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Development and characterization of oxaprozin loaded solid lipid Nanoparticles for effective management of pain

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ABSTRACT: Background: Solid lipid nanoparticles loading oxaprozin was developed to address an effective drug packaging and targeted delivery, improving the drug pharmacokinetics and pharmacodynamics properties and avoiding the local gastric side-effects. **Aim:** The study was aimed to design and prepare oxaprozin solid lipid nanoparticles. **Method:** The oxaprozin was subjected to pre-formulation studies that are color, odor, solubility, melting point, Loss on drying, moisture content and FTIR. Oxaprozin loaded solid lipid nanoparticles were prepared by solvent injection method. The manufactured Oxaprozin loaded SLNs were evaluated for particle size, zeta potential, entrapment efficiency, in vitro drug release, drug release kinetics and stability studies. **Results:** Optimization of process and formulation parameters resulted in the production of Oxaprozin loaded SLNs with particle size 402.1 nm and entrapment efficiency of 75.65±0.32 % of Optimized SLN formulation F3. *In-vitro* drug release pattern of optimized formulation of SLN showed fast and control drug release. It was found that the *in-vitro* drug release of the Oxaprozin loaded SLNs was best explained by Pappas release Kinetics as the plot showed the highest linearity (R^2 = 0.996), Zero order (R^2 = 0.962), First order (R^2 = 0.992), Pappas plot (R^2 = 0.996) of regression analysis data of SLN F3Formulation. **Conclusion:** The Solid lipid nanoparticles were successfully developed for systemic delivery of Oxaprozin. The solid lipid nanoparticle formulation F3 (Drug 100 mg and Soya lecithine 75 mg) was the best optimized formulation, which could be successfully used for safe and effective management of pain.

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INTRODUCTION:

Many drug delivery systems have been tried and formulated for nasal and pulmonary drug delivery. A variety of delivery systems includes Liposomes, Proliposomes, Microspheres, Gels, Prodrugs and Nanoparticles. Nanoparticles composed of biodegradable polymers show assurance in fulfilling the stringent requirements placed on these delivery systems, such as the ability to be transferred into an aerosol, stability against forces generated during aerosolization,

biocompatibility, targeting of specific sites or cell populations in the lung, release of the drug in a predetermined manner, and degradation within an acceptable period of time [1]. It is interesting to note that considerable work and many publications from the USA, Europe are authored by Indian researchers [2,3].

Many research understood the pharmacokinetic and pharmacodynamic principles that govern the action and disposition of potent opioid analgesics, inhalation anesthetic agents, sedative/hypnotics, and muscle relaxants. The studies suggest that skin, buccal and nasal mucous membranes may have been used as an alternate route of analgesic and anesthetic delivery. The controlled-release technology (CRT) are transdermal and transmucosal controlled-release delivery systems, nasal and buccal aerosol sprays, drug-impregnated lozenges, encapsulated cells, oral soft gels, iontophoretic devices to administer drugs through the skin, and a variety of programmable, implanted drug-delivery devices [4-6].

Novel drug delivery systems are designed to achieve continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation. The potential advantages of this concept include minimization of drug related side effects due to controlled therapeutic blood levels instead of oscillating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered [8-9]. Nanoparticles are solid colloidal particles ranging from 10 to 1000 nm (1.0 μm), in which the active drug is dissolved or entrapped [10]. The objective of nanotechnology is to diagnose as accurately and early as possible and to treat as effectively as possible without any side effects using a controlled and targeted drug delivery approach [11]. Nanoparticles made from solid lipids are attracting major attention as a novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system. The system consists of spherical solid lipid particles in the nanometer ranges, which are dispersed in water or in an aqueous surfactant solution [12].

Oxaprozin is a non-narcotic, non-steroidal anti-inflammatory drug (NSAID), used to relieve the inflammation, stiffness, and joint pain associated with osteoarthritis and rheumatoid arthritis [13].

The objective of the present study is to formulate and evaluate the solid lipid nanoparticles of Oxaprozin for management of pain.

MATERIALS AND METHODS:

Materials:

Oxaprozin was obtained from Sigma – Aldrich®, Mumbai. Soya lecithin, ethanol and Tween 80 were purchased from Merck, India. All other chemicals and reagents used in this study were of analytical grade and procured from an authorized dealer. Glassware used was procured from Borosil, India.

Pre-formulation studies of Oxaprozin [13-16]:

***Physical evaluation*:**

It refers to the evaluation by sensory characters appearance, odor and feel of the drug.

***Solubility*:**

Solubility of the drug was determined by taking some quantity of drug (About 1 mg) in the test tube separately and 5 ml of the solvent (Water, ethanol, methanol, 0.1N HCl, 0.1N NaOH, and 7.4 pH buffer) was added separately to a different test tube. The mixture was shaken vigorously and kept for some time. The solubility of the drug was recorded at room temperature.

