FORMULATION AND EVALUATION OF NIOSOMAL GEL LOADED WITH BOSWELLIC ACID

Ashish Ranjan[1*], Parul Mehta[2], Priyanka Namdeo[3]

[1,2,3] Lakshmi Narain College of Pharmacy, Raisen Road, Kalchuri Nagar, Bhopal, 462022, India

Corresponding Author Details: Ashish Ranjan,

Mobile: 9162637765

kuppoashish@gmail.com

ABSTRACT

A skin disease, like inflammation, is very common and normally happens to everyone at least once in their lifetime. One of the best options for successful drug delivery to the affected area of skin is the use of elastic vesicles which can be transported through the skin through channel-like structures. The present research work was to formulate and evaluate boswellic acid loaded niosomal gel for the management of Inflammation. Niosomal gel was successfully prepared by lipid-thin film hydration process and niosomes prepared using varying ratio of surfactant (span 20 and tween 20) and cholesterol were evaluated for entrapment efficiency and *in vitro* release. From the result of experimental investigations, it was observed that using either of the surfactants a 1:3 ratio of surfactant and cholesterol exhibited the maximum entrapment of the drug in the core. The prepared formulations were evaluated *in-vitro* drug release studies found that the maximum amount of drug was released from formulations F3 (78.37 %) and F6 (79.84 %) over a period of 24 h at an almost steady rate. The higher amount of drug release along with the higher entrapment efficiency make the formulations F3 and F6 containing surfactant to cholesterol ratio of 1:3 the most promising formulations. The study indicated the successful development of boswellic acid loaded niosomal gels with improved penetration, good homogeneity and enhancement of duration of action. It can thus be concluded that the developed gel could be an effective treatment for skin inflammation.

KEYWORDS: Boswellic acid, Cholesterol, Inflammation, Niosomes, Span 20.

DOI: 10.48047/ecb/2023.12.Si11.038

INTRODUCTION

Inflammation is a protective response involving immune cells, immune blood vessels, and molecular mediators that is a part of the intricate biological response of body tissues to harmful stimuli such as pathogens, damaged cells, and irritants. The main criteria of anti-inflammatory are to discard the initial cause of cell injury and to discard necrotic cells and damaged tissues and initiate the repair. Plenty of drugs such as non-steroidal anti-inflammatory, and corticosteroids are used to decrease joint pain and swelling. [1] The anti-inflammatories are available in different forms such as gel ointments sterile preparation etc. Anti-inflammatories are used in combination for their differing effects. Synthetic drugs such as NSAID drugs may cause gastric haemorrhage, stomach burn, ulcers etc. [2]

Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes. However, the major barrier of the skin is the stratum corneum, the top layer of the epidermis. Low molecular weight (≤500 Da), lipophilicity, and effectiveness at a low dosage are the ideal characteristics of the drugs for transdermal delivery. [3]

Niosomes (non-ionic surfactant vesicles) are microscopic lamellar structures obtained on an admixture of non-Ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol (CHO) with subsequent hydration in aqueous media. [4] Niosomes attracts much attention because of its advantages in many aspects, such as chemical stability, high purity, content uniformity, low cost, convenient storage of non-ionic surfactants, and large numbers of surfactants available for the design of niosomes. [5] Niosomes are promising vehicle for drug delivery. The encapsulation of drugs in niosomes can minimize drug degradation and inactivation after administration; prevent undesirable side effects, increase drug bioavilability and targeting to the pathological area. [6] Surfactants also act as penetration enhancers as they can remove the mucus layer and break functional complexes. The non-ionic surfactants form a closed bilayer vesicle in aqueous media based on its amphiphilic nature using some energy, for instance, heat and physical agitation to form this structure. Their effectiveness is strongly dependent on their physiological properties, such as composition, size, charge, lamellarity and application conditions. Niosomes as delivery devices have also been studied with anticancer, anti-tubercular, anti-leishmanial, anti-inflammatory, hormonal drugs and oral vaccine. [7-10]

Hence, in the present investigation, an attempt is made to Formulate and Evaluate niosomal gel loaded formulation of Boswellic acid.

MATERIAL AND METHODOLOGY

Preformulation Studies

The Preformulation studies were carried out for confirming the identity of the drug and to ascertain the compatibility amongst the drug and the excipient (polymers) used in formulation.

Organoleptic Characters

The organoleptic properties of the procured drug sample were examined using sensory organs and include color, odor, taste and appearance. The solubility of the drug in various solvents was also observed.

Partition Coefficient

This study was performed by using octanol as oil phase (30ml) and water as aqueous phase (30ml). The Two phases were mixed by keeping them in a separating funnel and 5 mg of drug was added in it then Two phases were separated from each other when it was shaken continuously and then separated from each other by separating funnel. Both phases were taken in a conical flask and then analysed against their respective blank solution and the partition coefficient was calculated by following formula.

