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International Journal of Pharmaceutical Sciences and Drug Research 2015; 7(1): 13-21

Research Article

ISSN: 0975-248X
CODEN (USA): IJPSPP

Formulation and Evaluation of Nasal Niosomal *in situ* Gels of Loratadine

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ABSTRACT

Loratadine is an antihistaminic drug, used in the treatment of allergic inflammation. Poor bioavailability of the drug from conventional dosage forms is especially attributable to mucociliary clearance and transient residence time. These problems can be reduced by the employment of niosomal *in situ* gelling system. *In situ* gelling of niosomal drops was developed to maintain the drug localization for extended period of time. The niosomal *in situ* gel formulation was transformed into gel once it is instilled into the nasal cavity. Niosomes were formulated using various surfactants (span 20, 40, 60 and 80) in different ratios using thin film hydration technique. Niosomes were evaluated for particle size, drug entrapment efficiency and *in-vitro* drug release. Niosomes prepared using cholesterol and span 60 in the ratio 1:1 (F3) showed higher entrapment efficiency (94.87%) and *in-vitro* drug release (59.90%) was optimized. The optimized niosomes were developed into *in situ* gel (pH induced and thermoreversible). The gels were evaluated for gelling capability, pH, viscosity, drug content and in-vitro drug release. Ex-vivo permeation was performed for optimized *in situ* gels (G2 and T5). The flux (Jss) and Permeability Coefficient (Kp) was found to be higher for G2. Hence niosomal *in situ* gelling system may have its potential applications than the conventional nasal formulations and to improve the bioavailability of the drug through its longer residence time and ability to sustain drug release with minimal loss of drug.

Keywords: Loratadine, Niosomes, Spans, Carbopol, Poloxamer, Sustained release.

INTRODUCTION

Loratadine (LOR) is an antihistaminic drug employed in treatment of allergies like rhinitis and urticaria. Loratadine, once given orally, is well absorbed from the alimentary tract and reaches peak plasma levels within 1–1.5 hours. It undergoes fast first-pass hepatic metabolism that results in poor oral bioavailability of 40%. So to bypass the liver, an alternate route of administration would be preferred. [1]

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Received: 25 September, 2014; **Accepted:** 30 October, 2014

Transmucosal routes of drug delivery provide the benefits of bypassing first-pass effect and avoidance of presystemic elimination of GI tract. Therapeutic result could also be achieved in smaller dose of a selected drug. Intranasal drug delivery may be a promising transmucosal route for administration of drugs because it possesses massive absorptive surface area with high vascularity. [2]

Drug delivery through niosomes is one of the approaches to obtain localized drug action since their size and low permeability through epithelium and connective tissue keep the drug localized at site of administration. Niosomes function as drug depots that release the drug in a controlled manner.

However, the disadvantage associated with the nasal route is fast elimination of the instilled drug from the

nasal cavity by mucociliary clearance. This limits the time accessible for drug absorption from the applied dosage form and therefore ends up in poor nasal bioavailability. [3] So to prevent rapid mucociliary clearance and improve the residence time in situ gelling system is utilized. These systems adhere onto the mucus and increase the residence time. This intensifies the contact between nasal membrane and the the drug and facilitates the drug absorption which results in augmented bioavailability. [3]

Niosomal *in situ* gel is used as an efficient vehicle to enhance the patient compliance by reducing the frequency of administration, sustain the drug release and enhance bioavailability of Loratadine. [4]

Table 1: Composition of niosomes

Surfactant used	Formulation Code	Cholesterol Content	Surfactant	Cholesterol : Surfactant
Span 60	F1	50	50	1:1
	F2	50	100	1:2
	F3	100	100	1:1
	F4	100	200	1:2
	F5	150	150	1:1
	F6	150	300	1:2
	F7	100	300	1:3
Span 40	F8	50	50	1:1
	F9	50	100	1:2
	F10	100	100	1:1
	F11	100	200	1:2
	F12	150	150	1:1
	F13	150	300	1:2
	F14	100	300	1:3
Span 80	F15	50	50	1:1
	F16	50	100	1:2
	F17	100	100	1:1
	F18	100	200	1:2
	F19	150	150	1:1
	F20	150	300	1:2
	F21	100	300	1:3
Span 20	F22	100	100	1:1
	F23	100	200	1:2
	F24	150	300	1:2
	F25	200	400	1:2
Span 60+Span 40	F26	100	100+100	1:2
	F27	100	125+75	1:2
	F28	100	75+125	1:2

MATERIALS AND METHODS

Loratadine was a kind gift sample from Vasudha Pharma Chem Ltd, Hyderabad. Cholesterol, span 20, span 40, span 60, span 80, methanol, chloroform, Methyl Cellulose were obtained from S.D Fine chemicals, Mumbai. Carbopol was gift sample from Loba Chemie Pvt Ltd, Mumbai. HPMC K4M was procured from Colorcon Asia Pvt. Ltd, Goa. All other reagents used were of analytical grade.

Preparation and Evaluation of Loratadine Niosomes

Preparation of niosomes

Loratadine niosomes were prepared using lipid film hydration technique with non ionic surfactants namely Span 20, Span 40, Span 60 and Span 80. Drug, Surfactant and cholesterol in different ratios (Table 1) were accurately weighed and dissolved in 15 ml mixture of chloroform and methanol (2:1 v/v). The contents were subjected to evaporation in a Rota evaporator at 60°C for 30 minutes at a speed of 100 rpm and reduced pressure of 25 mm Hg for solvent removal. The resulting film was hydrated with 10 ml of phosphate buffer saline pH 7.4. The obtained colloidal dispersion was sonicated using bath sonicator for 20 min. The niosomal suspension was left to mature overnight at 4°C. [4]

Preparation of *in situ* gelling systems

Preparation of pH induced *In situ* gelling system

Optimized niosomal formulation was selected for the preparation of *in situ* gel. The *in situ* gels of Loratadine niosomes were prepared by using Hydroxy Propyl Methyl Cellulose (K4M) and Carbopol 940 and Carbopol 934. In order to reduce the acidic nature of the formulation and to improve the gelling properties, HPMC K4M was used in combination with carbopol. Niosomal *in situ* gels were prepared by adding viscosifier (HPMC K4M) to the suspension and then gelling agent (carbopol) was added and allowed to hydrate overnight as shown in the Table 2 and 3. The solution was made isotonic with sodium chloride (0.9%). Benzalkonium chloride was added as a preservative. The prepared gels were filled in glass vials and stored in refrigerator at a temperature of 4 to 8°C.

