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Development and Characterization of Topical Niosomal Gel of Loxapine Succinate

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Rama Shukla[1*], Nisha Thakre[1], Manu Singhai[2], Akhlesh K. Singhai[1]

[1]Department of Pharmaceutics, Lakhsmi Narain college of Pharmacy, Bhopal M.P. India

[2]ISF College of pharmacy, Moga, Punjab

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ABSTRACT

Loxapine succinate is used as an antipsychotic drug, which is used daily. Currently, in the market, capsule and injectable dosage forms (Intramuscular) are available. However, these dosage forms are difficult to take by the psychotic patient daily and even sometimes they do not cooperate to administer. The purpose of the present study was to prepare the topical niosomal gel of Loxapine succinate for the treatment of schizophrenia. Niosomes were prepared using different ratios of surface-active agents (Span 60, Span 80) by thin film (layer) hydration method. The Topical Niosomal gel formulations of Loxapine succinate were characterized for its vesicle size, entrapment efficiency, *in-vitro* release study, stability study, pH, viscosity, drug content and uniformity of the gel. Topical Niosomal gels are preferred in the treatment of psychosis as the incorporation of Loxapine succinate into niosomes can provide better patient compliance and improve the amount and time of retention within the skin, which in turn can increase the therapeutic efficacy and also reduces the toxicity of the drug. The emphasis of this research is on the potential of the niosomal drug delivery system which provides consistent, prolonged release of Loxapine succinate and also reduces its side effects associated with oral administration.

INTRODUCTION

Loxapine succinate is an anti-psychotic drug used over 40 years with a well-established profile. Loxapine is a dibenzoxazepine tricyclic antipsychotic agent, available for oral, intramuscular and inhalation administration (agitation) [1].

Niosomes are non-ionic surfactant vesicles, used to entrap various drugs to increase their sustainability [2]. There is an interaction with epidermal tissue when niosome containing drugs for dermal application without any systemic action [3].

Niosomes and liposomes are unilamellar or multilamellar vesicles wherein an aqueous phase is encapsulated in closed bilayer made up of nonionic surfactant (niosomes) or lipid (liposomes) with or without other components like cholesterol and diacetyl phosphate [4].

Common side effects of the Loxapine succinate include dizziness, changes in menstrual periods, skin rash, etc. It can also cause serious effects which lead to death like Neuroleptic malignant syndrome (NMS) and Neuromuscular reactions (Extrapyramidal syndrome) have been reported frequently often during the first few days of treatment[5].

In this research, we developed topical liposomal gel to provide patient compliance to release the drug for a prolonged period (12hr) which in turn reduces the drug-associated side effects.

MATERIALS AND METHOD

MATERIALS

Loxapine succinate was gifted by Centaur Pharmaceuticals, Mumbai. Span 60, Span 80 was purchased from Oxford lab reagents, Mumbai. Cholesterol (CHO) was purchased from Thomas baker (case no.57885), Mumbai. Carbomer 934 was gifted by USV Ltd., Mumbai. All materials were of analytical grade.

METHOD

Niosomes were prepared by a thin-film hydration method with some modifications. The accurately weighed quantities of surfactants (span 60, span 80) and Cholesterol (CHO) in different ratios were dissolved in 10 ml of the chloroform: methanol mixture (2:1) along with Loxapine succinate (10mg) in a round bottom flask and the solvent was evaporated under reduced pressure at room temperature, rotated continuously until the formation of thin lipid

film. The formed film was hydrated with 10ml of PBS (pH 7.4). The hydrated niosomes were sonicated for 20 min using a bath sonicator to obtain niosomal dispersion containing both free and entrapped drugs of varying size [6-7].

CHARACTERIZATION OF NIOSOMES

Vesicle size analyzes niosomes: The vesicle formation of niosomes was confirmed by optical microscopy in 45x resolution. Prepared niosomal suspension was placed over a slide and fixed over it, the dry thin film of niosomes suspension was observed. The microphotography of the niosomes was obtained by using digital cameras from the microscope [8]. The size of vesicles was measured using ocular and stage micrometers [9].