$K_{o/w}$ = Concentration of drug in octanol/ Concentration of drug in water

Determination of Absorbance maximum (λmax)

Boswellic acid was dissolved in phosphate buffer pH 6.8 and a solution with 25 µg/ml concentration was prepared by suitable dilution. The boswellic acid solution was scanned using UV spectrophotometer from 200 to 400 nm using phosphate buffer pH 6.8 as blank. Absorbance maximum was determined as 260 nm. The drug was later quantified by measuring the absorbance at 260 nm in phosphate buffer pH 6.8. [11]

Standard curve for Boswellic acid

Preparation of primary stock solution

Boswellic acid 100 mg was weighed and dissolved in phosphate buffer pH 6.8 in a 100 ml volumetric flask. The flask was shaken and volume was made up to the mark with phosphate buffer pH 6.8 to give a solution containing 1 mg/ml.

Preparation of secondary stock solution

From the primary stock solution, pipette out 2 ml and placed into 100 ml volumetric flask. The volume was made up to mark with phosphate buffer pH 6.8 to give a stock solution containing 20 μg/mL.

Preparation of sample solution

Appropriate volume of aliquots (1 to 10 ml) from boswellic acid secondary stock solution were transferred to different volumetric flasks of 10 ml capacity. The volume was adjusted to the mark with methanol to obtain concentrations of 10, 20, 30, 40 and 50 μg/mL. Absorbance of each solution against phosphate buffer pH 6.8 as blank were measured at 260 nm.

Formulation of Boswellic acid Niosomes

Boswellic acid loaded niosomes were prepared by thin film hydration technique. Accurately weighed quantity of cholesterol and surfactant were dissolved in chloroform methanol mixture ratio (2:1 v/v) in a 100 mL volumetric flask. The weighed quantity of drug and dicetyl phosphate was added to the solvent mixture. The solvent mixture was removed from liquid phase using rotary evaporator at 60°C to obtain a thin film on the wall of the flask at a rotation speed of 150 rpm. The complete removal of solvent can be ensured by applying vacuum. The dry lipid film was hydrated with 5 ml phosphate buffer saline of pH 7.4 at a temperature of 60±2°C for a period of 2 hour until the formation of niosomes. All the batches were subjected to sonication process for 2 min using probe sonicator. [12] The ratios of cholesterol and surfactant used in the formulation are presented in Table 01.

Table 01: Composition of Boswellic Acid Niosomes

Formulation Code	Boswellic Acid (mg)	Surfactant	Surfactant: Cholesterol (μM)
F1	100	Span 20	100:100
F2	100	Span 20	100:200
F3	100	Span 20	100:300
F4	100	Tween 20	100:100
F5	100	Tween 20	100:200
F6	100	Tween 20	100:300

Dicetyl phosphate: 15μM

Evaluation of Boswellic Acid loaded Niosomes

FTIR spectroscopic analysis

The Fourier transformed infrared spectroscopic analysis of the procured drug sample was performed and the major absorption bands were compared with that of the spectral database of the drug to ascertain its identity. FTIR of physical mixture of the drug and the used polymers was also performed to observe to any possible interaction between the drugs and excipients (Carbopol 934, cholesterol, span 20, tween 20).

Removal of non-trapped boswellic acid from niosomes

The unentrapped drug from niosomal formulation was separated by centrifugation method. The niosomal suspension was taken in centrifuge tube. The formulation was centrifuged at 15,000 rpm for 30 min using cooling centrifuge and temperature was maintained at 5°C. The supernatant was separated. Supernatant contained non trapped boswellic acid and pellet contained drug encapsulated vesicles. The pellet was resuspended in methanol to obtain a niosomal suspension free from un-entrapped drug.

Encapsulation efficiency

Drug entrapped vesicles were separated from un-entrapped drug by centrifugation method. 0.5 ml of boswellic acid loaded niosome preparation was added with 0.5 ml of 10% triton X 100 and mixed well then incubated for 1 hour. The triton X 100 was added to lyse the vesicles in order to release the encapsulated boswellic acid. The solution was diluted with phosphate buffer pH 6.8 and filtered through Whatman filter paper. The filtrate was measured spectrophotometrically at 260 nm using phosphate buffer pH 6.8 and triton X 100 mixture as blank. [13]

$$\text{Percent entrapment} = \frac{\text{Amount of drug entrapped}}{\text{Total amount of drug added}} \times 100$$

In vitro release study for niosomal preparation

The niosomal formulation was taken in a dialysis membrane of 5 cm length and suitably suspended in a beaker containing 100 ml diffusion medium of phosphate buffer saline pH 7.4.

