INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

PREPARATION, CHARACTERIZATION AND OPTIMIZATION OF PRONIOSOMAL GEL OF ANTI-INFLAMMATORY AGENT

Vamshi Krishna Lekkala [1]*, N Siva Subramanian [2], K Srikanth Gupta [3]
[1] Research Scholar, Himalayan University, Itanagar, Arunachal Pradesh, India
[2] Research Guide, Himalayan University, Itanagar, Arunachal Pradesh, India
[3]Scientist, Formulation Research & Development, Aizant Drug Research Solutions, Hyderabad, Telangana, India
*Corresponding Author Email: vamsilekkala84@gmail.com

Article Received on: 17/09/20 Approved for publication: 31/10/20

DOI: 10.7897/2230-8407.111086

ABSTRACT

Proniosomal gel of anti-inflammatory agent (Diclofenac Sodium) was developed using two different non – ionic surfactants (Span 60 and Span 40) with an objective to develop stable, robust, controlled release gel of diclofenac sodium as it has short half-life and narrow therapeutic index. Various proniosomal gels were developed using different concentration of nonionic surfactants and one formulation was selected as optimized formulation based on the size, shape and % entrapment efficiency. FS603 was selected as an optimized formulation and was characterized further for zeta potential and stability and was found as stable at both refrigerated and room temperatures. No edema and erythema were observed in rats treated with formulation FS603 for four days and skin irritation index found as zero. *In vivo* anti-inflammatory activity with optimized formulation was carried out in rats against marketed preparation using carrageenan induced rat paw method and shown greater % inhibition of inflammation and extended period when compared with marketed preparation.

Key words: Therapeutic index, Proniosomes, Topical gel, Stability, Skin irritation, Anti Inflammation

INTRODUCTION

To overcome the inconveniences like poor patient compliances, poor bioavailability of drugs, etc. with conventional dosage forms[1] (capsules, tablets, ointments, etc), researchers developed variety of naval dosage forms like drug carriers, osmotic pumps, etc. and also to achieve the desired objectives such as sustained drug delivery, targeted drug delivery[2], etc. Lipid vesicles[3] are a type of drug carriers which includes liposomes, niosomes, transferosomes, etc. Researchers substantiating that these lipid vesicles have greater applications in the formulations field. Liposomes are considered as conventional lipid vesicles[4]. Generally, these will be prepared using lipid molecules and founds as bilayer vesicles. These will act as carriers for both lipophilic and hydrophilic drugs and can be administer through the different routes like oral, nasal, topical, etc[5]. Apart from these advantages, these are biodegradable and biocompatible.

Though these carriers have variety of advantages, their importance is decreased because of their poor physical and chemical stability[6]. They exhibit properties like sedimentation, fusion, aggregation or leakage of drug (i.e. Physical instability) and oxidation, hydrolysis[7] (i.e. Chemical instability). To avoid these drawbacks of liposomes, a new concept namely provesicular carrier systems like proliposomes, proniosomes were developed. Proniosomes are hybrid technology of conventional niosomes which will be converted into niosomes upon hydration with water. In Transdermal route of administration, these proniosomes converted as niosomes consuming the water present on the skin under occlusion condition[8] and act as potential carriers for delivery of drugs across the skin. These proniosomes crosses the stratum corneum as niosomes and releases the drug for prolonged period in controlled fashion. Apart from these advantages, the proniosomes also have merits[9] like easy transportation, distribution, storage, dosing, etc. these advantages made to choose these carriers for delivery of anti-inflammatory agents, Diclofenac sodium, transdermally.

Diclofenac sodium a non-steroidal anti-inflammatory drug (NSAID) with potent analgesic and moderate anti-inflammatory activity and is used in the treatment of osteoarthritis, rheumatoid arthritis ankylosing spondylitis[10]. Currently it is available as IM injection and oral tablets and is administered as divided multiple doses for management of pains. As it has narrow therapeutic index and short biological half-life[11], it is administering as multiple doses which causes highly incontinence to patients. This enforces to develop a dosage form which deliver the drug prolonged period of time there by one can decrease the number of doses.

