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FORMULATION OF FLURBIPROFEN LOADED NANOSTRUCTURED LIPID CARRIERS OF FLURBIPROFEN

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Abstract:

Nanostructured lipid carriers (NLCs) are recently invented second-generation lipidic carriers. Flurbiprofen exhibits poor cutaneous bioavailability and systemic side effects on topical administration, so there is an unmet need for a novel carrier and its optimized therapy. The aim of present work to develop flurbiprofen loaded Nanostructured lipid carriers gel for effective treatment of topical disease. The Entrapment efficiency of formulation F1 to F16 were found to be 60.66±0.60 to 78.51±0.25 respectively. The maximum entrapment efficiency was found in formulation F16 (88.76±0.44). The Drug content of formulation F16 was also found high in formulation F16 select as optimized formulation. The prepared gel at least rpm of 10 exhibited a viscosity of 3145±11 to 3145±11cps that indicates that the formulation has the desired viscosity required for semisolid formulation for proper packaging. It was found that the viscosity decreases as the rotational speed of viscometer increased suggesting that greater the shearing the lower viscosity favours easy spreadability further confirmed by spreadability and rheological testing. When the regression coefficient values of were compared, it was observed that 'r^2' values of First Order was maximum i.e. 0.955 hence indicating drug release from formulations was found to follow First Order.

Keywords: *Flurbiprofen, Nanostructured lipid carriers, Formulation, Evaluation*

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INTRODUCTION:

In recent years, it has become evident that the development of novel drugs is insufficient for guaranteeing progress in drug therapy. Exciting experimental data obtained in-vitro is often followed by disappointing results in the in-vivo or clinical situation. Predominant reason for this failure are the insufficient drug concentration in the body, high drug toxicity because of extensive distribution, poor drug solubility in formulation and high drug fluctuation or inter subject variability of plasma drug level [1] .

A promising approach to overcoming this problem is the development of feasible drug delivery system. During the past decades, some strategies have been developed such as nano-sized drug carrier system [2], which is a great approach in drug delivery with the promising features of protection of drug from degradation and cleavage, controlled release and the delivery of drug molecules to the target sites [3]. Drug carrier materials play a significant role in delivery of drug. These carriers can be processed into different release system such as microspheres, microcapsules and nanoparticle [4]. Lipid nanoparticles made with a solid matrix is derived with the help of pharmaceutical nanotechnology which gains a huge impact on the pharmaceutical field. Generally a solid lipid nanoparticle is composed of physiological lipids disposed in an aqueous surfactant solution. It has certain benefits like improvement in solubility, bioavailability and also improvement in drug therapy [5].

There are some drawbacks such as loading insufficiency due to formation of perfect crystalline structure, drug expulsion and also high water content in the preparation [6,7]. In order to overcome these drawbacks a new drug carrier system is developed known as nanostructured lipid carriers (NLCs). NLCs are a blend of a solid and the liquid lipids that form an imperfection in lipid matrix in which high amount of drug can accommodate. Problems like drug expulsion, loading insufficiency also reduced with the introduction of the NLCs. NLCs are the asset in the terms of targeted drug delivery of the drug to the respective organ of the body such as brain targeting and tumor targeting [8,9].

Nanostructured lipid carriers (NLCs) are a type of submicron particulate drug delivery system based on mixture of solid lipids with spatially incompatible liquid lipids [10]. The usual particle diameters of the NLCs are in the range of approximately 10–1000 nm. It remains solid at room temperature. It has various advantages like controlled release of drug from the carrier, biocompatible lipids, feasible to produce on large scale using the existing machinery, avoid first pass metabolism and drug protection from biochemical degradation [11].

Topical drug delivery offers many advantages over oral delivery, such as avoidance of first-pass metabolism, targeting of the active ingredients for a local effect, and patient compliance. However, the achievement of dermal and transdermal delivery needs to conciliate difficulties in permeation across skin barrier at different levels (skinsurface, epidermis, dermis, and hypodermis). Nanostructured lipid carriers (NLCs) are recently invented second-generation lipidic carriers. Flurbiprofen exhibits poor cutaneous bioavailability and systemic side effects on topical administration, so there is an unmet need for a novel carrier and its optimized therapy. The aim of present work to develop flurbiprofen loaded Nanostructured lipid carriers gel for effective treatment of topical disease.