The temperature of medium was maintained at 37±0.5°C. The medium was stirred by means of magnetic stirrer at a constant speed. 1 ml of sample was withdrawn at every 1 hour and replaced with 1 ml of fresh buffer, so that the volume of diffusion medium was maintained constant at 100 ml. The withdrawn samples were made upto 10 mL using phosphate buffer pH 6.8 as the solvent for dilution. The samples were measured spectrophotometrically at 260 nm.[14]

Preparation of boswellic acid niosomal gel

Gel formulations were prepared by soaking varying concentration of Carbopol 934 in water for 24 h. The niosomes equivalent to 2% w/w boswellic acid were dissolved in ethanol and was added to the gel with continuous stirring. The plasticizer and other ingredients were added and stirred to obtain the gel noisome loaded gel formulation. [15]

Table 02: Composition of gel formulation

Ingredients	G1	G2	G3	G4
Boswellic acid noisome with span 20 (%w/w), F3	2	2	-	-
Boswellic acid noisome with Tween 20 (%w/w), F6	-	-	2	2
Carbopol 934 (%w/w)	1	1.5	1	1.5
Propylene glycol (% w/w)	10	10	10	10
Ethanol (mL)	5	5	5	5
Triethanolamine (% w/w)	0.1	0.1	0.1	0.1
Water (g)	15	15	15	15

Evaluation of Niosomal gel

Determination of pH

The pH of each formulation was determined by pH meter. The pH meter was calibrated using standard buffer solutions of pH 4 and pH 7. 1 mL of the formulation was diluted with distilled water and the pH of the solution was recorded by dipping the electrode in the solution.

Drug content

The drug content of the prepared gel was carried out by dissolving accurately weighed quantity of gel equivalent to 10 mg of the drug in 100 ml volumetric flask and volume was made up to 100 ml with phosphate buffer pH 6.8. The content was filtered through Whatman filter paper and 5 ml of this solution was taken into a 25 ml volumetric flask and volume was made up to mark with phosphate buffer pH 6.8. The content of boswellic acid was determined at 260 nm against methanol as blank by using UV-visible spectrophotometer. The drug content was determined from the calibration curve of phosphate buffer pH 6.8.

V**iscosity Determination**

Viscosity of the gel was determined using Brook field viscometer DV-1. Temperature of 37±0.5ºC was maintained and the spindle no. 52 was lowered into gel formulations which were placed in a beaker. The viscosity of each formulation was determined by applying 10rpm speed.

Spreadability

Spreadability of the formulations was determined using indigenously developed apparatus. The apparatus consisted of a wooden block provided with a pulley at a one end. A rectangular ground glass was fixed on the block. An excess of gel (3-5 g) was placed on this plate sandwiched using another glass plate having the dimensions as that of fixed ground plate. A 1 kg weight was placed on the top of the plates for 5 minutes to expel air and to provide a uniform film of the gel between the plates. Excess of the gel was scrapped off from the edges. Weight of 80 g was hung on the hook of the top plate with the help of string attached to the hook and the time (in seconds) required by top plate to cover a distance of 10 cm was noted. Spreadability of the formulation was determined by the following formula:

$S = M * L/T$

where, S – spreadability; L – distance travelled by the glass slide; T – time in seconds; M - weight in the pan

In-vitro drug release study

Drug release from gel was determined by using Franz diffusion cell. Artificial dialysis membranes were soaked in receptor medium for 12h prior to use. Phosphate buffer saline (12

ml) pH 6.8 enriched with 10% v/v methanol was added into the receptor chamber maintained at 34 ± 1°C. Gel equivalent to 10mg of drug was placed into donor compartment and the setup was kept on stirring. Aliquots of 5ml were withdrawn at predetermined time intervals from receptor compartment and replaced with fresh buffer till 12 h. The samples were diluted suitably and analyzed spectrophotometrically at 260 nm and the amount of drug released was determined using calibration curve.

RESULTS AND DISCUSSION

Organoleptic characters

The observed organoleptic characteristic of the drug sample is presented in Table 03 and 04.

Table 03: Organoleptic properties of Boswellic Acid

S.No	Test	Observation
1	Colour	Off white
2	Odour	Odourless
3	Appearance	Amorphous powder
4	Taste	Bitter

The melting point of the procured drug sample was found to be 229-232°C which was equivalent to the reported standard for boswellic acid. Partition coefficient of the procured specimen of boswellic acid was found to be 5.17.

Table 04: Solubility profile of boswellic acid

S.No	Solvent	Solubility Observed
1	Water	Partially soluble
2	Methanol	Soluble
3	Dichloromethane	Soluble
4	Acetonitrile	Soluble

Calibration Curve

The calibration curve of boswellic acid was prepared according to the reported procedure using phosphate buffer pH 6.8 as the solvent. The absorbance observed is presented in Table 05 and the calibration curve along with the equation for straight line is presented in Figure 01.