Preparation of Thermo reversible *In situ* gelling system

Thermo reversible *in situ* gels were prepared by cold method described by Schmolka *et al* [1] The niosomal dispersions were refrigerated and stored at 4°C. Poloxamer 407 and Methyl Cellulose were added slowly with continuous stirring and allowed to hydrate overnight as shown in the Table 4. Potential drawbacks of pluronic gels include their weak mechanical strength, rapid erosion, and the non-biodegradability. So it is used in combination with other bioadhesive polymers, so methyl cellulose was used in combination with poloxamer. The solution was made isotonic with sodium chloride (0.9%). Benzalkonium chloride was added as a preservative. The prepared gels were filled in glass vials and stored in refrigerator at a temperature of 4 to 8°C.

Preliminary Studies

FTIR Studies: The drug excipient compatibility was determined by Shimadzu 8400 S FTIR using KBR pellets of 0.1 mm. Samples of pure drug and physical mixtures of drug and excipients were scanned in the range between 400-4000 cm^{-1}.

FTIR spectrum of pure drug and mixture of drug and polymers are shown in Fig. 1, 2 and 3. From the spectral study, as shown in Table 5, 6 and 7 it was observed that there was no significant change in the peaks of pure drug and drug polymer mixture. Hence, no specific interaction was observed between the drug and the polymers used in the formulations.

Evaluation of Niosomes

Vesicle shape and size analysis of niosomes: Size and shape of the vesicles were determined using optical microscopy and SEM (Hitachi S 3700N).

Table 2: Formulation of niosomal pH induced *in situ* gels using carbopol 934 and HPMC K4M

Ingredients	G1	G2	G3	G4	G5	G6	G7	G8
Niosomal dispersion	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
Carbopol 934 (%w/v)	0.1	0.2	0.2	0.2	0.3	0.3	0.4	0.5
HPMC K4M (%w/v)	0.3	0.2	0.3	0.4	0.3	0.4	0.5	0.5
Sodium chloride (%w/v)	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Benzalkonium chloride (%v/v)	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001

Table 3: Formulation of niosomal pH induced *in situ* gels using carbopol 940 and HPMC K4M

Ingredients	G9	G10	G11	G12	G13	G14	G15	G16
Niosomal dispersion	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
Carbopol 934 (%w/v)	0.1	0.2	0.2	0.2	0.3	0.3	0.4	0.5
HPMC K4M (%w/v)	0.3	0.2	0.3	0.4	0.3	0.4	0.5	0.5
Sodium chloride (%w/v)	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Benzalkonium chloride (%v/v)	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001

Table 4: Formulation of niosomal thermoreversible *in situ* gels using poloxamer 407 and methyl cellulose

Formulation code	Niosomal Dispersion	Poloxamer 407 (% w/v)	Methyl cellulose (% w/v)	Sodium chloride (% w/v)	Benzalkonium chloride (% w/v)
T1	10 ml	16	2	0.9	0.001
T2	10 ml	16	1	0.9	0.001
T3	10 ml	17	2	0.9	0.001
T4	10 ml	17	1	0.9	0.001
T5	10 ml	18	2	0.9	0.001
T6	10 ml	18	1	0.9	0.001
T7	10 ml	19	2	0.9	0.001
T8	10 ml	19	1	0.9	0.001
T9	10 ml	20	2	0.9	0.001
T10	10 ml	20	1	0.9	0.001

Table 5: Characteristic IR peaks of Loratadine plain drug

Functional group	Reported frequencies (cm^{-1})	Observed frequency (cm^{-1})
N-H stretching	3300-3500	3443
C-O stretching	1000-1300	1016
C-Cl stretching	600-800	617

Table 6: Characteristic IR peaks of Loratadine pH induced *in situ* gel

Functional group	Reported frequencies (cm^{-1})	Observed frequency (cm^{-1})
N-H stretching	3300-3500	3443
C-O stretching	1000-1300	1016
C-Cl stretching	600-800	617

Table 7: Characteristic IR peaks of Loratadine thermo reversible *in situ* gel

Functional group	Reported frequencies (cm^{-1})	Observed frequency (cm^{-1})
N-H stretching	3300-3500	3446
C-O stretching	1000-1300	1018
C-Cl stretching	600-800	617

Particle size measurement: The average diameter of sonicated vesicles was determined by laser diffraction technique using Horiba particle size analyzer.

Zeta potential: Zeta potential was determined using Zetasizer (Malvern Instruments). Measurements were performed on the same samples prepared for size analysis. Zeta potential indicates the degree of repulsion between adjacent, similarly charged particles in dispersion system.

Entrapment Efficiency (EE): The entrapment efficiency of niosomes was estimated by ultracentrifugation method where the niosomal dispersions were centrifuged at 14000 rpm for 90 minutes. The clear supernatant from the resulting solution was diluted appropriately using phosphate buffer saline pH 7.4 and analyzed for Loratadine spectrophotometrically. The percent of encapsulation efficiency (EE %) was calculated using the following equation:

$$EE\% = \frac{[\text{Total drug}] - [\text{free drug}]}{\text{Total drug}} \times 100$$

***In-vitro* drug release**

In-vitro release studies were carried out using bichambered donor receiver compartment (Franz diffusion cell). Donor compartment was covered with Himedia dialysis membrane (cut-off molecular weight: 12000-14000) which was previously soaked in simulated nasal fluid (SNF) pH 7.4. The temperature was maintained at 37°C, with the help of a thermostat. Simulated nasal fluid pH 7.4 was placed in the receptor cell. A 1 ml sample of each formulation was transferred to the diffusion cell. Samples were withdrawn from the receptor cell at specified time intervals of 1, 2, 3, 4, 5, 6, 7 and 8 hours. Each time immediately after the removal of the sample, the medium was compensated with fresh SNF (pH 7.4). The samples were analyzed for drug content using a UV spectrophotometer at 247 nm.

Evaluation of Niosomal *in situ* gel

Visual Appearance and pH: The formulations were observed for the presence of any particular matter. The pH of niosomal *in situ* gels was measured in triplicate using digital pH meter.