MATERIAL AND METHOD:

Preparation of Flurbiprofen loaded Nanostructured lipid carriers:

Nanostructured lipid carriers were prepared by using microemulsion technique[71-72] and o/w microemulsions were initially prepared. The oil phase, lipophilic surfactant and continuous phase used are glyceryl tripalmitate, soy lecithin and pluronic F-68 (hydrophilic surfactant) respectively. The lipid and soy lecithin were melted at 70oC and the drug was added with constant stirring. 10 ml of aqueous surfactant solution containing pluronic F-68 heated at the same temperature was added to the melted lipid with mechanical stirring for 15 min. A clear microemulsion was obtained at a temperature close to the melting point of the lipid used. Stearyl amine was used as a positive charge inducer and added to melted lipid. Nanostructured lipid carrierswere obtained by dispersing the warm o/w microemulsion which is added drop wise into ice cold water in a beaker under continuous stirring. After completion of stirring, the Nanostructured lipid carriersdispersion was subjected to ultrasonication for 15 min [10].

Preparation of Gel Base:

Carbopol 934 (1-3% w/v - Nanostructured lipid carriers based gel formulation i.e. G-1 of 1% w/v, G-2 of 2% w/v, G-3 of 3% w/v) was accurately weighed and dispersed into double distilled water (80ml) in a beaker. This solution was stirred continuously at 800 rpm for 1 hour and then 10ml of propylene glycol was added to this solution. The obtained slightly acidic solution was neutralized by drop wise addition of 0.05 N sodium hydroxide solutions, and again

mixing was continued until gel becomes transparent. Volume of gel was adjusted to 100 ml and then sonicated for 10 min on bath sonicator to remove air bubbles. Final pH of the gel base was adjusted to 6.5. The same procedure was used to formulate Nanostructured lipid carriers containing gel in which previously prepared Nanostructured lipid carriers was added. Nanostructured lipid carriers preparation corresponding to 5% w/w of drug was incorporated into the gel base to get the desired concentration of drug in gel base[11].

Study on the Effect of Lipid Quantity:
The effect of lipid quantity on the particle size was studied by varying one parameter, keeping the others constant. Three different batches of Nanostructured lipid carrierswere prepared corresponding to varying concentrations of lipid such as 50, 100 and 200 mg keeping the amount of soy lecithin (1% w/w), stearyl amine (1% w/w), pluronic F-68 (1% w/v), stirring time (3 hours) and stirring speed (1500 rpm) constant.

Effect of stirring time:
Five different batches of Nanostructured lipid carriers were prepared corresponding to 1, 2, 3, 4, 5 hours of stirring time keeping the lipid concentration (50 mg), soy lecithin (1% w/w), stearyl amine (1% w/w), pluronic F-68 (1% w/v) and stirring speed (2000 rpm) constant.

Effect of stirring speed:
Four different batches of Nanostructured lipid carrierswere prepared corresponding to 1000, 1500, 2000 and 2500 rpm of stirring speed keeping the lipid concentration (50 mg), soy lecithin (1% w/w), stearyl amine (1% w/w), pluronic F-68 (1% w/v) and stirring time (4 hours) constant.

Effect of surfactant concentration:
Four different batches of Nanostructured lipid carriers were prepared corresponding to 0.5%, 1%, 1.5% and 2% w/v of pluronic F-68 keeping the lipid concentration (50 mg), soy lecithin (1% w/w), stearyl amine (1% w/w), stirring time (4 hours) and stirring speed (2000 rpm) constant.

Preparation of drug loaded Nanostructured lipid carriers batches:
One optimized formulation of drug loaded Nanostructured lipid carriers were prepared by microemulsion method.

Table 1: Composition of optimized batch

Components	Formulation code (F16)
Lipid	50
Soy lecithin	1
Stearyl amine	1
Pluronic F-68 (1% w/v)	1.5
Stirring speed	2000
Stirring time	4

Evaluation of Nanostructured lipid carriers [12]
Particle size and zeta potential:
Particle size and zeta potential of the Nanostructured lipid carrierswere measured by photon correlation spectroscopy using a Malvern Zetasizer the results shown in table 6.6.

Entrapment efficiency:
Entrapment efficiency was determined by dialysis method. Nanostructured lipid carriers entrapped Flurbiprofen were separated from the free drug by dialysis method. The above said formulations were filled into dialysis bags and the free Flurbiprofen dialyzed for 24 hours into 50 ml of phosphate buffer 7.4 saline. The absorbance of the dialysate was measured at 258 nm against blank phosphate buffer 7.4 saline and the absorbance of the corresponding blank phosphate buffer 7.4 saline was measured under the same condition. The concentration of free Flurbiprofen could be obtained from the absorbance difference based on standard curve. Standard curve was made by measuring the absorbance at 244.0 nm for known concentrations of Flurbiprofen solution. The entrapment efficiency of the drug was defined as the ratio of the mass of formulations associated drug to the total mass of drug the result was show in table 6.6 and 6.7.

Total drug content:
From the prepared nanostructured lipid carriers formulation 1ml of suspension is dissolved in the 10 ml of 7.4 PBS buffer and ethanol mixture. The amount of Flurbiprofen was determined using UV spectrophotometer at 244nm.The placebo formulation

prepared similarly to drug loaded nanostructured lipid carriers is used as blank. The total drug content was calculated.