MATERIALS AND METHODS

Diclofenac sodium was obtained as gift sample from Cadila Pharmaceuticals Ltd, Ahmedabad, India. Span-40, Span-60 and Lecithin were procured from S.D. Fine Chemicals, Mumbai, India. Cholesterol was purchased from Loba Chemicals Ltd, Chennai. Other solvents were obtained from Merck Pharma Pvt. Ltd.

Preparation of Proniosomal gel

Proniosomal formulations were manufactured by a method reported by Fang et al[12] using two different types of non-ionic surfactants (Span-40 and Span-60), lecithin and cholesterol. Composition of all formulations are presented in table 1.

All the ingredients as mentioned in table - 1 were dispensed and dissolved in 125 ml absolute ethanol in a wide-mouth glass beaker. The open end of the glass beaker was covered with aluminum foil and warmed in a water bath at 65 ± 5°C for 5 min. 100µl of pH 7.4 phosphate buffer was added and warming was continued on the water bath for about 5 min till a clear solution was observed. The mixture was allowed to cool to room temperature to obtain proniosomal gel.

CHARACTERIZATION

Morphology of proniosomes

Proniosomal formulations were observed for their physical appearance under optical microscope using 45X magnification. The gel was spread as thin layer on glass slide and observed under microscope.

Particle Size of Proniosomes

0.5 g proniosomal gel was dispersed in 10 ml of pH 7.4 phosphate buffer. A drop of above solution was placed on glass slide and proniosomes were examined under 45x magnification and the average particle size was determined.

Separation of Un-Entrapped Drug from proniosomal Suspension[13]

The free drug was separated from the proniosomal suspension by ultra-centrifugation method. 50mg of proniosomal gel was dispersed in the 10ml of phosphate buffer pH 7.4 and kept aside. From the above solution 2ml was drawn into centrifuge tube and was centrifuged at 11000RPM for 15mins at 4-6°C. After centrifugation, the supernatant liquid was separated and analyzed for free drug by means of UV- Visible spectrophotometer which represents the unentrapped drug.

$$\text{The entrapped drug} = \text{Total amount drug taken} - \text{toal amount of un entrapped drug}$$

$$\%\ Entrapment\ of\ effciency - \frac{Entrapped\ drug}{Total\ drug}\ x\ 100$$

In Vitro Drug Release[14]

In-vitro release studies were carried out in modified franz diffusion apparatus and dialysis membrane as semi permeable membrane. A two-side opened glass tube having diameter 2.95 cm^2 and 250ml capacity glass beaker was used as donor and receptor compartments respectively. One end of the donor compartment tube was closed with dialysis membrane and was fixed in receptor compartment which is already filled with 100ml of phosphate buffer pH 7.4. Donor compartment was mounted in receptor compartment. Care should be taken that the donor compartment tube should immerse in receptor fluid.

The donor compartment was filled with niosomal suspension equivalent to 5mg of drug and drug release study was carried out at a temperature of 37 ± 0.5°C. The agitation was induced in the receptor fluid by stirring the magnetic bead at 100 rpm. Samples from the receptor fluid (1ml) were withdrawn at predetermined time intervals, namely 1, 2, 3, 4, 6, 8, 12 and 24h, from the receptor compartment and refilled with an equivalent amount of fresh receptor solution.

The samples were then assayed after suitable dilutions using UV-Vis Spectrophotometer (Shimadzu Corporation, Japan 1800) at 225nm and the percentage of drug release was calculated by considering the encapsulated drug as 100%.

In vitro drug release data of all formulations was tabulated in table 3 and graphically presented in Fig 2 & 3.

Based on the particle size, % entrapment efficiency and in vitro drug release, formulation FS603 was selected as optimized formulation and the optimized formulation was loaded for stability. Zeta potential of the proniosomes and Skin irritation of the optimized formulation was also studied.

Zeta potential

Surface charge of the proniosomes was determined by means of Zeta potential analyzer[15]. 0.5g of proniosomal gel was hydrated with phosphate buffer and the resultants proniosomes surface charge was measured as zetapotential. Zetapotential was determined at 25 °C in zeta analyser. The result was the average of three runs.