***Melting point*:**

It is one of the parameters to judge the purity of drugs. In the case of pure chemicals, melting points are very sharp and constant. Since the drugs contain mixed chemicals, they are described with a certain range of melting points.

A small quantity of powder was placed into a fusion tube. That tube was placed in the melting point apparatus (Chemline CL-725, Mumbai) containing castor oil. The temperature of the castor oil was gradually increased automatically and the temperature at which powder started to melt was recorded as the melting point of the drug.

***FTIR Spectroscopy*:**

Identification of Oxaprozin was done by FTIR Spectroscopy with respect to the marker compound. Oxaprozin was obtained as white to off-white powder. It was identified from the result of IR spectrum as per specification. The chromatogram was recorded for Oxaprozin by using the FTIR (IR Tracer 100, Shimadzu, Japan) at a frequency range of 3500 to 500 cm^{-1}. The IR spectrum of sample drug shows the peak values which are characteristics of the drug

***Loss on drying*:**

The moisture in a solid can be expressed on a wet weight or dry wet basis. On a wet weight basis, the water content of a material is calculated as a percentage of the

weight solid. The term loss on drying is an expression of moisture content on a wet weight basis.

Loss on drying (LOD) was measured by Hot air oven (Scientific Instruments, Mumbai). About 1 g sample (powder) was weighed and set at the temperature of 100 to 105 °C for 15 min and constant reading set the knob. The weight of powder was recorded till constant weight was observed. The LOD was calculated by using the following formula.

LOD (%) = [Wi–Wf)/Wi] × 100 …..(1)

Where, Wi and Wf are initial and final weights.

***Moisture content determination*:**

Karl Fischer is a micro-method and is particularly suitable for samples with low water content, from 10 µg up to 10 mg. Here, the required iodine is generated electrochemically in the titration vessel by anodic oxidation from iodide contained in the coulometric reagents. The amount of consumed electric charge is used to calculate the consumption of iodine and therefore the amount of water in the sample.

Moisture Content (MC) was determined by Karl Fischer titration method. It was calculated by using the following formula.

MC (mg) = KFF × KFRC ……(2)

Where KFF is Karl Fischer factor and KFRC is Karl Fischer reagent consumed.

Moisture content in the drug or the formulation plays an important role to check the accurate purity of the pure drugs.

Standard curve preparation of Oxaprozin:

The λ_{max} of Oxaprozin was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Accurately weighed 10 mg of drug was dissolved in 10 ml of phosphate buffer solution of 7.4 in 10 ml of volumetric flask. The resulted solution was thus prepared with a strength of 1000 µg/ml. From this solution, 1 ml pipette out and transfers into 10 ml volumetric flask and volume were made up to 10 ml with a phosphate buffer solution of 7.4. Suitable dilutions were made for solution strength of 5, 10, 15, 20 and 25 µg/ml. The spectrum of this solution was run in 200 to 400 nm range in U.V. spectrophotometer (Labindia-3000+).

Preparation of Solid Lipid Nanoparticles:

The solvent injection technique was used to prepare the solid lipid nanoparticles of oxaprozin using ethanol as an organic solvent. Soya lecithin, drug and steric acid were dissolved in the ethanol in a definite ratio and warmed to 70 °C. The phosphate buffer solution (pH 7.4) and a definite amount of tween 80 were mixed to prepare the aqueous phase and it was stirred which was maintained at 70 °C. The organic phase was added drop-wise with stirring to the pre-warmed aqueous solution with the help of a hypodermic needle. The mixture was then sonicated (Ultra sonicator, Bath type, Electronic India) for varying times to obtain nanoparticles. The prepared nanoparticles were stored at -4 °C [16,17].

Evaluation of solid lipid nanoparticles [17-22]:

***Particle size and zeta potential*:**

The vesicles size, size distribution and surface charge were determined by Dynamic Light Scattering method (DLS) (Malvern Zetamaster, ZEM 5002, Malvern, UK, SOPS RGPV, and Bhopal (M.P.). Zeta potential measurement of the nanoparticles was calculated according to Helmholtz – Smoluchowsky from their electrophoretic mobility. For measurement of zeta potential, a zeta sizer was used with a field strength of 20 V/cm on a large bore measures cell. Samples were diluted with 0.9 % NaCl and adjusted to a conductivity of 50 lS/cm.

***Entrapment efficiency*:**

About 0.1 ml of the freshly prepared formulation was taken and diluted with 9.9 ml with phosphate buffer of pH 7.4. The obtained suspension was vortexed for 1 h and centrifuged for 45 min at 6,000 rpm. The supernatant was separated and filtered through a 0.2 µm filter.