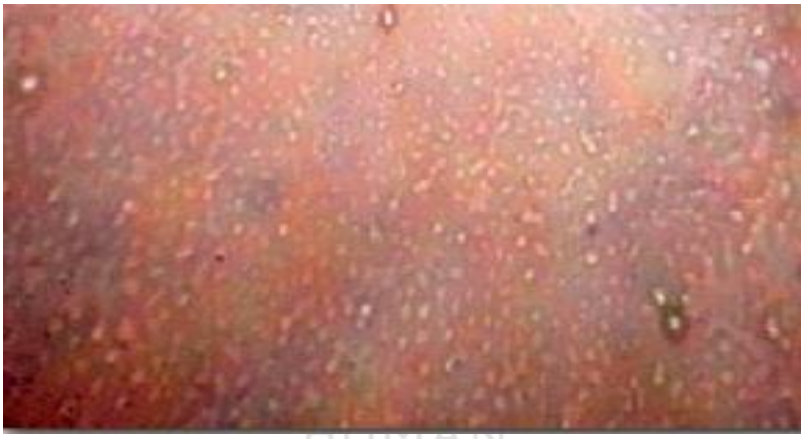

Figure No. 1: Drug loaded Niosomes under Optical microscope (45X)

Entrapment Efficiency: Entrapment efficiency (EE %) was determined using micro-centrifuge RM-12CDX. Niosomal suspension was centrifuged at 12000 rpm for 20 min. Drug concentration in the resulting supernatant was assayed by UV Spectrophotometer at 252nm. The absorbance of the drug was compared with the calibration curve and dilution factor were also calculated [10]:

% of drug encapsulated was calculated by the following equation –

$$EE\% = [(Ct-Cf)/Ct)] \times 100$$

Where,

C_t is the concentration of total drugs

C_f is the unentrapped drug.

Table No. 1: Optimization of Surfactant and Cholesterol concerning Vesicle size and Entrapment efficiency (EE%)

Surfactant & Cholesterol Composition	Molar Ratio	Formulation Code	Vesicle Size (µm)	Entrapment Efficiency (%)
SPAN 60:CHO	1:1	F_1	1.8± 0.5	18.23±4.61
	1:2	F_2	2.0±0.3	66.10±4.06
	2:1	F_3	1.6 ±0.1	20.52±2.1
	2:2	F_4	1.4 ±0.3	25.65±2.5
SPAN 80:CHO	1:1	F_5	1.6 ±0.1	30.23±3.5
	1:2	F_6	1.7 ±0.14	67.22±4.01
	2:1	F_7	2.0 ±0.06	27.35±2.2
	2:2	F_8	1.5 ±0.02	19.56±4.04

PREPARATION OF GEL BASE

1gm of carbopol 934 was taken and dispersed in double-distilled water (80ml). This solution was stirred, at 800 rpm for 1 hour. 10ml of propylene glycol was added to this solution. This mixture was neutralized by dropwise addition of 10% NaOH solution while mixing was continued until a transparent gel appeared and finally the volume was adjusted to 100ml. the pH of the gel base was adjusted to 6.5 [11].

CHARACTERIZATION OF GEL BASE

Visual appearance: Gel appeared clear and transparent.

Spreadability: Therapeutic potency of formulation depends upon its spreadability. To meet favorable properties, the gel must pass the test for spreadability and express in terms of seconds. The test was carried out by placing 1 slide to slip off from gel, which was placed in between the scales under the direction of weight [12]. Good spreadability show lesser time to slip off. Spreadability of the gel was found to be well shown in Table2.