Stability studies of proniosomal gel

Stability study of optimized proniosomal gel of was carried out by exposing to refrigerated and room temperatures for three months. Every month, size, shape and Assay of the proniosomes was measured. Assay was studied considering the encapsulated drug as 100% and the data was tabulated in table no. 4

Skin irritation study[16]

This study was carried out to evaluate the irritation on applied site of the skin as the safety of skin is at most important for topical administration. Skin irritation study was carried out on healthy wistar albino rats. The animals were kept under acclimatization for a period of 5 days before carrying out of skin irritation study. After acclimatization, the rats were divided into two group's i.e. control and Test groups having 3 rats in each group.

Placebo gel and optimized gel was applied on the left ear of the control and test animals respectively. The gels were applied daily morning once in a day for 4 days. At the end of study, the animals were observed for any skin irritation like erythema or edema and scores were given as per the irritation scale.

The grades of the erythema developed were visually monitored for six days and reported as: 0 (no erythema development), 1 (very slight erythema), 2 (barely visible few blood vessels), 3 (light erythema development), 4 (main blood vessels visible), 5 (slight erythema development) and 6 (main blood vessels more obvious and slight erythema development). Equation (1) was used to calculate the irritation potential.

$$Irritation\ index = \frac{A\ x\ B}{n}$$

Where, A – the erythema value, B - the corresponding day and n – number of observation day.

In vivo evaluation of anti-inflammatory activity[17]

In vivo anti-inflammatory activity will be evaluated on the basis of the inhibition of the volume of the hind paw edema induced by

various phlogistic agents. For the present study 1% w/v carrageen solution in 0.9% w/v was used as phlogistic agent.

Ethical issues

Before carrying out the study, the study protocol was reviewed and approved by the Institutional Ethics Committee (Registered no: 1758/PO/ERe/S/14/CPCSEA).

Animals

White male albino rats weighting between (170 and 200 gm) were selected for evaluation of the anti-inflammatory activity by measuring the size of edema resulting from carrageenan injection in the right hind paw region of the body.

Animals were housed 6 per cage in the standardized conditions at animal facility. All animals were acclimatized and kept under constant temperature (25 ± 2°C) and for a week prior to the experiment. Each animal was allowed free access to standard food pellets and water during acclimatization period. Animals were kept under fasting before initiation of the study for a period of 24 h.

Treatment

The animals were divided
randomly into three groups consisting of six animals per each group. The gels (0.5 g) were applied to the planter surface of the left hind paw by gently rubbing 50 times with the index finger. The three groups treated as follows.

Group I……Gel base (Control)
Group II…. Reference gel (Standard)
Group III…Optimized proniosomal gel (Test)

After applying the gels as described, the applied area is occluded lightly with bandages. Then allowed the animals left in cages for two hours. The dressing was then removed from all animals and the left-over gel was cleaned off with a piece of cotton. The paw thickness was measured using digital Vernier caliper immediately before carrageenan injection and was considered as zero time. Then the animals were injected 0.1ml of 1% freshly prepared sterile carrageenan solution in saline. The right hind paw thickness was measured after 0h, 2h, 4h, 6h, 8h and 10 h using mercury Vernier caliper after the sub planter injection of carrageenan.

The mean % of inflammation was measured from the difference % swelling between treated group and control group.

$$\% \ Inhibition = \frac{(C_t - C_o)_{Control} - (C_t - C_o)_{Treated}}{(C_t - C_o)_{Control}} \times 100$$

Where C_t= thickness of paw after carrageenan injection.

C_o = thickness of paw before carrageenan injection.

RESULTS AND DISCUSSION

Morphology of proniosomes

All the formulations appeared as slight brownish to brown in color. The proniosomes found as discreet round shaped vesicles with rough surface. The vesicles appeared in various sizes. The SEM images proniosomes are appeared as shown in Figure 1.

Particle Size of Proniosomes

The average size of the proniosomes in all the formulations was found in range of 278±1.4 to 431±1.2nm. The size of the proniosomes prepared with Span 60 was smaller in size than the proniosomes prepared with span 40. It was also found that the size of proniosomes was inversely proportional to the concentration of the surfactant added. This may be because of the decreased surface tension with increased concentration of non-ionic surfactants.