Table 05: UV absorbance of boswellic acid

Concentration (µg/mL)	Absorbance at 260 nm
0	0
5	0.096
10	0.201
15	0.295
20	0.381
25	0.446

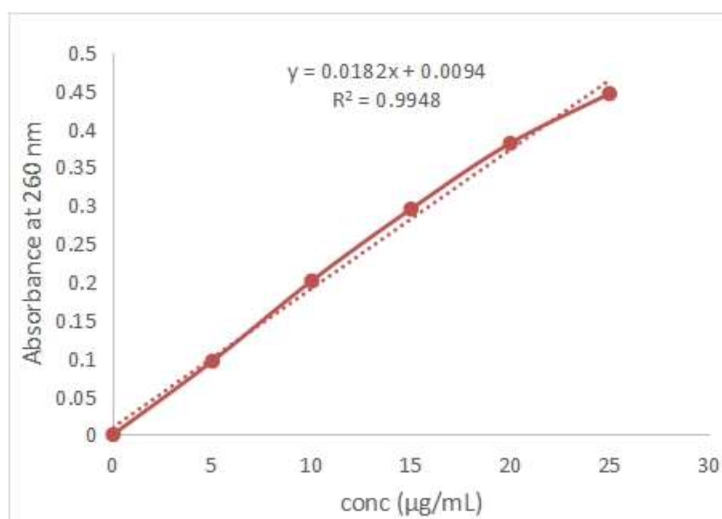

Figure 01: Calibration curve of boswellic acid

The equation for calibration curve was calculated using Microsoft Excel and was found to be absorbance = 0.01825concentration + 0.0094, with a regression coefficient of 0.9948. This equation was hereafter used for calculating the amount of boswellic acid wherever required.

Development of boswellic acid niosomes

In this study, boswellic acid loaded niosomes were prepared by thin film hydration technique using cholesterol and non-ionic surfactants such as span 20 and tween 20. Chloroform-methanol mixture (2:1v/v) was used as solvent. After evaporation of solvent from the formulation, thin film was formed. The thin film was hydrated and removed by phosphate buffer saline pH 7.4. Size of the vesicles in formulation was reduced by sonicating the formulation in Probe sonicator. Formulations with different ratios of surfactant and cholesterol were prepared. Several physicochemical characteristics of niosomes such as morphology, vesicle size determination, drug release profile was investigated. Dicetyl phosphate (DCP) was included in the formulation as charge inducing agent. The inclusion of charge inducing agent (DCP) prevented the aggregation and fusion of vesicles. Integrity and uniformity also maintained by dicetyl phosphate.

Evaluation of boswellic acid niosomes

FTIR and compatibility study

The FT-IR spectra (Figure 02) exhibits the major peaks of the functional groups present in boswellic acid. All these peaks were observed in the FT-IR spectra of the physical mixture of drug and excipients (Figure 03, 04) also providing evidence for the absence of any chemical incompatibility between pure drugs with the excipients.

