AND DISCUSSION

Ethyl cellulose microspheres of Lxm were successfully prepared by emulsion solvent evaporation method and evaluated for *in-vivo* activities and stability study. The carrageenan-induced hind paw oedema and Eddy's hot plate methods were used for evaluating the *in-vivo* anti-inflammatory and analgesic activity respectively. The effect of LECM formulations (Group-III) was compared with other two groups-: Group-I did not receive any medication considered as a control and Group-II (Standard) received pure Lxm. The two parameters are: % inhibition of oedema and protection against thermal pain has been utilized to assess the anti-inflammatory and analgesic effect of Lxm, respectively. In carrageenan induced rat paw oedema test, Lxm loaded ethyl cellulose microspheres (LECM) showed statistically significant ($p<0.05$) inhibitory effect on the mean increase in paw volume at all the time intervals as compared to control and standard groups (Table 1 and Fig. 1). Lxm pure drug (Group-II) exhibited maximum % inhibition of oedema of 86.20 % at 4 h, whereas LECM (Group-III) showed maximum % inhibition of oedema (89.74 %) up to 12 h. It indicates that % inhibition of oedema was greater than that of standard drug at an interval of 6, 8, 10 and 12 h (Table 1).

The results was observed (Table 2 and Fig. 2) that Lxm showed a significant increase of the analgesic effect ($p<0.05$) in mice after 0.5 h of oral drug administration as compared to control. The maximum analgesic response i.e. reaction time was observed 7.84 ± 0.066 seconds and the % protection for plain drug was observed 84.03% after 4 h, which gradually decreased and diminished after 6 h. On the other hand, oral administration of LECM formulation showed a significant increase of the analgesic effect ($p< 0.05$) in mice after 0.5 h as compared to control and standard group. LECM shows maximum reaction time of 8.19 ± 0.110 seconds and protection observed was 85.71% response at 10 h and duration of drug action was maintained for more than 10 h (Fig. 2). This sustained action may be due to the lower ability of ethyl cellulose (EC) to absorb fluid and swell, therefore, a

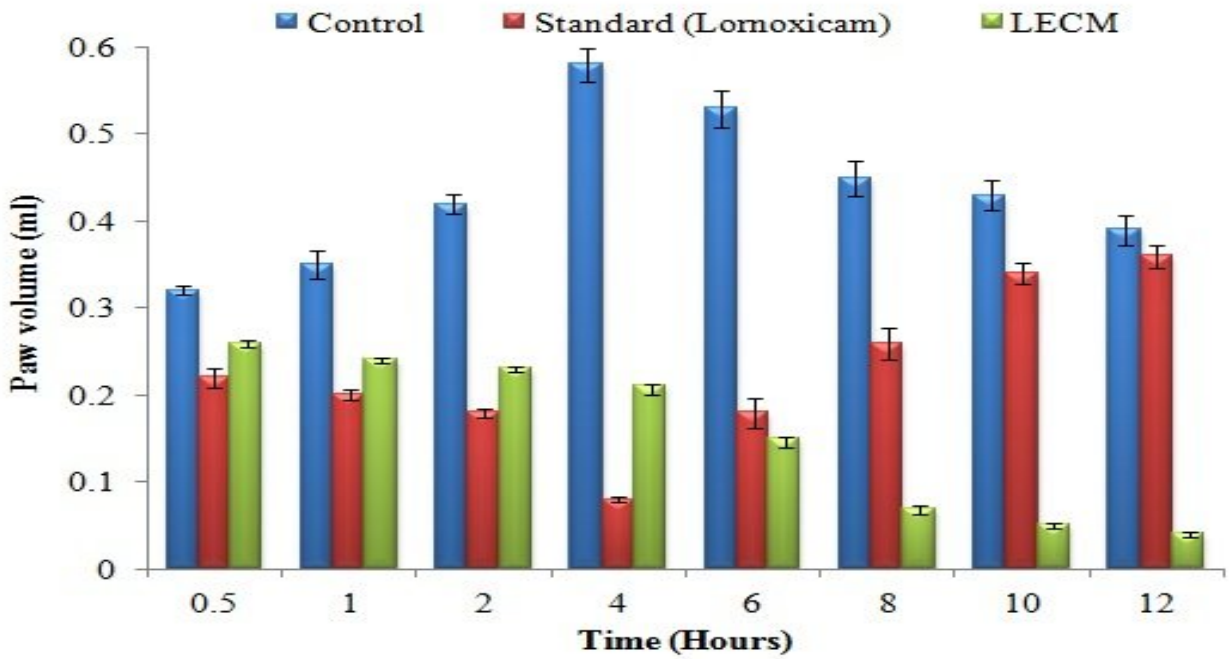

Fig. 1: Anti inflammatory activity of Lxm loaded ethyl cellulose microspheres (LECM) formulation on carrageenan induced paw oedema in rats