Entrapment efficiency

Entrapment efficiency increased with increased concentration of the surfactant. These results demonstrating that the entrapment efficiency is directly proportional to the concentration of the surfactant. Though the size of the vesicles decreased with increased concentration of the vesicles, the number of the vesicles may be increased with increased concentration of the proniosomes. Size, shape and Entrapment efficiency of proniosomes present in all formulations are reported in table 2.

Formulations prepared with Span 60 exhibited more entrapment efficiency than the formulations prepared with Span 40 which may be because of variation in the transition temperature[18] (Tc) of the span 60 and span 40. Tc=53°C and Tc= 42°C are the transition temperatures of the Span 60 and Span 40 respectively. As Span 60 have more transition temperature, formulations prepared with Span 60 exhibited more entrapment efficiency vice versa.

In Vitro Drug Release

The in vitro release profile of all formulations was studied in fabricated franz diffusion cell using dialysis membrane as semi permeable membrane. After 9h, about 62.3%, 57.3%, 41.6%, 81.6%, 66.8% and 59.4% of diclofenac sodium was released from formulations FS601, FS602, FS603, FS401, FS402 and FS403 respectively.

In both formulations prepared with span 60 and span 40, drug release was decreased with increased concentration of the surfactant. This substantiate that the drug release from proniosomes is inversely proportional the concentration of surfactant. Drug release from formulations prepared with span 60 was less when compared with formulations prepared with span 40. This may be because of variation in the length of alkyl chains present in span 60 and span 40[19]. Increased chain length may increase the rigidity of the outer layer of the vesicle which may hinder the drug release from the vesicles.

FS603 was considered as an optimized formulation as it exhibited highest entrapment efficiency and slowest drug release profile and the same formulation evaluated further for zeta potential, Stability and In vivo efficacy study.

Zeta potential

Surface charge of the proniosomes was determined by means of Zeta potential analyzer. 0.5g of proniosomal gel was hydrated with phosphate buffer and the resultants proniosomes surface charge was measured as zetapotential. Zeta potential of the proniosomes present in optimized formulation was found as –26mV. The result was the average of three runs. This validating that the vesicles are physically stable and will not exhibit physical aggregation due to the presence of sufficient charge to repel each other.

TABLE 1: COMPOSITION OF PRONIOSOMAL GELS

S. No	Formulation Code	Diclofenac sodium, mg	Cholesterol, mg	Lecithin, mg	Non-Ionic Surfactant, mg
1	FS601	50	200	1800	1200
2	FS602	50	200	1800	1800
3	FS603	50	200	1800	2400
4	FS401	50	200	1800	1200
5	FS402	50	200	1800	1800
6	FS403	50	200	1800	2400

TABLE 2: SIZE, SHAPE AND % ENTRAPMENT EFFICIENCY OF ALL FORMULATIONS

S. No	Formulation Code	Shape of the Proniosomes	Particle size, µm	% entrapment efficiency
1	FS601	Discreet round shape	2.92	64.09
2	FS602	Discreet round shape	2.72	68.12
3	FS603	Discreet round shape	2.50	72.29
4	FS401	Discreet round shape	2.74	54.42
5	FS402	Discreet round shape	2.68	61.71
6	FS403	Discreet round shape	2.54	64.99

TABLE 3: PERCENT IN VITRO DRUG RELEASE FROM ALL PRONIOSOMAL GELS

S. No	Formulation Code	In vitro drug release (%) various time intervals (h)								
		1	2	3	4	5	6	7	8	9
1	FS601	4.5	7.8	8.9	14.8	25.7	32.6	42.1	51.7	62.3
2	FS602	3.4	6.6	8.1	12.2	23.3	29.7	39.1	45.6	57.3
3	FS603	2.6	3.7	4.4	6.8	11.7	19.5	26.7	31.5	41.6
4	FS401	6.9	11.1	18.9	27.6	39.4	47.8	59.0	69.3	81.6
5	FS402	5.1	9.6	14.4	25.6	32.7	46.2	51.3	62.2	66.8
6	FS403	4.4	6.6	7.9	21.6	31.4	40.9	44.3	51.7	59.4