Table No. 2: Observation table for spreadability of topical niosome based gel

Sr. No.	Time Taken (Sec)	Weight Required	Mean Reading (Sec)
1.	7	190gm	6
2.	5	150gm	
3.	6	170gm	

Measurement of viscosity: Viscosity of prepared gel was measured by Brookfield viscometer. Measurements were carried out using spindle no.63 with the optimum speed of 10rpm; viscosity was reported to be 3780 cps [13].

Extrudability study: In the present study, the method adopted for evaluating gel formulation for extrudability was based upon the quantity of the gel extruded from the collapsible tube on the application of a certain load. More the quantity extruded better was extrudability. Extrudability of the gel was found to be good as shown in Table3 [14].

Table No. 3: Observation table for extrudability of the gel base

Sr. No.	Weight Required (in gm)	Volume Extruded (in cm)	Mean Volume (in cm)
1.	170	0.6 cm	0.4
2.	150	0.4 cm	
3.	120	0.2 m	

INCORPORATION OF NIOSOMES INTO GEL:

10 mg/ml niosomes containing Loxapine succinate was incorporated into the gel base to get the desired concentration of drugs in the gel base.

Assessment of the physical stability of topical niosomal gel: Physical stability study of the prepared topical niosomes gel was carried out to observe the leaching out of drug from niosomes at different temperature refrigerator condition (4±5˚C) and room temperature (25±31˚C). Niosomes were observed for drug content respectively.

Table No. 4: Observation table of the physical stability of topical niosomes based gel concerning vesicle size & EE%

F2	T_1		T_2	
	1 month	2 month	1 month	2 month
Vesicle size	1.9±0.3	2.2±0.2	3.2 ±0.4	4.0±0.5
% entrapment efficiency	66.10±4.5	65.20±1.7	63.56±2.34	61.68±0.18

Where, T_1 =Refrigerator condition (4ºC), T_2 = Room temperature (25-28ºC).

Table No. 5: Observation of physical stability of topical niosomes based gel concerning vesicle size and entrapment efficiency

SF6	T_1		T_2	
	1 month	2 months	1 months	2 months
Vesicle size	1.8±0.4	2.4 ±0.1	3.4 ±0.3	4.5±0.2
% entrapment efficiency	67.22±5.5	67.15±1.5	66.70±1.6	65.5±2.5

Where, T_1 =Refrigerator condition (4ºC), T_2 = Room temperature (25-28ºC).

Measurement of viscosity: Viscosity measurements of prepared topical niosome based gel were measured by Brookfield viscometer using spindle no. 63 with the optimum speed of 10rpm; viscosity was found to be 3776cps.

Drug content: Accurately weighed equivalent to 10 mg of topical niosomal gel was taken in a beaker and added 20 mL of 0.01N HCl. 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 up to 10 mL with 0.01 N HCL. This solution was analyzed using UV-Spectroscope at λ_{max} 251 nm. The drug content of topical niosomal based gel is shown in table no 6.

Table No. 6: Drug content of niosomal gel

Sr. No.	Optimized niosomes	Drug content
1	F_2	6.61 %
2	F_6	6.70%

Drug release study: The release study of prepared niosomal gels was determined by Franz diffusion cell which consisted of PBS (pH 7.4).1 mL of topical niosomal gel were applied in a cellophane membrane (1200 Daltons) of diameter 2.5 cm & observed at different intervals of time [15]. Zero-order, first-order, Hixson Crowell, Higuchi, Korsmeyer peppas equations were applied to *in-vitro* release results and the correlation coefficient was found [16].