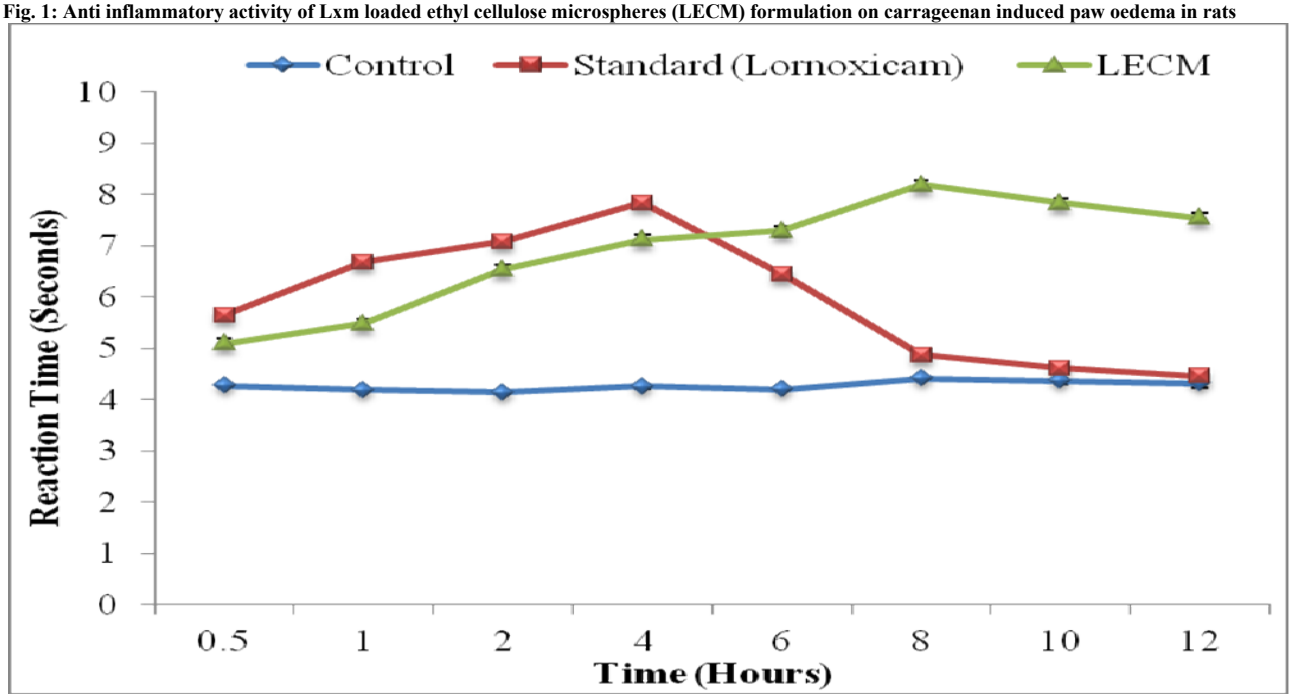

Fig. 2: Analgesic effect of Lxm loaded ethyl cellulose microspheres (LECM) formulation in mice using Eddy's hot plate method

long time is taken for fluid to penetrate the system, dissolve the drug then for the drug solution to diffuse outward. [24]

The stability of Lxm loaded ethyl cellulose microspheres (LECM) formulations were evaluated at different conditions of temperature (5±3°C, 25±2°C and 40±2°C/75±5% RH). These were evaluated at the regular intervals for a period of 6 months. The results of stability studies (Table 3), showed that no changes in physical appearance and shape were observed in all temperature conditions up to 3 months while smaller changes (non significant) was observed at the end of 6 months. There was no significant changes in particle size, but little increment in particles size might be due to aggregation of microspheres stored in refrigerated conditions (5±3°C). The particle size of the microspheres was found to decrease slightly at 25±2°C and 40±2°C, which may be attributed due to the evaporation of residual amount of organic solvent at higher temperature from the microspheres. After 6 months storage period, entrapment efficiency of Lxm loaded microspheres was found to be 70.72 ± 1.53 %, 70.76 ± 1.46 % and 70.32 ± 1.50 at conditions of refrigeration (5±3°C), room temperature (25±2°C) and accelerated (40±2°C/75±5% RH), respectively. The drug content was found to be maximum at room temperature (Table 3). The microspheres formulations (LECM) showed 77.62 ± 1.43**,** 77.48 ± 0.87 and 77.04 ± 1.27 % drug release (after 6 months) at the end of 12 h of drug release on storage under refrigerated (5±3°C), room temperature (25±2°C) and accelerated (40±2°C/75±5% RH) conditions, respectively (Table 3). It was found that no

remarkable changes in the drug release from microspheres formulation at different storage conditions was observed. The results of the stability studies indicated that the LECM formulation was stable at all conditions but most stable at room temperature.

In the present study, ethyl cellulose microspheres of Lxm were prepared successfully by using emulsion solvent evaporation method and *in-vivo* study revealed the sustained analgesic and anti-inflammatory effect of the prepared microspheres. The stability studies at different conditions were performed according to ICH guidelines for a period of 6 months and the results met the terms of the ICH guidelines providing a safety profile of storage of Lxm loaded ethyl cellulose microspheres in varying temperature. Therefore, it may be concluded that ethyl cellulose microspheres of Lornoxicam are a suitable delivery system for prolonged activity with increased stability without losing its therapeutic activity.

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