TABLE 4: STABILITY DATA OF THE OPTIMIZED FORMULATION AT REFRIGERATED AND ROOM TEMPERATURES

Condition	At Refrigerated Temperature			At Room Temperature		
Parameters	Shape	Size (µm)	Assay (%)	Shape	Size (µm)	Assay (%)
Initial	Discreet round shape	2.50	100.0	Discreet round shape	2.50	100.0
1 month	Discreet round shape	2.51	99.8	Discreet round shape	2.62	98.1
2 months	Discreet round shape	2.53	99.6	Discreet round shape	2.89	97.0
3 months	Discreet round shape	2.53	99.0	Discreet round shape	3.21	96.3

TABLE 5: IN VIVO SKIN IRRITATION REPORT OF OPTIMIZED PRONIOSOMAL GEL (FS603)

Day	Parameter	Rat number (Test Formulation)			Rat number (Placebo)			Irritation index
		1	2	3	1	2	3	
1	Erythema	0	0	0	0	0	0	0
	Edema	0	0	0	0	0	0	0
2	Erythema	0	0	0	0	0	0	0
	Edema	0	0	0	0	0	0	0
3	Erythema	0	0	0	0	0	0	0
	Edema	0	0	0	0	0	0	0
4	Erythema	0	0	0	0	0	0	0
	Edema	0	0	0	0	0	0	0
5	Erythema	0	0	0	0	0	0	0
	Edema	0	0	0	0	0	0	0

TABLE 6: IN VIVO ANTI-INFLAMMATORY ACTIVITY OF OPTIMIZED PRONIOSOMAL GEL (FS603) AGAINST MARKETED PREPARATION

Time (h)	Control	Reference gel	Proniosomal gel
0	0.99	0.95	0.97
1	1.23	1.14	1.19
% Inhibition	0.24	20.83	8.33
2	1.41	1.22	1.25
% Inhibition	0.42	35.71	33.33
4	1.72	1.38	1.35
% Inhibition	0.73	41.1	47.95
6	2.19	1.65	1.49
% Inhibition	1.2	41.67	56.67
8	2.32	1.73	1.45
% Inhibition	1.33	41.35	63.91
10	2.45	1.8	1.49
% Inhibition	1.46	41.78	64.38