The filtrate was diluted using a phosphate buffer of pH 7.4 and analyzed at 284 nm using a UV spectrophotometer (Labindia 3000 plus). The SLNs formulated without drugs were treated similarly and used as a control for the measurements. The assay was repeated 3 times using different preparations. Entrapment efficiency (EE) was calculated by using the formula as given below.

EE (%) = [(TDC-PDC)/TDC] × 100 …..(3)

***In vitro drug release study*:**

The *in vitro* drug release study was carried out by using the Franz diffusion cell. The cellophane membrane approximately 25 × 2 cm was taken and washed in the running water. It was then soaked in distilled water for 24 h. So that the glycerine shall be removed before use in the study.

The optimized Oxaprozin-SLNs formulation F3 was injected into a dialysis bag and dialyzed against 18 ml PBS (pH 7.4) containing 0.3 % tween 80 (v/v) (receiver solution) in a 25 ml tube at 24 and 37 °C with shaking at 130 rpm. Plain oxaprozin (with the same amount of drug as the formulation) was also filled with a dialysis bag with the same pore size and dialyzed against 18 ml 0.3% (v/v) tween 80 to examine the permeability of the membrane to the drug. At a specific time interval, 2 ml of samples were withdrawn from the receiver solution and 2 ml of fresh medium was added to the receptor compartment. The oxaprozin in the collected samples were assayed spectrophotometrically at λ_{max} 284 nm.

Drug Release kinetics:

In-vitro dissolution has been recognized as an important element in drug development. Under certain conditions, it can be used as a surrogate for the assessment of bioequivalence. Several kinetic models describe drug dissolution from immediate and modified release dosage forms. In order to determine the mechanism of drug release, the *in vitro* drug release data were fed to zero order, first order, and Korsmeyer-Peppas kinetic model. The highest value of the regression coefficient will determine the best fit model.

Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of 30 days at 4±1° and 25± 2 ºC as per the ICH guidelines. The particle size of the formulation was determined by a particle size analyzer.

RESULTS AND DISCUSSIONS:

Pre-formulation studies:

The pre-formulation study reveals that the color and odor of the Oxaprozin was white to off-white powder and slight characteristic odor. The solubility data of the drug is given in Table 1. The drug was freely soluble in an organic solvent that is freely soluble in ethanol, whereas slightly soluble in methanol but practically insoluble in water. The melting point was found to be 158 to 159 °C, which was very close to the literature value that is 162 to 163 °C. The FTIR data of Oxaprozin is presented in Table 2. The major peaks obtained were in the frequency range of 2913.93 cm^{-1} (OH Stretching), 1825.52 cm^{-1} (C=O Stretching) and 896 cm^{-1} (OH Bending) [24]. The loss on drying value was found to be very less that is 1.1 %. It shows that the drug was non-hygroscopic in nature at room temperature. The moisture content of the drug was determined by Karl-Fischer Titration and was found to be 0.0760. Very least amount of moisture was found out in the drug.

Table 1. Solubility of Oxaprozin.

Solvent	Solubility	Results	Parts soluble
Distilled Water	Insoluble	- - -	>1000
0.1 N HCl	Slightly Soluble	+	100-1000 Parts
Ethanol	Soluble	+++	10-30 Parts
Methanol	Slightly Soluble	+	100-1000 Parts
0.1N NaOH	Sparingly soluble	++	30-100 Parts
Phosphate buffer pH 7.4	Sparingly soluble	++	30-100 Parts

Table 2. IR Interpretation of Oxaprozin.

Sl. No.	Group	Peak Position
1	$OH_{str.}$	2913.93
2	$C=0_{str.}$	1825.52
3	OH	1461.82
4	C-GYYUGYU	1262.23
5	$O\text{-}H_{Bend}$	896.93

Analysis of drug:

The calibration curve of the pure drug Oxaprozin was plotted, whose regression equation was y = 0.024x + 0.019, with regression coefficient of 0.998. The standard curve data of Oxaprozin is given in Table 3.

Table 3. Calibration curve of Oxaprozin.

Sl. No.	Conc. (µg/ml)	Absorbance
1	5	0.135
2	10	0.258
3	15	0.387
4	20	0.509
5	25	0.611

Preparation of SLNs:

The solvent injection technique was found to be a successful method for the effective preparation of the Oxaprozin solid lipid nanoparticles. The formulation design of Oxaprozin SLNs is given in the Table 4. The manufactured SLNs are found to be small, discrete and free-flowing in nature in physical form.

Evaluations of SLNs:

***Entrapment efficiency*:**

The entrapment efficiency values of all manufactured SLN are given in Table 5. The entrapment efficiency was found to be in the ranges of 52.12±0.65 % (F6) to 75.65±0.32 % (F3). On basis of entrapment efficiency

value, the SLNs formulation F3 was the optimized formulation.

Table 4. Formulation design of development of Oxaprozin SLN.