Table No. 7: The cumulative percentage release of optimized formulations

Time (hr)	% Release of topical niosomal gel (F_2)	% Release of topical niosomal gel (F_6)
0.25	3.21±1.12	1.2±0.17
0.5	4.23±2.54	6.23±1.42
1	13.25±0.45	16.8±0.24
2	18.75±4.40	26.13±1.22
4	25.73±1.56	32.24±2.30
6	29.9±1.77	36.12±4.57
8	34.56±2.60	39.89±2.68
10	38.45±4.20	44.53±0.56
12	41±2.44	47.07±2.59

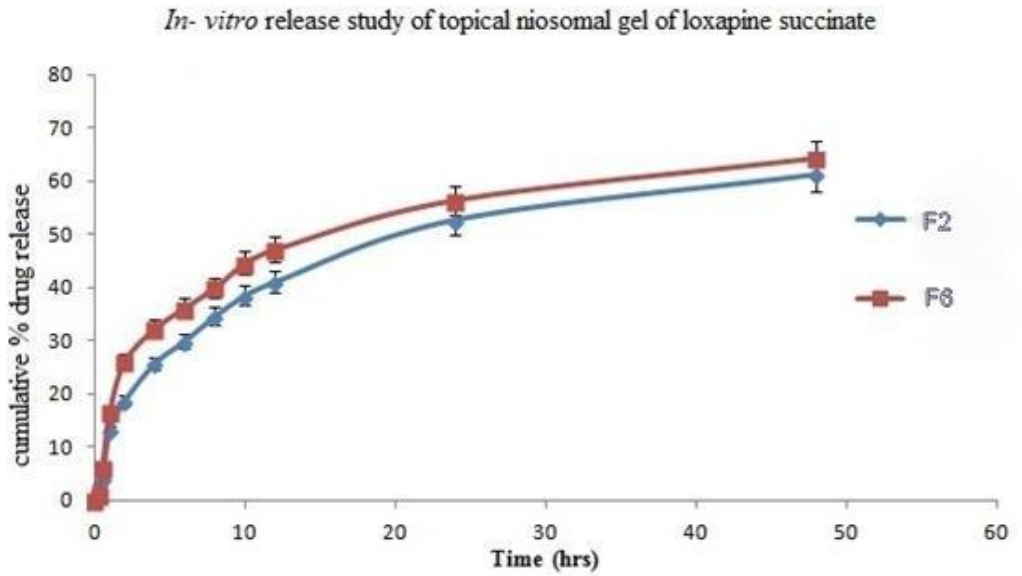

Figure No. 2: *In- vitro* release study of Topical Niosomal base gel of Loxapine Succinate

Table No. 8: Observation table for release order of optimized formulation of F_2

S.no	Release order	Equation	r^2 value
1.	Zero-order	y=2.307x+ 19.988	0.7333
2.	First-order	y=-0.0104x+1.9063	0.8573
3.	Hixson Crowell	y=0.2286x+4.5943	0.9709
4.	Higuchi	y= 10.395x+6.7999	0.9434
5.	Korsmeyer peppas	y=0.4722x+1.1535	0.9148

Table No. 9: Observation table for release order of optimized formulation of F_6

S.no	Release order	Equation	r^2 value
1.	Zero-order	y=1.2763x+ 24.881	0.6627
2.	First-order	y=-0.0108x+1.8773	0.8243
3.	Hixson crowell	y=0.2385x+4.5181	0.9619
4.	Higuchi	y= 10.477x+11.227	0.9032
5.	Krosmeyer peppas	y=0.4059x+1.2764	0.8928