***In-vitro* gelation study:** Gelling strength of formulations was evaluated by placing a drop of polymeric solution in vials containing 2 ml of freshly prepared simulated nasal fluid pH 7.4, equilibrated at 37°C. The gel formation and time taken for gelation was assessed visually.

Drug content: Drug content of niosomal *in situ* gel was determined by adding n-propanol to the formulation

for lysis of the vesicles. 0.1 ml of niosomal *in situ* gel was then diluted to 100 ml with SNF of pH 7.4. Drug content was estimated spectrophotometrically at 247 nm.

Viscosity Studies: Viscosity of the formulations was determined using Brookfield synchroelectric viscometer (DV Pro II) fitted with S-63 spindle at 5, 10, 20, 50 and 100 rpm.

***In-vitro* drug release studies:** *In-vitro* release studies were carried out using Franz diffusion cell and the temperature was adjusted to 37±0.5°C. Samples were withdrawn at periodic intervals for 8 hours and replaced with fresh buffer solution to maintain sink conditions. The drug content was analyzed using UV-Visible Spectrophotometer at 247 nm using simulated nasal fluid pH 7.4 as blank.

***Ex-vivo* permeation studies**

The use of natural membranes is very important to predict the real drug release characteristic. So in this experimental section of the study goat nasal mucosa was chosen because of easy availability and handling. Fresh nasal tissue extracted from the nasal cavity of sheep was used. Tissue was inserted in the diffusion cell with permeation area of 0.785 cm^2. Temperature was adjusted to 37±0.5°C. *In situ* gel was placed in the donor compartment. At predetermined time intervals, sample was withdrawn, and replaced with fresh SNF pH 7.4 to maintain sink conditions. The samples were analyzed using UV-Visible Spectrophotometer at 247 nm using simulated nasal fluid pH 7.4 as blank. Cumulative amount of drug permeated in $\mu g/cm^2$ were calculated and plotted against time. Drug flux ($\mu g/hr/cm^2$) at steady state was calculated by dividing the slope of the linear portion of the curve by the area of the exposed tissue and the permeability coefficient was deduced by dividing the flux by initial drug load.

Stability studies: The optimized niosomal *in situ* gel was placed in vials and sealed with aluminium foil for a short term accelerated stability study at 25°±2°C/ 60±5% RH and 5°±3°C as per modified International Conference on Harmonization guidelines. Samples were analyzed every 30 days for appearance, gelling studies and drug content.

RESULTS AND DISCUSSION

Evaluation of Niosomes

Vesicle shape and size of niosomes: SEM images and microscopic evaluation showed that most of the vesicles were spherical in shape as shown in Fig. 4. From the Fig 5 it was found that the diameter (nm) of niosomes was found to be in the range of 200 to 1000 nm and the average particle size was found to be 266 nm.

Zeta potential: The zeta potential of the niosomes was determined using Zetasizer and the value of the niosomes was found to be -77 mV as shown in Fig. 6 which indicates that niosomes were stable.

Entrapment efficiency: Percentage entrapment efficiency of Loratadine in niosomes was found to be in the range of 70-94 % as shown in Fig. 7. The entrapment efficiency was found to be higher (94.87%) with the formulation F3 prepared using span 60. The order of entrapment efficiency is span 60 > span 40> span 20 > span 80. The order of entrapment efficiency increased as the lipophilicity of the surfactant increased (HLB value decreased). Span 80 has the lowest HLB value but it has an unsaturated alkyl chain in its structure leading to lower entrapment efficiency. Span 60 having higher T_C, provides better entrapment. Span 80 and span 20 have low phase transition temperature so they form less rigid membrane which forms leaky membrane. So niosomes prepared using span 80 and span 20 show low entrapment efficiency.

Table 8: Evaluation of niosomal pH induced *in situ* gels

Formulation code	State of the gel	Appearance	pH	Drug content (%)	Gelation capacity
G1	Liquid	Translucent	6.8	95.36	+
G2	Liquid	Translucent	6.4	97.63	++
G3	Liquid	Translucent	6.5	96.04	+++
G4	Liquid	Translucent	6.1	93.25	+++
G5	Liquid	Translucent	6.2	90.01	+++
G6	Liquid	Translucent	6.2	92.21	+++
G7	Liquid	Translucent	5.9	89.71	+++
G8	Semi-solid	Translucent	5.8	90.62	+++

\- : No gelation
\+ : Gels slowly and dissolves
++ : Gelation immediate and remains for hours
+++ : Gelation immediate and remains for extended period of time

Table 9: Evaluation of niosomal thermoreversible *in situ* gels

Formulation code	State of the gel	Appearance	pH	Drug content (%)	Gelation capacity
T1	Liquid	Translucent	6.7	89.01	+
T2	Liquid	Translucent	6.8	91.53	+
T3	Liquid	Translucent	6.7	94.81	++
T4	Liquid	Translucent	6.6	91.76	++
T5	Liquid	Translucent	7.0	96.64	+++
T6	Liquid	Translucent	6.7	92.54	+++
T7	Liquid	Translucent	6.8	93.68	+++
T8	Liquid	Translucent	6.8	94.92	+++
T9	Semi-solid	Translucent	7.1	85.15	+++
T10	Semi-solid	Translucent	7.0	89.92	+++

\- : No gelation
\+ : Gels slowly and dissolves
++ : Gelation immediate and remains for hours
+++ : Gelation immediate and remains for extended period of time

Table 10: *Ex vivo* permeation data for optimized *in situ* gel formulations

Formulation code	Jss ($\mu g/cm^2/h$)	Kp (cm/h)
G2	2.874	0.00287
T5	2.687	0.00268

Table 11: Stability data of optimized *in situ* gel formulations

Optimized *In situ* gel Formulations	Storage conditions	Drug content			
		Initial	1 month	2 months	3 months
G2	5°C±3°C	97.63%	96.41%	94.83%	93.16%
	25°C±2°C/60±5% RH	97.63%	95.16%	93.54%	92.86%
T5	5°C±3°C	96.64%	95.89%	95.11%	94.73%
	25°C±2°C/60±5% RH	96.64%	95.03%	92.65%	91.96%