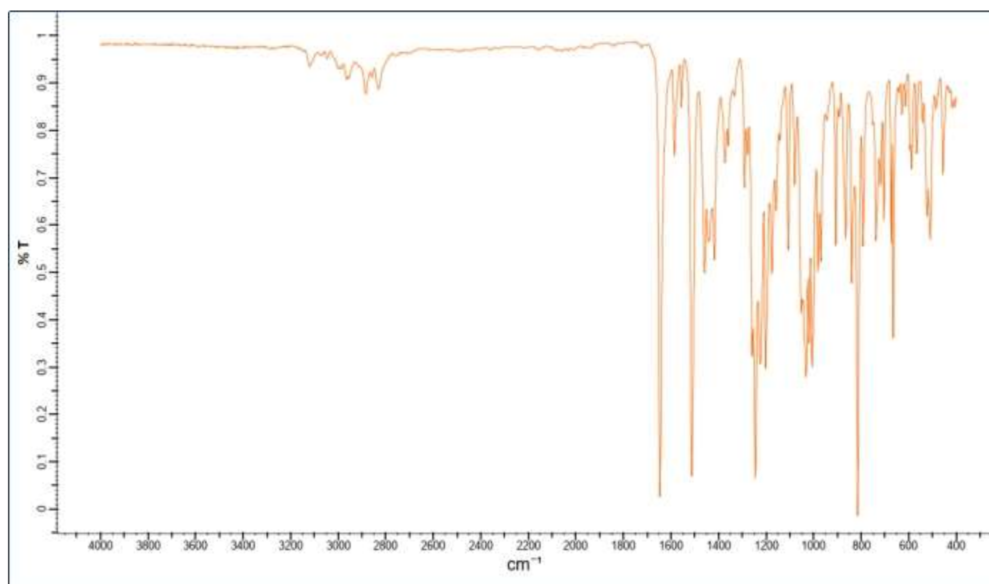

Figure 02: FT-IR spectra of boswellic acid

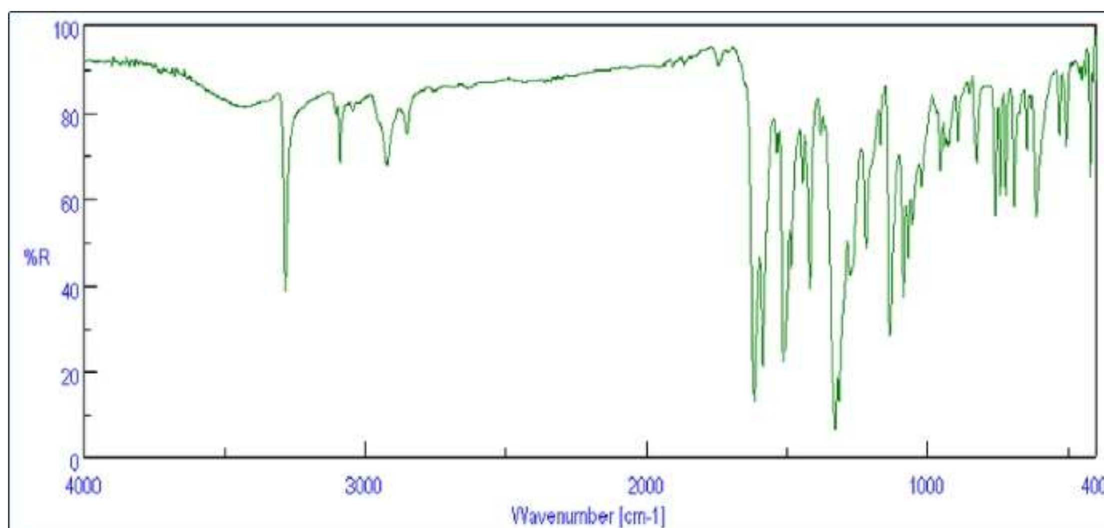

Figure 03: FT-IR spectra of boswellic acid + cholesterol

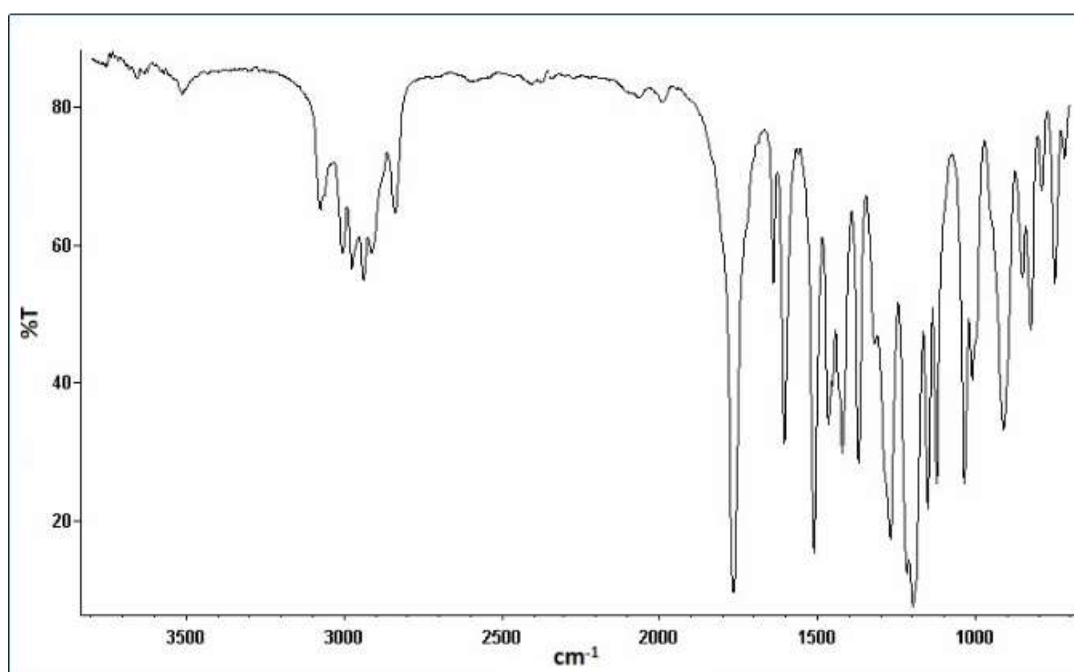

Figure 04: FT-IR spectra of boswellic acid + Carbopol 934

Percentage drug entrapment efficiency

The unentrapped drug from niosomes was removed by centrifugation technique. The results are presented in Table 06. The entrapment efficiency of the niosomes is governed by the ability of formulation to retain drug molecule in aqueous core or in bilayer membrane of vesicles. After removal of unentrapped drug, the entrapment of all formulation was studied. Entrapment efficiency was varied with varying the surfactant and cholesterol ratio. Various factors like lipid

concentration, drug to lipid ratio, and cholesterol content are liable to affect the entrapment efficiency.

Table 06: Entrapment efficiency

Formulation Code	Surfactant: Cholesterol Ratio	Surfactant Used	Percentage Entrapment Efficiency (%)
F1	100:100	Span 20	57
F2	100:200	Span 20	63
F3	100:300	Span 20	69
F4	100:100	Tween 20	62
F5	100:200	Tween 20	69
F6	100:300	Tween 20	73

The entrapment efficiency using both the surfactants was determined and it was found that a 1:3 ratio of surfactant and cholesterol exhibited the maximum entrapment of the drug in the core.

***In vitro* release study**

The release of boswellic acid from niosomes was determined using the membrane diffusion technique. Release study was carried for 24 hours and results are presented in Table 07.