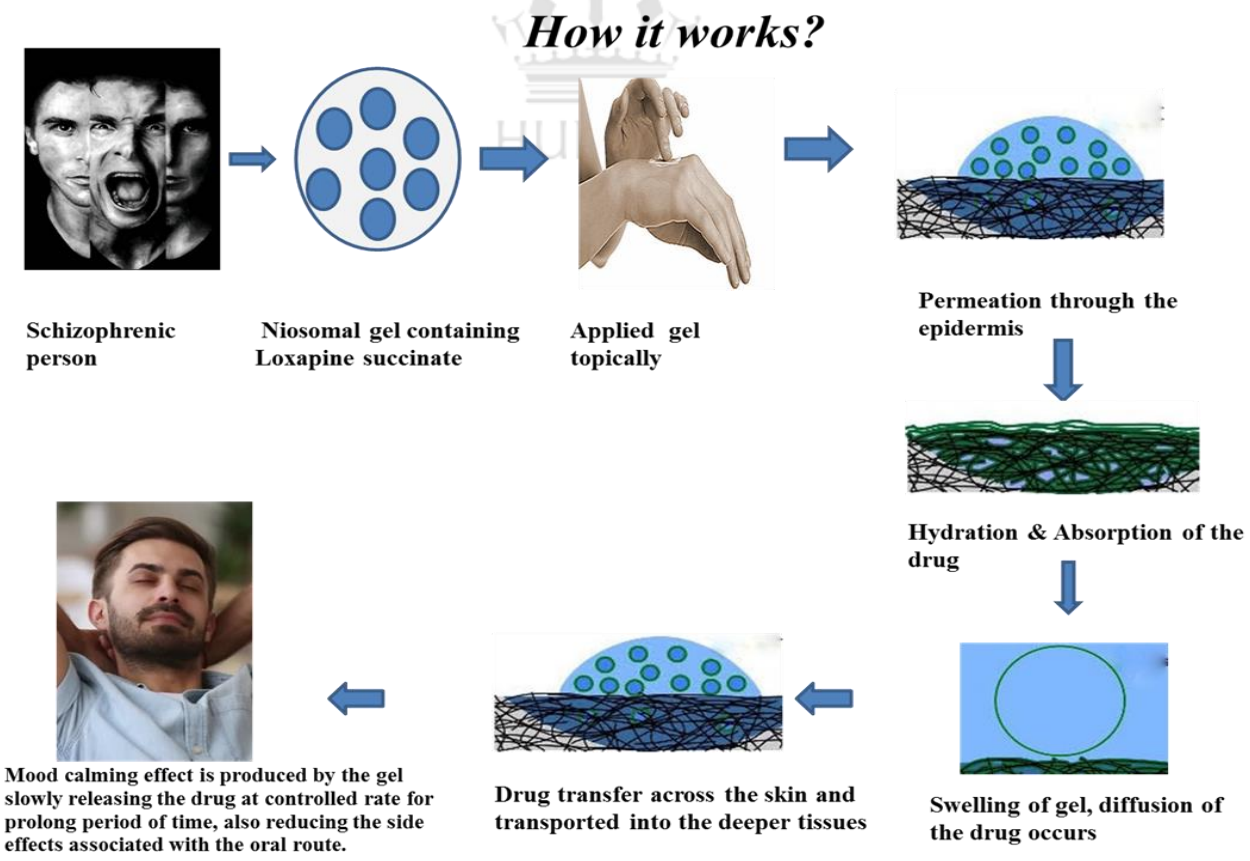

Figure No. 3: Mechanism of Niosomal gel acting on the schizophrenic patient

RESULTS AND DISCUSSION

It the present study topical niosomal gels was prepared by the handshaking method because of its greater drug entrapment efficiency and smaller vesicle size, this method was selected. We have chosen Spans (surfactants) for making niosomes. Span 60 and span 80 were taken in a different molar ratio which was then evaluated for entrapment efficiency. Optimized formulation i.e F_2 and F_6 show better drug entrapment, 66%, and 67%, respectively. Present work was carried out to overcome the problems associated with the oral route of administration, for improving patient compliance by providing sustain release of the drug.

The solubility and chemical structure of the drug plays a major role in the transdermal drug delivery system. Results of the physical stability of niosomes show higher leaching of the drug at room temperature and found to be stable at refrigerated conditions. Niosomes stability improved by incorporating it with a gel base because it prevents the fusion of niosomes [17].

CONCLUSION

It can be concluded from the study that topical niosomal formulation can provide consistent and prolonged release of loxapine succinate. It will lead to sustained activation of the entrapped drug that reduces the side effects associated with frequent administration of the drug through the oral route. It may be concluded that Loxapine succinate could be administered topically. It shows that topical niosomal gel base drug delivery systems may be a promising carrier for the delivery of loxapine succinate.

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