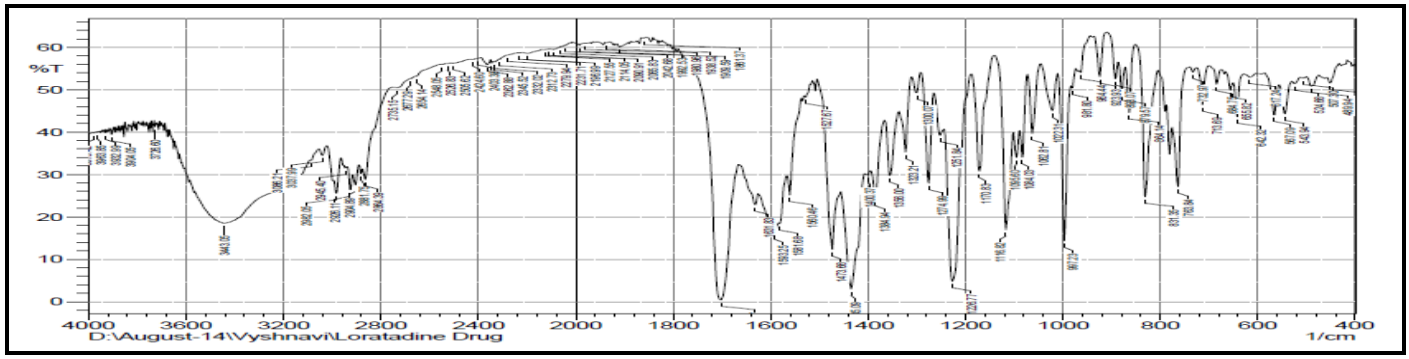

Fig. 1: IR spectrum of drug

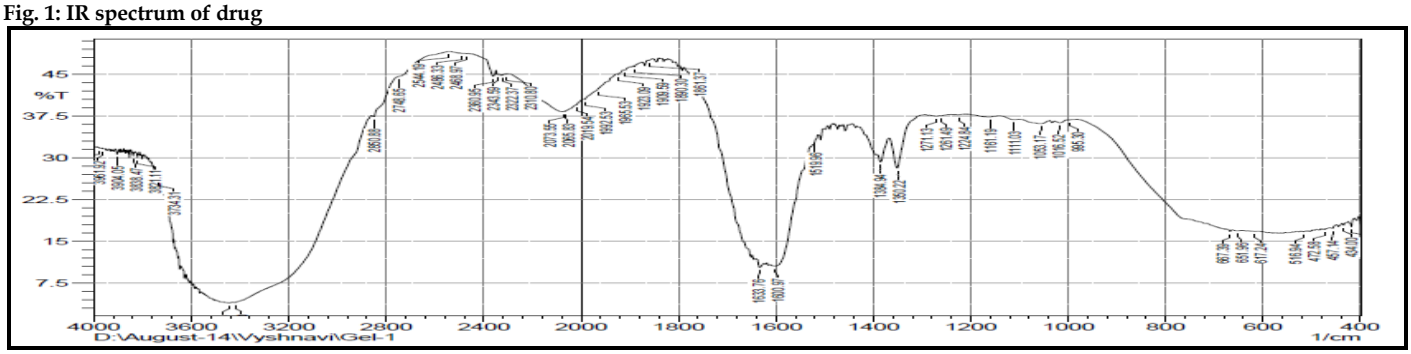

Fig. 2: IR spectrum of drug and excipients (Span 60 + Carbopol 934 + HPMC K4M)

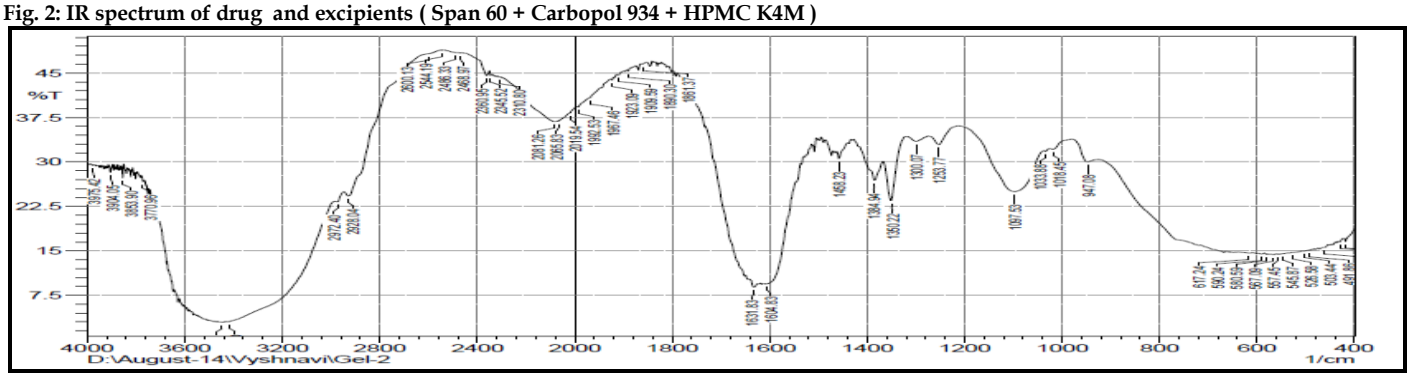

Fig. 3: IR spectrum of drug and excipients (Span 60 + poloxamer 407 + Methyl cellulose)