Table 07: *In vitro* release of boswellic acid from niosomes

Time (h)	Cumulative percentage of drug released (%)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	4.18	7.06	9.45	3.69	8.64	11.65
2	9.13	15.9	13.4	7.3	19.42	21.29
4	17.29	20.51	24.11	17.41	24.81	29.83
8	34.82	36.23	43.63	35.92	42.43	44.08
10	42.53	42.63	49.18	44.62	50.24	51.69
12	53.34	52.84	54.74	55.15	55.96	57.53
24	67.16	75.96	78.37	69.74	76.54	79.84

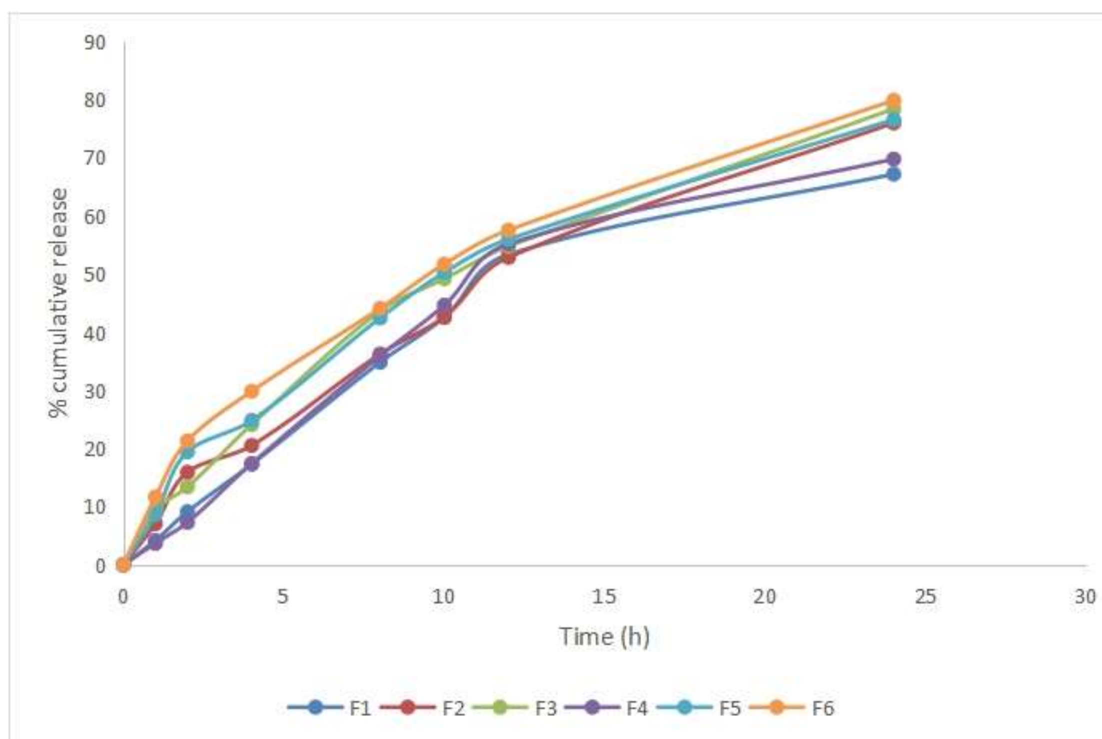

Figure 05: Comparative i*n vitro* release from niosome formulations

From the results of the release studies, it was found that the maximum amount of drug was released from formulations F3 (78.37 %) and F6 (79.84 %) over a period of 24 h at an almost steady rate. The higher amount of drug release along with the higher entrapment efficiency make the formulations F3 and F6 containing surfactant to cholesterol ratio of 1:3 the most promising formulations.

These two formulations were further processed to formulate gel loaded with niosomes containing boswellic acid.

The gel loaded with niosomal formulations F3 and F6 were prepared using Carbopol 934 as the gelling agent and propylene glycol as the plasticizer. The niosomes were suspended in ethanol prior to mixing with the Carbopol gel employing cold gelling procedure. The gel formulations were evaluated for various parameter to ascertain the most suitable formulation.

Figure 06: Gel formulation loaded with boswellic acid niosomes

Evaluation of niosomal gel

The gel formulations were prepared using two concentrations of the gelling agent and were evaluated for physical appearance, pH, viscosity, drug content and *in vitro* diffusion of the drug.

The gel formulations were found to be colorless. The formulation G1 was homogenous and non-gritty when observed under microscope whereas G2 and G4 were non-homogenous and gritty. The formulation G3 was homogenous but was gritty in its texture. The pH of the all the formulations ranged from 6.43 to 6.87 making them suitable to use topically. The formulations were found to possess sufficient viscosity to make then suitable for application to the surface and extrusion from the collapsible tube in which they were packed. The drug content in all the formulations ranged from 94.97 to 98.46 % confirming the incorporation of the niosomes into the gel base. The results of the evaluation parameters are presented in Table 08.