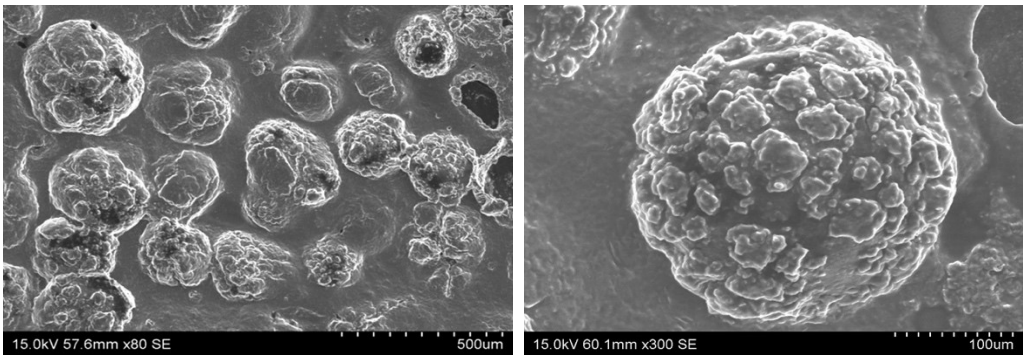

Fig 1: SEM images of the proniosomes

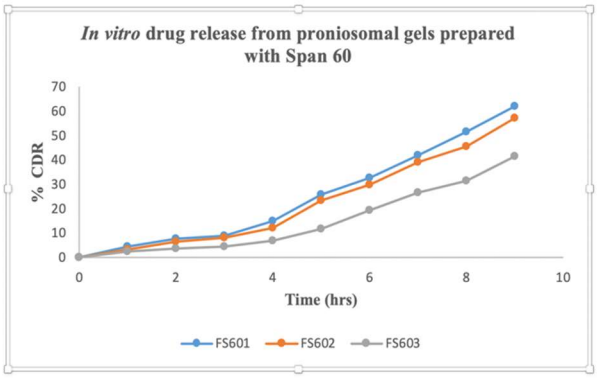

Fig 2. In vitro drug release from proniosomal gels prepared using Span 60

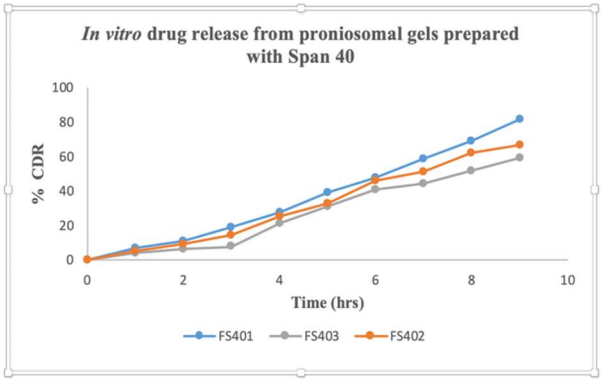

Fig 3. In vitro drug release from proniosomal gels prepared using Span 40

Stability studies of proniosomal gel

During the 3 months stability period, the shape of the vesicles was not changed at both refrigerated and room temperatures. The size of the proniosomes and % assay at refrigerated temperature was not changed much when compared with initial stage. However, at room temperature the size of the vesicles was increased and the % assay was decreased. The size of the proniosomes may increased because of aggregation of the proniosomes. % assay was also dropped at room temperature. The % assay was with in the ICH guidelines both refrigerated and room temperatures and the increased size of the proniosomes and dropped in assay at room temperature was not substantial. Based on the results it was concluded that the formulation was extensively stable.

Skin irritation study

During the 5 days treatment with optimized and control formulations, no animal was shown erythema and/or edema. Based on the scale, erythema and edema scored as zero subsequently irritation index of the optimized formulation was evolved as zero and was found within the acceptable range of 0 to 9. The acceptable range 0-9 was reported earlier by Van-Abbe N. et al. This concludes that the formulation is non-irritant and may also act similarly when applied on human skin. Thus, the developed formulation was validated to have a completely non-irritant effect. The complete skin irritation report of optimized formulation present in table 5.

In vivo evaluation of anti-inflammatory activity

Ant inflammatory activity of proniosomal gel was studied against placebo and standard gel (Diclofenac sodium gel). Onset of time of both test and reference samples was more or less equal (1h). However, the efficacy (% inhibition of Inflammation) was more with reference sample when compared with test sample at 1h, at 2nd h average % inhibition was approximately equal in both test and reference groups and after 2h, the average % inhibition is more in test group than the reference group.

The under efficacy of test formulation for first two hours when compared with reference may be because of two reasons. They may be, one, time to generate the moisture from surroundings by occlusion and second, to form the niosomes from proniosomes using generated moisture. Though test formulation efficacy was poor at first hour when compared with reference, its efficacy was extended for period of 10h whereas the test formulation shown its efficacy till 4 hours only. % inhibition of inflammation was constant after four hours in reference group (G2). Reference sample has shown average % inhibition of inflammation of 41.10% whereas the proniosomal gel has shown % inhibition of 64.38% and also the activity of the gel was extended for 9 hours. These results substantiating that the proniosomal gel releases the drug at controlled manner for extended period than the conventional reference gel and produces the maximum efficacy. The detailed report of anti-inflammatory activity of optimized proniosomal and marketed gels are reported in table 6.

CONCLUSION

From the above research work, it is confirmed that the concept of incorporating the drug into proniosomes is one of the best advantageous technique as they provide better targeting of the drug to appropriate tissue destination, additional convenience of transportation, distribution, storage and dosing. The study data substantiated that the proniosomal gel of diclofenac sodium offers controlled release of the drug and provide outstanding therapeutic efficacy.

ACKNOWLEDGMENTS

The authors would like to thank the support given by Dr Ramachandra, Hyderabad, India while carrying out the in vivo study.

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Cite this article as:

Vamshi Krishna Lekkala *et al*. Preparation, characterization and optimization of proniosomal gel of anti-inflammatory agent. Int. Res. J. Pharm. 2020;11(10):23-28.
http://dx.doi.org/10.7897/2230-8407.111086

Source of support: Nil, Conflict of interest: None Declared