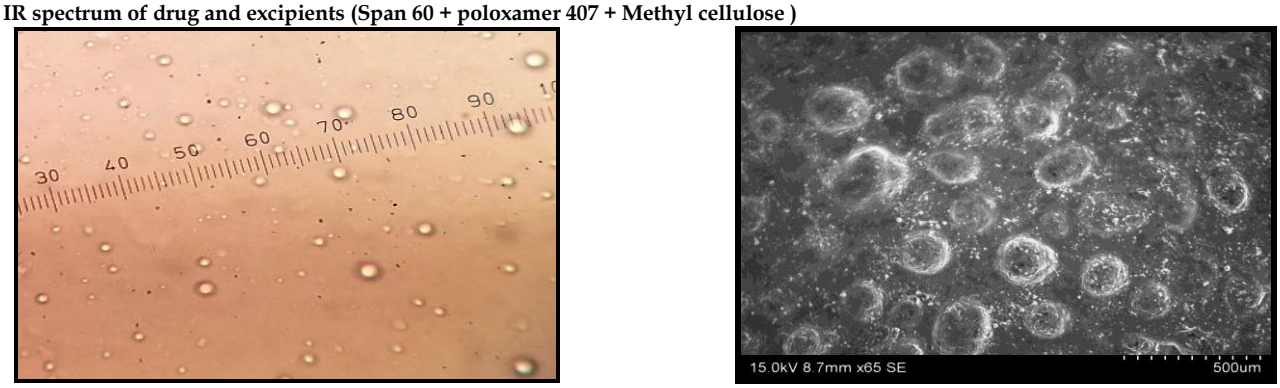

Fig. 4: Photomicrograph and SEM image of Loratadine loaded niosomes

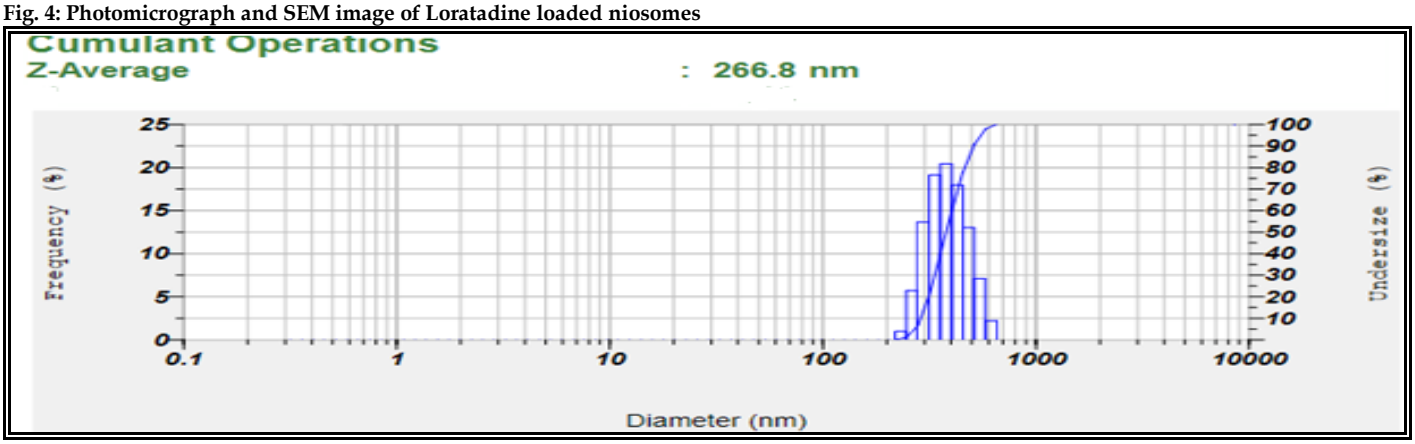

Fig. 5: Particle size analysis of niosomes

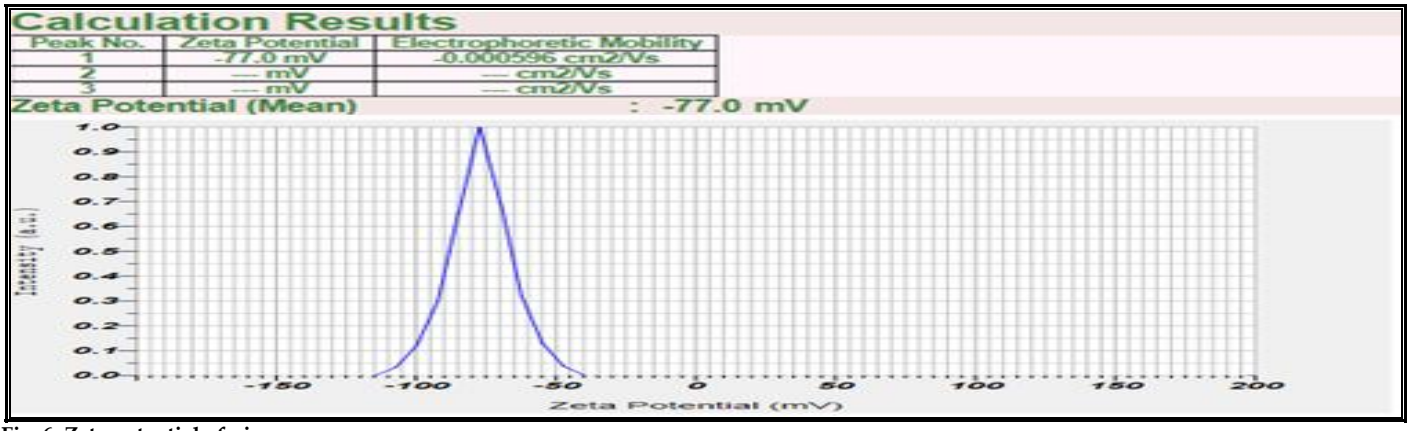

Fig. 6: Zeta potential of niosomes

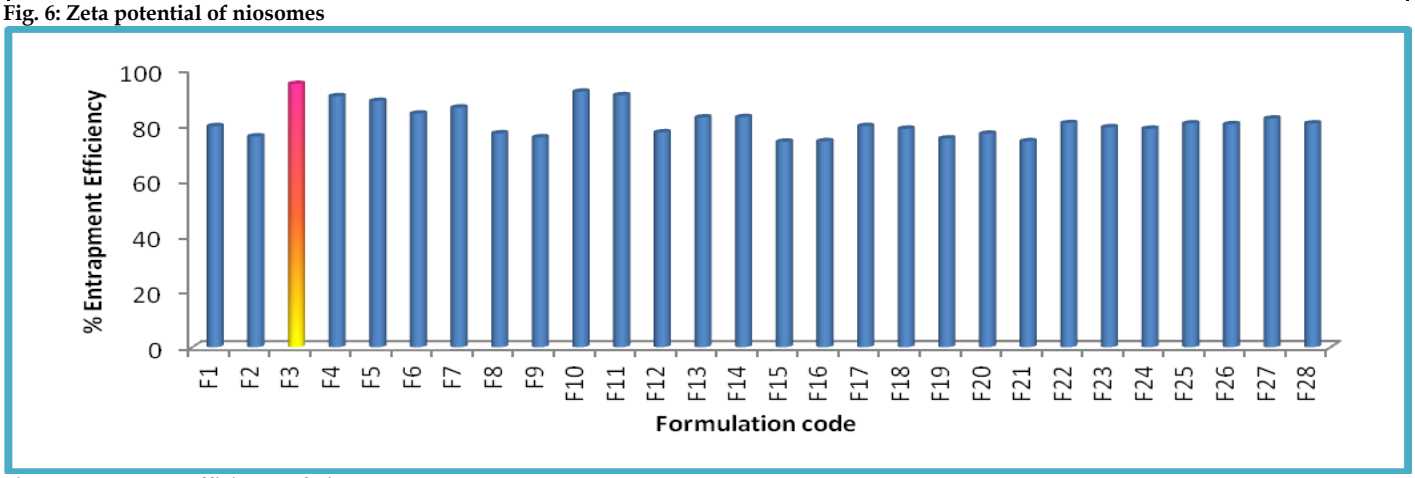

Fig. 7: Entrapment efficiency of niosomes

***In vitro* drug release:** The cumulative percentage of drug release from various niosomal formulations were shown in Fig. 8-12. The experimental studies showed that the rate of drug release depends on the percentage of drug entrapment efficiency. Formulation N3 showed higher drug release than other formulations. Hence, it was chosen to be formulated as niosomal *in situ* gel.

Evaluation of niosomal pH induced *in situ* gel

Gelation studies: From the Table 8, it was observed that the formulations G2, G3, G4, G5, G6 and G7 showed immediate stiff gelation which remained for extended period of time while G1 showed immediate gelation and remained for 2-3 hours.

Formulations G9 to G16 were unstable in nature so they were not further evaluated.

Drug content: The solutions were analyzed for drug content spectrophotometrically at 247 nm. The drug content was estimated by measuring the amount of drug present in gel. Results shown in Table 8 revealed that the drug content of all developed formulations was in the range of 89 to 97%. All the formulations exhibited fairly uniform drug content. This ensures intended delivery of drug to the site after administration of the gel formulation.

Viscosity Studies: The rheological study of the formulations exhibited decrease in viscosity on increase in shear rate because of the pseudo plastic behavior of the formulations as shown in Fig. 13 and 14.

***In-vitro* release:** The results of *in-vitro* drug release of niosomal *in situ* gel were shown in the Fig.15 and it was observed that as the concentration of polymer increased the % Drug release was decreased.