Table 08: Evaluation of the niosomal gel formulations

Formulation code	Color	Appearance	pH	Viscosity (cps)	Drug content (%)	Spreadability (g.cm/sec)
G1	Colorless	Translucent	6.43	8359	94.97	16.48
G2	Colorless	Translucent	6.67	8522	98.46	13.65
G3	Colorless	Translucent	6.79	8327	96.58	16.81
G4	Colorless	Translucent	6.87	8498	98.19	13.74

In vitro drug diffusion from gel formulations

The *in-vitro* drug diffusion study of boswellic acid niosomal gel was done using dialysis membrane in Franz diffusion cell using phosphate buffered saline (PBS) pH 6.8 enriched with 10% v/v of methanol as the diffusion medium.

Table 09: *In vitro* diffusion of boswellic acid from gel

Time (h)	Cumulative percentage of drug released (%)			
	G1	G2	G3	G4
0	0	0	0	0
1	3.36	3.3	3.12	2.69
2	6.79	4.57	5.89	4.11
4	14.67	9.17	14.21	8.46
8	28.19	21.9	26.78	20.51
10	35.85	26.17	32.86	25.19
12	44.65	31.23	38.89	29.62
24	52.90	37.22	46.34	34.72

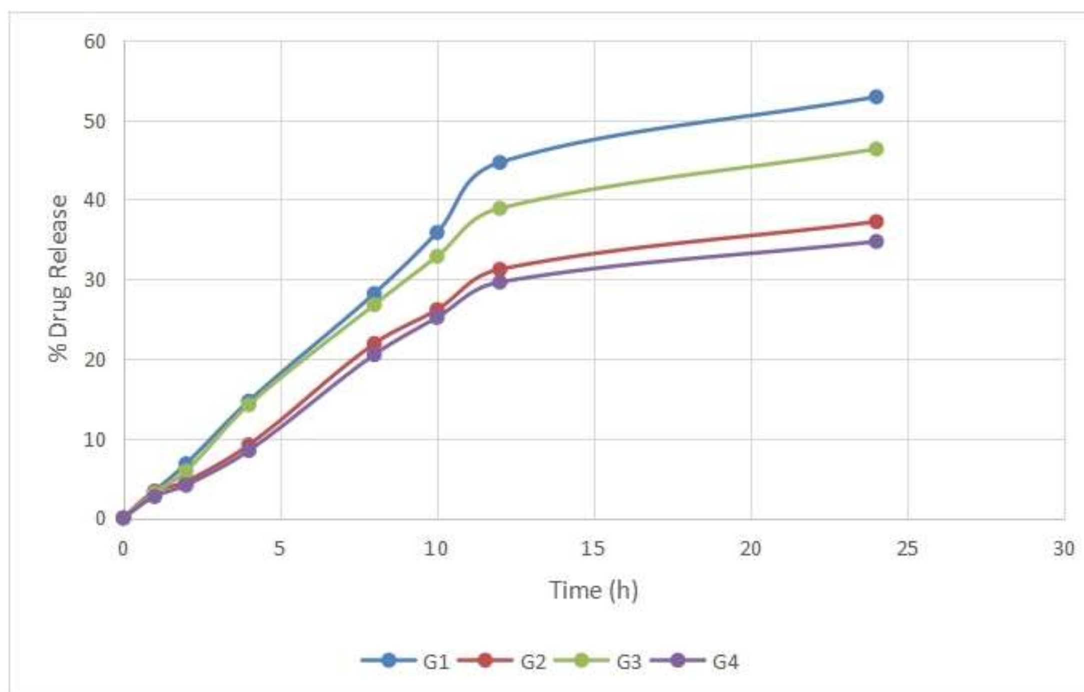

Figure 07: *In vitro* release profile of boswellic acid from gel formulations

The results of the *in vitro* diffusion study revealed that increasing the concentration of the gelling agent (Carbopol 934) decreased the release of drug from the gel. The formulations G1 (52.90 %) and G3 (46.34 %) containing 1% Carbopol 934 were found to release significant amount of drug from the gel over a period of 24 h. Also the formulations prepared from Tween 20 released lower amount of boswellic acid. Thus it was concluded that 1% Carbopol 934 was an appropriate concentration for formulating the niosomal gel and Span 20 was the appropriate surfactant for preparing the niosomes.

In the present study niosomes of boswellic acid were developed by thin film hydration technique and incorporated into gel formulation suitable for topical application.

All the major absorption peaks of boswellic acid were obtained in the FTIR spectra of the physical mixture of boswellic acid and the excipients confirming the compatibility of the ingredients used for formulating the niosomes as well as the gel.The niosomes prepared using varying ratio of surfactant (span 20 and tween 20) and cholesterol were evaluated for entrapment efficiency and *in vitro* release. From the result of experimental investigations it was observed that using either of the surfactants a 1:3 ratio of surfactant and cholesterol exhibited the maximum entrapment of the drug in the core.

From the results of the release studies it was found that the maximum amount of drug was released from formulations F3 (78.37 %) and F6 (79.84 %) over a period of 24 h at an almost steady rate. The higher amount of drug release along with the higher entrapment efficiency make the formulations F3 and F6 containing surfactant to cholesterol ratio of 1:3 the most promising formulations.