***In vitro* drug release in gastrointestinal fluids of different pH:**

The prepared Nanostructured lipid carriersdelivery system was evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 100 rpm maintained at 37±0.2°C.

A weighed quantity of formulation (100 mg) was spread over the surface of dissolution media (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml by PBS (pH 7.4). The samples withdrawn were assayed spectrophotometrically at 244.0 nm for Flurbiprofen and using UV visible spectrophotometer. The release of Flurbiprofen was calculated with the help of Standard curve of Flurbiprofen.

The observations of drug release for the drug in uncoated formulation and coated formulation is tabulated in Table.

Evaluation of gel:

Measurement of viscosity

Viscosity measurements of prepared topical Invasomes based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm.

pH measurements:

pH of selected optimized formulations was determined with the help of digital pH meter. Before each measurement of pH, pH meter should be calibrated with the help of buffer solution of pH 4, pH 7 and pH 9.2. After calibration, the electrode was dipped into the vesicles as long as covered by the vesicles. Then pH of selected formulation was measured and readings shown on display were noted [58].

Drug content:

Accurately weighed equivalent to 100 mg of topical Invasomes gel was taken in beaker and added 20 ml of methanol. This solution was mixed thoroughly and filtered using Whatman filter paper no.1. Then 1.0 mL of filtered solution was taken in 10 mL capacity of volumetric flask and volume was made upto 10 mL with methanol. This solution was analyzed using UV-Spectroscope at λmax 244 nm.

Extrudability study:

Extrudability was based upon the quantity of the gel extruded from collapsible tube on application of certain load [60]. More the quantity of gel extruded shows better extrudability. It was determine by applying the weight on gel filled collapsible tube and recorded the weight on which gel was extruded from tube.

Spreadibility:

Spreadibility of formulation is necessary to provide sufficient dose available to absorb from skin to get good therapeutic response. It was determined by method reported by Multimer *et al.,* [61]. An apparatus in which a slide fixed on wooded block and upper slide has movable and one end of movable slide tied with weight pan.To determine spreadibility, placing 2-5 g of gel between two slide and gradually weight was increased by adding it on the weight pan and time required by the top plate to cover a distance of 10 cm upon adding 80 g of weight was noted. Good spreadibility show lesser time to spread.

$$Spreadibility\,(g.cm/\sec) = \frac{Weight\ tide\ to\ Upper\ Slide \times Lenth\ moved\ on\ the\ glass\ slide}{Time\ take\ nto\ slide}$$

***In-vitro* drug diffusion study:**

The *in-vitro* diffusion study is carried by using franz diffusion cell. Egg membrane is taken as semi permeable membrane for diffusion [62]. The franz diffusion cell has receptor compartment with an effective volume approximately 60 mL and effective surface area of permeation 3.14 sq.cms. The egg membrane is mounted between the donor and the receptor compartment. A two cm^2 size patch taken and weighed then placed on one side of membrane facing donor compartment. The receptor medium is phosphate buffer pH 7.4. The receptor compartment is surrounded by water jacket so as to maintain the temperature at 32±0.5°C. Heat is provided using a thermostatic hot plate with a magnetic stirrer. The receptor fluid is stirred by Teflon coated magnetic bead which is placed in the diffusion cell.

During each sampling interval, samples are withdrawn and replaced by equal volumes of fresh receptor fluid on each sampling. The samples

withdrawn are analyzed spectrophotometrically at wavelength of 244 nm.

RESULTS AND DISCUSSION:

Sixteen formulations of nanostructured lipid carriers prepared by using using OVAT (One variable at Time) optimization technique. Variables along with amount of lipid and attention of surfactant had been optimized additionally technique variables as stirring speed and stirring time have been optimized.

Particle size and Entrapment efficiency of drug loaded Nanostructured lipid carriers were carried out and the entrapment efficiency of formulations F1 to F16 was found to be 260.25±4.11, 274.62±6.23, 249.66±4.77, 259.62±5.95, 261.37±4.82, 262.46±6.00, 255.58±6.20, 240.63±7.62, 262.11±4.10, 255.58±6.20, 240.63±7.62, 262.11±4.10, 257.92±3.95, 239.54±7.62, 289.20±5.39, 276.59±1.28, 299.63±4.62, 245.29±6.33 and 205.60±6.05 respectively.

The Entrapment efficiency of formulation F1 to F16 were found to be 60.66±0.60 to 78.51±0.25 respectively. The maximum entrapment efficiency was found in formulation F16 (88.76±0.44). The Drug content of formulation F16 was also found high in formulation F16 select as optimized formulation.