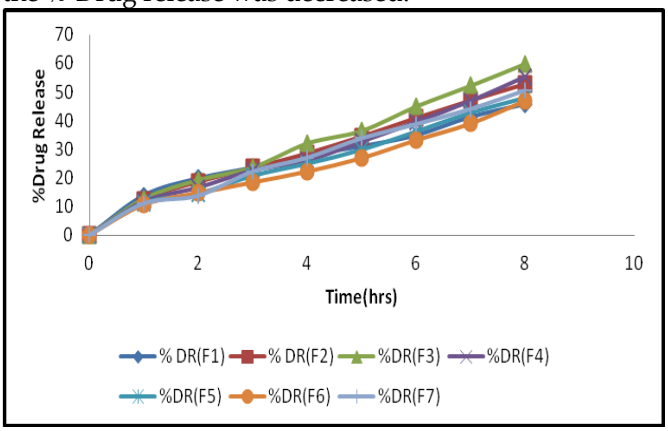

Fig. 8: *In-vitro* release profile of niosomes formulated using Span 60

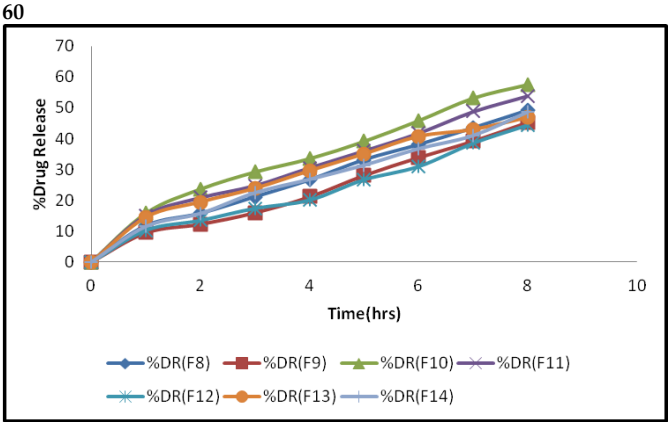

Fig. 9: *In-vitro* release profile of niosomes formulated using Span 40

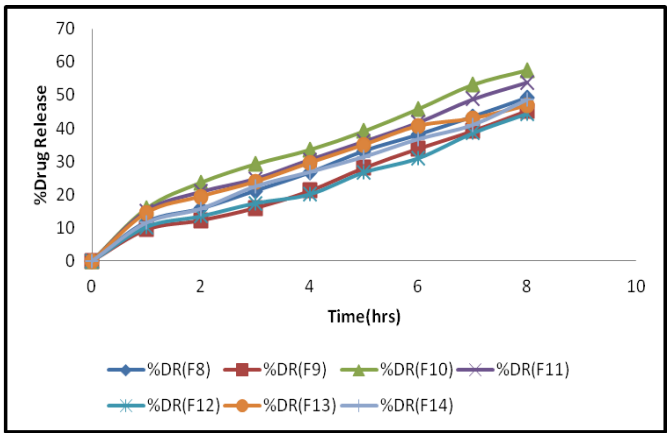

Fig. 10: *In-vitro* release profile of niosomes formulated using Span 80

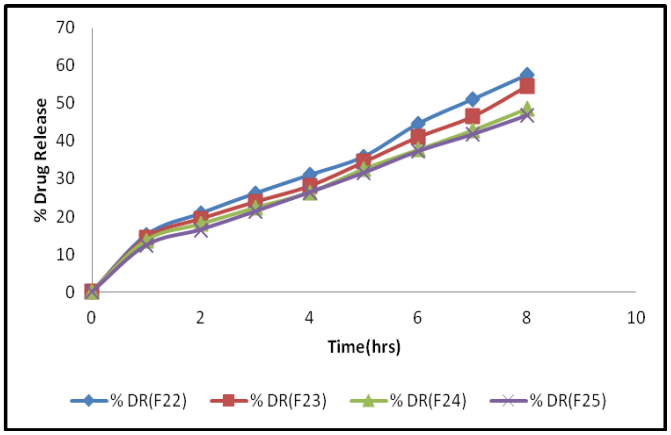

Fig. 11: *In-vitro* release profile of niosomes formulated using Span 20

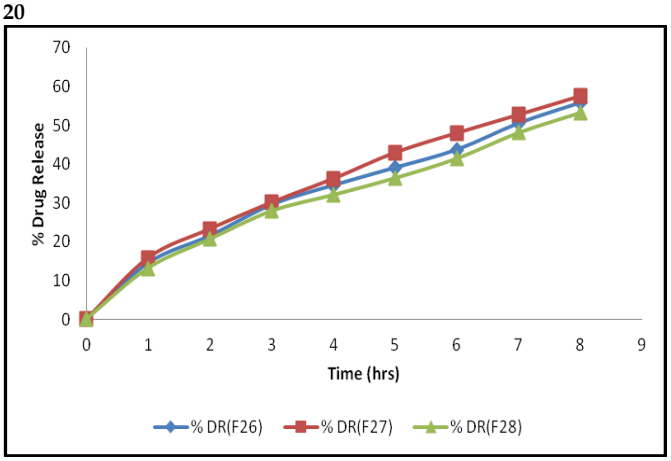

Fig. 12: *In-vitro* release profile of niosomes formulated using Span 60 and Span 40

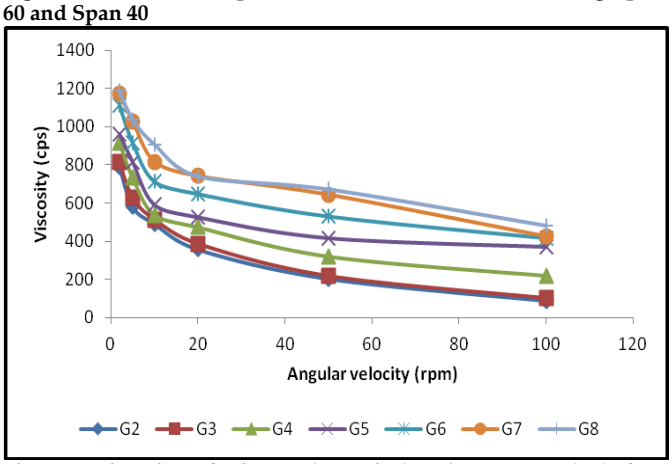