The gel loaded with niosomal formulations F3 and F6 were prepared using Carbopol 934 as the gelling agent and propylene glycol as the plasticizer.

The gel formulations were found to be colorless. The formulation G1 was homogenous and non-gritty when observed under microscope whereas G2 and G4 were non-homogenous and gritty. The formulation G3 was homogenous but was gritty in its texture. The pH of the all the formulations ranged from 6.43 to 6.87 making them suitable to use topically. The drug content in all the formulations ranged from 94.97 to 98.46 % confirming the incorporation of the niosomes into the gel base.

The *in-vitro* drug diffusion study of boswellic acid niosomal gel was done using dialysis membrane in Franz diffusion cell using phosphate buffered saline (PBS) pH 6.8 enriched with 10% v/v of methanol as the diffusion medium. The formulations G1 (52.90 %) and G3 (46.34 %) containing 1% Carbopol 934 were found to release significant amount of drug from the gel over a period of 24 h. Also the formulations prepared from Tween 20 released lower amount of boswellic acid.

CONCLUSION

The objective of the present investigation was to develop non-ionic surfactant-based delivery system for topical application of boswellic for use in inflammation. The idea was to increase the bioavailability and skin permeation of boswellic acid and decrease the side effects like skin rashes that are associated with the contact of drug to skin. Niosomes are known to present a solution to these side effects and the study proved that niosomes of boswellic acid could be easily prepared and formulated as gel for topical application that can provide good skin contact and improve drug bioavailability.

Conflict of Interest; The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Acknowledgement: The authors are thankful to his/her parents.
Funding: None.

Ethics approval and consent to participate: Not applicable.
Human and animal rights: Not applicable.
Consent for publication: Not applicable.

REFERENCES

1. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, *et al*. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9(6):7204-18.

2. Nordqvist C. 'Everything you need to know about inflammation.' Med News Today. Medi Lexicon Int. 2017;5(8):6-9.

3. Manosroi A, Khanrin P, Lohcharoenkal W, Werner RG, Götz F, Manosroi W, et al. Transdermal absorption enhancement through rat skin of gallidermin loaded in niosomes. *Int J Pharm.* 2010;392:304–10.

4. Malhotra M, Jain NK. Niosomes as drug carriers. *Indian Drugs.* 1994;31:81–6.

5. Hao YM, Li K. Entrapment and release difference resulting from hydrogen bonding interactions in niosome. *Int J Pharm.* 2011;403:245–53.

6. Di Marzio L, Marianecci C, Petrone M, Rinaldi F, Carafa M. Novel pH-sensitive non-ionic surfactant vesicles: Comparison between Tween 21 and Tween 20. *Colloids Surf B Biointerfaces.* 2011;82:18–24.

7. Vyas SP. *Theory and Practice in Novel Drug Delivery System.* New Delhi: CBS Publishers and Distributors; 2009; 284–98.

8. Bharti N, Loona S, Khan MMU. Proniosomes: A recent advancement in nanotechnology as drug delivery. International Journal of Pharmaceutical Sciences Review and Research. 2012; 12 (1): 67-75.

9. Karim KM, Mandal AS, Guha A, Chatterjee S, Behera M, Kuotsu K. Niosome: A future of targeted drug delivery systems. Journal of Advanced Pharmaceutical Technology & Research. 2010; 1(4): 374-380

10. Agrawal A, uyal N, Kukreti G, Yadav C. Niosomes as targeted drug delivery systems. International Journal of Pharmaceutical Sciences Review and Research. 2012; 12(1), 53-60

11. Pal P, Shams S, Alam S. Formulation and Evaluation of Herbal Gel of Boswellia Serrata for the Management of Gout. International Journal of Pharmaceutical Research Scholars. 2014; 3(3): 242-250.

12. Qumbar M, Ameeduzzafar, Imam SS, Ali J, Ahmad J. Formulation and optimization of lacidipine loaded niosomal gel for transdermal delivery: In-vitro characterization and in-vivo activity. Biomed Pharmacother 2017; 93: 255-266

13. Imam SS, Aqil M, Akhtar M, Sultana Y, Ali A. Formulation by design-based proniosome for accentuated transdermal delivery of risperidone: in vitro characterization and in vivo pharmacokinetic study, Drug Deliv 2015; 22(8): 1059–1070.

14. Ahad A, Aqil M, Kohli K, Sultana Y, Mujeeb M, Ali A. Formulation and optimization of nanotransfersomes using experimental design technique for accentuated transdermal delivery of valsartan, Nanomedicine 2012; 8: 237– 249

15. Dantas MGB, Reis SAGB, Damasceno CMD, Rolim LA, Rolim-Neto PJ, Carvalho FO, Quintans-Junior LJ, da Silva Almeida JRG. Development and Evaluation of Stability of a Gel Formulation Containing the Monoterpene Borneol. The Scientific World J 2016. Dx.doi.org/10.1155/2016/7394685