The prepared gel at least rpm of 10 exhibited a viscosity of 3145±11 to 3145±11cps that indicates that the formulation has the desired viscosity required for semisolid formulation for proper packaging. It was found that the viscosity decreases as the rotational speed of viscometer increased suggesting that greater the shearing the lower viscosity favours easy spreadability further confirmed by spreadability and rheological testing.

pH of prepared gel was measured by using digital pH meter. The pH of the Gel was found to be in range of 6.58±0.03 to 6.90±0.02 which is good for skin pH. All the formulation of Gel was shown pH nearer to skin required i.e. pH of G1- 6.90±0.02, 6.81±0.01 and G3-6.58±0.03.

Spreadability plays considerable role in patient compliance and ensures uniform application of Gel to a larger area of the skin. The spreadability of the formulation G-2 was calculated as 12.15±0.14cm/sec. The low value of spreadability coefficient of the Gel was sufficient suggesting easy spreading and no signs of grittiness. The lower value of spreadability indicates the lesser work required to spread the Gel over the skin, which means formulation was easily spreadable by applying small amount of shear.

Drug content of drug incorporated gel for formulation G-1, G-2 and G-3 was found to be 96.65±0.12**,** 98.85±0.25 and 97.05±0.14 respectively. The maximum drug content was found in formulation G-2 (98.85±0.25), select as optimized formulation.

When the regression coefficient values of were compared, it was observed that 'r^2' values of First Order was maximum i.e. 0.955 hence indicating drug release from formulations was found to follow First Order.

Table 2: Result for particle size, entrapment efficiency and drug content of drug loaded nanostructured lipid carriers

Formulation Code	Particle size	Entrapment Efficiency	Drug Content
F1	260.25±4.11	86.40±0.79	98.25±0.12
F2	274.62±6.23	77.59±0.11	99.45±0.15
F3	249.66±4.77	82.85±0.24	98.56±0.23
F4	259.62±5.95	72.89±0.53	98.75±0.25
F5	261.37±4.82	82.55±0.22	97.98±0.45
F6	262.46±6.00	76.54±0.19	97.98±0.65
F7	255.58±6.20	84.13±0.68	98.89±0.85
F8	240.63±7.62	75.24±0.54	99.54±0.14
F9	262.11±4.10	79.34±0.18	99.56±0.25
F10	257.92±3.95	67.50±0.57	99.45±0.36
F11	239.54±7.62	82.71±0.36	98.48±0.78
F12	289.20±5.39	72.50±0.42	97.56±0.78
F13	276.59±1.28	60.66±0.60	98.45±0.54
F14	299.63±4.62	66.20±0.47	99.65±0.87
F15	245.29±6.33	78.51±0.25	99.25±0.48
F16	205.60±6.05	88.76±0.44	99.78±0.65

Table 3: Particle size and Entrapment efficiency of Optimized Nanostructured lipid carriers

Formulation Code	Particle size (nm)	Entrapment Efficiency	Zeta potential
F16	205.60±6.05	88.76±0.44	-35.6

Table 4: Cumulative % drug release

S. No.	Time (hrs)	% Cumulative Drug Release
1	1	4.8
2	2	7.2
3	3	13.0
4	4	18.9
5	5	25.7
6	6	37.0
7	7	58.4
8	8	66.7
9	9	73.1
10	10	82.3
11	12	88.6

Table 5: Characterization of gel based formulation

Gel formulation	Viscosity (cps)	Ph	Drug Content (%)	Extrudability (g)	Spreadibility (g.cm/sec)
G-1	3545±10	6.90±0.02	96.65±0.12	170±3	13.25±0.32
G-2	3332±15	6.81±0.01	98.85±0.25	155±4	12.15±0.14
G-3	3145±11	6.58±0.03	97.05±0.14	142±5	11.41±0.21

Table 6: *In vitro* drug release study of optimized gel formulation G-2

S. No.	Time (hr)	% Cumulative Drug Release*		
		G-1	G-2	G-3
1	0.5	25.65	20.23	18.85
2	1	38.89	35.65	23.32
3	2	49.95	45.85	29.98
4	4	70.23	65.56	38.85
5	6	79.98	73.32	49.85
6	8	96.65	88.89	62.23
7	10	98.78	96.65	76.65
8	12	98.95	98.45	89.98

Table 7: Regression analysis data of optimized gel formulation G-2

Batch	Zero Order	First Order
	R^2	R^2
G-2	0.928	0.955

CONCLUSION:

This present work indicates that the NLCs of Flurbiprofen could be successfully prepared and evaluated. It is also found that the release rate can be modulated upon changing the ratio of solid lipid to liquid lipid. It can be concluded that the optimized NLC gels exhibit faster onset and prolonged action.

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