Fig. 13: Viscosity of niosomal pH induced *in situ* gels before gelation (in cps)

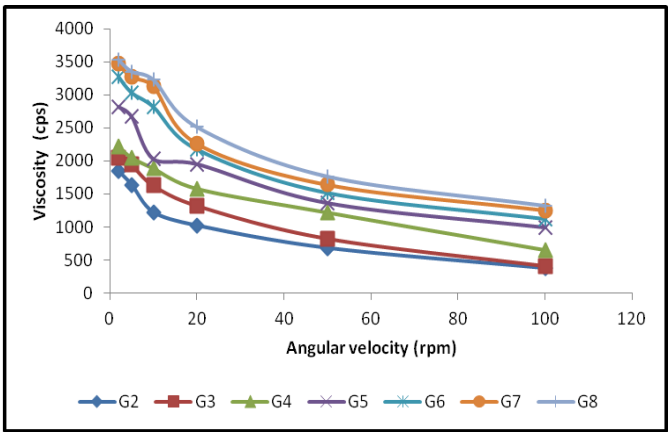

Fig. 14: Viscosity of niosomal pH induced *in situ* gels after gelation (in cps)

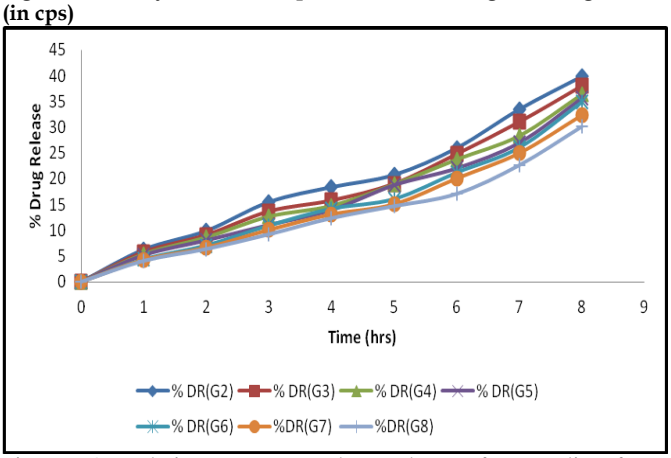

Fig. 15: Cumulative percentage drug release of Loratadine from niosomal pH induced *in situ* gel

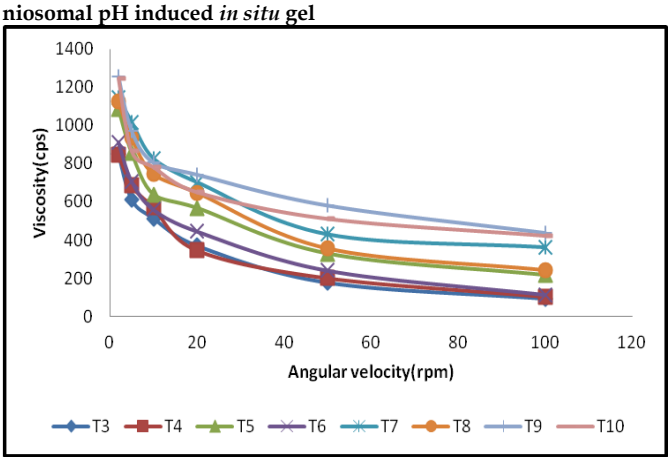

Fig. 16: Viscosity of niosomal thermoreversible *in situ* gels before gelation (in cps)

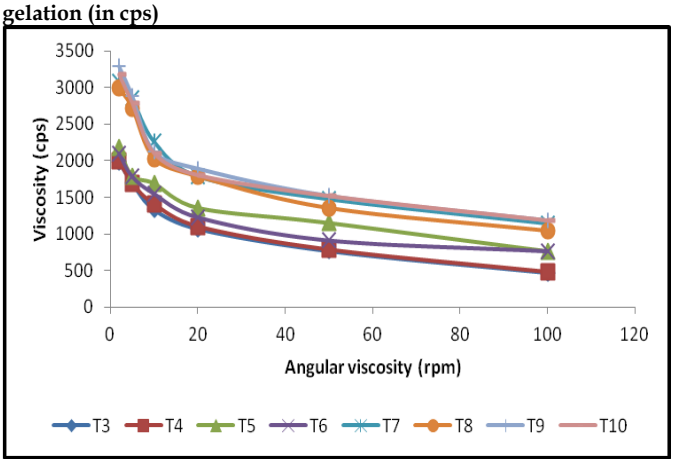

Fig. 17: Viscosity of niosomal thermoreversible *in situ* gels after gelation (in cps)