Components	Formulation code					
	F1	F2	F3	F4	F5	F6
Drug (mg)	100	100	100	100	100	100
SL (mg)	25	50	75	100	125	150
Steric acid (mg)	75	75	75	75	75	75
Tween 80 (ml)	0.5	0.5	0.5	0.5	0.5	0.5
Sonication time (min)	5	5	5	5	5	5

SL- Soya lecithin.

Table 5. The Entrapment efficiency data of various drug loaded SLN formulations.

Formulation	Entrapment Efficiency
F1	65.56±0.25
F2	68.98±0.36
F3	75.65±0.32
F4	62.23±0.45
F5	58.98±0.58
F6	52.12±0.65

Data are presented as mean ± Standard deviation (n=3).

***Particle size and zeta potential*:**

Thus particle size, zeta potential, *in vitro* drug release, drug release kinetics and stability studies were carried out on the optimized SLN formulation F3.

The average particle size of prepared SLNs was found to be 402.1 nm, it signifying that very small size nanoparticles are being formed. The zeta potential value of manufactured nanoparticles was found to be -20.2 mV, suggesting that the nanoparticles could be stable. The zeta potential values and particle characteristics are given in Table 6.

Table 6. Zeta Potential value and Interpretation.

Zeta Potential (mV)	Stability Behaviour
0 to ± 5	Rapid coagulation / flocculation
± 10 to ±30	Incipient instability
±30 to ±40	Moderate stability
±40 to ±60	Good stability
MT ±60	Excellent stability

***Drug release and kinetic studies*:**

The *in vitro* drug release study was carried out by using the Franz diffusion cell in the medium of saline PBS of pH 7.4. The total amount of the drug Oxaprozin was released from the SLNs in 12 h was 78.98 %. It was observed that the drug was released in control and constant manner. It may favor nonfluctuation of drug concentration within the therapeutic range, thus the least side effects may develop. The *in vitro* drug release data of optimized SLNs formulation F3 is given in Table 6. The drug release kinetic study revealed that that the drug is released with zero-order kinetics, as R^2 value was found more in the case of zero-order kinetics. Thus demonstrating that the drug release is independent of the concentration of the drug. The drug release kinetic data is given in Tables 7 and 8.

Table 7. The *in vitro* drug release data optimized Oxaprozin loaded SLN formulation F3.

Sl. No.	Time (h)	% Cumulative Drug Release
1	0.5	19.89±0.56
2	1	25.65±0.32
3	2	35.65±0.45
4	4	48.98±0.52
5	6	55.65±0.14
6	8	68.89±0.23
7	10	75.65±0.32
8	12	78.98±0.98

Data are presented as mean ± Standard deviation (n=3).

***Stability study*:**

The particle size of the SLN was found to increase at room temperature, which may be attributed to the aggregation of SLN at higher temperatures. At 25± 2°C °C the SLN aggregate i.e. these SLN were unstable at higher temperatures like 25±2°C. Percent efficiency of SLN also decreases at higher temperatures like 25± 2°C °C. The stability study data of optimized SLNs formulation F3 is given in Table 9.

CONCLUSION:

The Solid lipid nanoparticles were successfully developed for systemic delivery of Oxaprozin. *In-vitro the* drug release pattern of optimized formulation of SLN showed fast and control release. From the experimental data, it could be concluded that the Oxaprozin SLNs containing soya lecithin 75 mg, could be effectively used for control delivery of Oxaprozin for

safe and effective management of pain symptomatic diseases.

Table 8. *In vitro* Drug Release Data for F3.

Time (h)	SRT	Log Time	CUPD	Log CUPD	CPDR	Log CPDR
0.5	0.70	-0.301	19.89	1.298	80.11	1.903
1	1.00	0.000	25.65	1.409	74.35	1.871
2	1.41	0.301	35.65	1.552	64.35	1.808
4	2.00	0.602	48.98	1.690	51.02	1.707
6	2.45	0.778	55.65	1.745	44.35	1.646
8	2.83	0.903	68.89	1.838	31.11	1.492
10	3.16	1.000	75.65	1.878	24.35	1.386
12	3.46	1.079	78.98	1.897	21.02	1.322

SRT – Square root of time, CUPD – Cumulative percent drug release, CPDR – Cumulative Percent Drug Remaining.

Table 9. Effect of Storage on Particle Size and Percent Entrapment Efficiency of optimized Oxaprozin loaded SLN formulation F3.

Para-meters	Initial Observation	After 30 days	
		At 4ºC	At 25±2°C
Particle Size (µm)	402.1±0.45	398.2±0.25	565.56±1.25
PEE	75.65±0.32	72.12±0.45	65.56±1.32

PEE - Percent Entrapment, Efficiency Data are presented as mean ± Standard deviation (n=3).

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