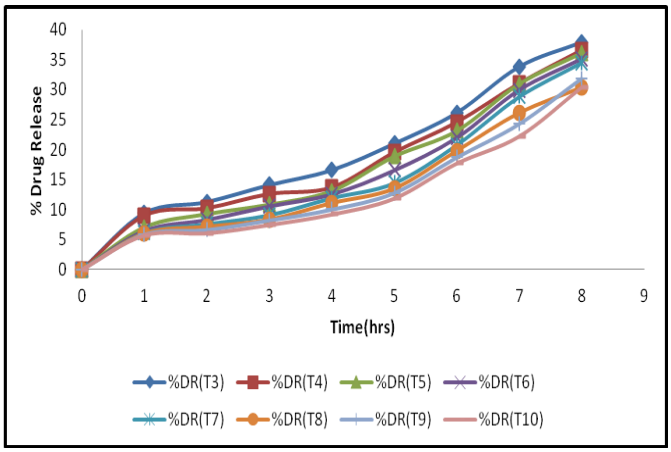

Fig. 18: Cumulative percentage drug release of Loratadine from niosomal thermoreversible *in situ* gel

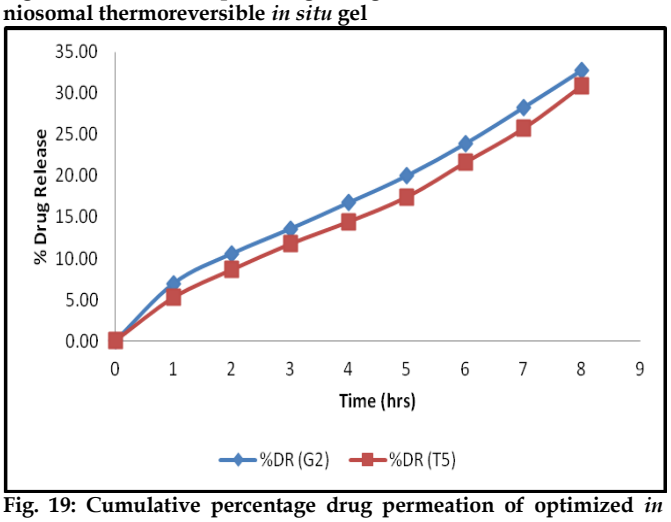

Fig. 19: Cumulative percentage drug permeation of optimized *in situ* gel formulations G2 and T5

Evaluation of niosomal thermoreversible *in situ* gel

Gelation studies: From the Table 9, it was observed that the formulations T5, T6, T7 and T8 showed immediate stiff gelation which remained for extended period of time while T3 and T4 showed immediate gelation and remained for 2-3 hours and formulations T1 and T2 showed slow gelation which has dissolved immediately.

Drug content: The solutions were analyzed for drug content spectrophotometrically at 247 nm. The drug content was estimated by measuring the amount of drug present in *in situ* gel. Results as shown in Table 9 revealed that the drug content of all developed formulations were in the range of 89 to 96%. All the formulations exhibited fairly uniform drug content. This ensures intended delivery of drug to the site after administration of the gel formulation.

Viscosity studies: The rheological study of the formulations exhibited decrease in viscosity on increase in shear rate because of the pseudo plastic behavior of the formulations as shown in Fig. 16 and 17.

***In-vitro* release:** The results of *in-vitro* drug release of niosomal *in situ* gel were shown in the Fig.18 and it was observed that as the concentration of polymer increased the % Drug release was decreased.

Optimization of niosomal *In situ* gels: pH induced *in situ* gel formulation G2 formulated using Carbopol 934 (0.2%w/v) and HPMC K4M (0.2%w/v) have shown good gelation characteristics and in vitro release of 39.84 % at the end of 8 hours.

Thermoreversible *in situ* gel formulation T5 was optimized. Though formulations T3 and T4 were showing higher release than T5, but the gelation capacity was less than T5. So formulation T5 was optimized as it was showing good gelation characteristics and the release was found to be 35.94% at the end of 8 hours.

***Ex-vivo* permeation study:** The results of *Ex-vivo* drug permeation of niosomal *in situ* gel were shown in the Fig.19.

The flux (Jss) for G2 was found to be 2.874 µg/cm²/h and for T5 it was found to be 2.687 µg/cm²/h. The permeability coefficient (Kp) for G2 was found to be 0.00287 cm/h and for T5 it was found to be 0.00268 cm/h as shown in the Table 10. The flux and permeability coefficient was found to be higher for formulation G2 indicating that niosomal pH induced *in situ* gel containing carbopol was showing more permeability coefficient and drug release than Thermoreversible *in situ* gels as it binds to Ca^{2+} ions of nasal mucosa and modifies the nasal epithelium and increases the permeability.

Stability studies: The stability studies of niosomal *in situ* gels was performed at 5°C±3°C and 25°C±2°C/ 60±5% RH for 3 months. The formulations were examined visually for precipitation. The drug content and gelling capacity were determined for every 30 days for 3 months. It was observed that there was no change in the physical appearance of the formulation and gelling capacity. The drug content was analyzed and there was marginal difference between the formulations kept at different temperatures as shown in Table 11. Niosomal *in situ* formulations retained good stability throughout the study.

From the study, it can be concluded that the niosomal *in situ* gel was able to produce sustained drug release, and is a viable alternative to conventional dosage forms by virtue of its ability to enhance bioavailability through its longer residence time in the nasal cavity. It also results in better patient compliance by reducing the frequency, minimizing side effects and ease of administration.

ACKNOWLEDGEMENT

The authors are thankful to Vasudha Pharma Chem Ltd and Loba Chemie, Mumbai, for providing gift samples for this work. We also thank Dean, Osmania University, Hyderabad and Principal, Sri Venkateshwara College of Pharmacy, Hyderabad for their kind support and encouragement to accomplish this work.

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Source of Support: Nil, Conflict of Interest: None declared.