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DESIGN, DEVELOPMENT AND EVALUATION OF LOMEFLOXACIN HYDROCHLORIDE NIOSOMAL GUM BASED IN SITU GELS FOR OTIC DRUG DELIVERY

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ABSTRACT

The aim of the present study was to design, formulate and evaluate lomefloxacin Hcl niosomal in situ gels to provide broad spectrum antibacterial activity for the treatment of ear infections aiming to increase drug concentration in the middle ear fluid, improve residence time and prolong drug release. LMN niosomes were prepared using different types of surfactants (Span20, Span 40, Span 60) with different molar ratios with respect to cholesterol (1:4, 1:6, 7:4, 7:6). Based upon the entrapment efficiency percentage (EE%) and acceptable release percentage of LMN after 8 hr and 24 hr formula F12 was chosen as the optimized formula as EE% found to be 90.3%, PS 537 nm and % drug released (Q8 64.8 %, Q24 87.9 %). Thus, niosomal in situ gels of the optimized formula F12 were prepared using Guar gum (GG) and Xanthan gum (XG) with the combination of Carbopol 940 as the gelling agent, Hydroxy propyl methyl cellulose (HPMCk100) and sodium alginate as viscosity imparting agents. The prepared formulations were evaluated for physical appearance, pH, gelling time, spreadability, drug content, rheological characteristic, in vitro drug release studies, accelerated stability and antimicrobial activity. The study revealed that physical appearance, pH, viscosity and drug content of all developed formulations were found to be satisfactory. The most effective combination of polymers were noted in F3 (0.2% GG, 0.4% CP, 0.5% SA) which gave satisfactory in situ gel forming formula, with a drug release 53.2% over7 hr and F8 (0.2% XG, 0.4% CP and 0.5% SA) showed release of 58.2% over7 hr and 100% for market product 0.3% at 5 hrs. The optimized formulations exhibited required viscosity with a remarkable increase in the viscosity after gelling. The optimized formulations were stable under accelerated temperature

conditions. Therefore, the developed niosomal gum based in situ gel therapeutically efficacious and can acts as a suitable, valuable alternative to the conventional systems to reduce side effects and improve patient compliance.

1. INTRODUCTION

Otitis Media is an infection that affects the middle ear and arises in the tympanic cavity (the hollow space between the tympanic membrane or ear drum and inner ear), there are two types of otitis media (i) acute and (ii) chronic otitis media. Chronic suppurative otitis media (CSOM) is inflammation of greater than two weeks that results in an initial episode of acute otitis media**,** it is characterized by a presence of discharge from the middle ear through tympanic perforation. (Jose, 2004). Ear infections can be treated with systemic antibiotics results in certain disadvantages such as antibiotic resistance and adverse effects like nausea, diarrhea and pseudomembranous colitis(Sato et al., 2008). Ototopical drug delivery presents a highly promising alternative to oral antibiotics therapeutics to treat ear canal infections and middle ear infections across the tympanic membrane (TM) and in patients with punctured TMs or tympanostomy tubes (Koulich et al., 2010) and could potentially enhance the local bioavailability of drug while minimizing antibiotic exposure of normal flora elsewhere in the body, which together reduce the selective pressures responsible for antibiotic resistance. On the other hand, ear drop suffers from drawback such as short residence time in ear so it is necessary to control the drug loss from the ear, in order to provide a prolonged delivery of drug. Therefore, insitu gelling system is very useful technique for enhancing the bioavailability of droppable formulations which are easily washed away from the site of administration, they can be delivered to the external, epidermal surface of the tympanic membrane in a liquid-like form then, upon delivery transform to a solid-like state such that the composition remains localized against the tympanic membrane and prolong drug release. Moreover, niosomes have the ability to deliver drug at target site in sustained manner which in turn will enhance drug efficacy. Delivery of such formulations to the tympanic membrane can provide more effective ways to treat outer and middle ear disorders thereby reduces the need for frequent administration and thus improves patient compliance. Hence, the aim of the present work was to design, formulate and evaluate ten vesicular niosomal droppable gum based in situ gels of a second generation fluoroquinolone derivative drug Lomefloxacin HCl (LMN) used for the treatment of chronic suppurative otitis media with the objective to increase drug concentration in the middle ear fluid, improve residence time and prolong drug release, improving the therapeutic efficacy of the drug and reducing the frequency of

administration to improve the patient compliance. Guar gum (GG) and Xanthan gum (XG)were used as gelling agent with the combination of Carbopol940 (CP),Hydroxyl Propyl Methyl Cellulose (HPMCk100) and Sodium Alginate were added to build up the viscosity of the gel. The developed formulations were evaluated for appearance, pH, gelling time, spreadability, drug content, rheological characteristic, in vitro drug release studies and accelerated stability.

2. EXPERIMENTAL

2.1 Materials

Lomefloxacin HCl was kindly supplied by(Orchidia Pharm., Egypt), Span20, Span 40, Span 60,Cholesterol PB(95%), guar gum were purchased from (Sigma -Aldrich Co. St. Louis, USA), Xanthan gum (Lucid colloids Ltd), hydroxyPropyl Methyl Cellulose k100 (Microlabs), Carbopol 940 was kindly provided by (Luna Pharma, Cairo, Egypt)., Sodium alginate (Microlabs), Benzylkonium chloride (Hi-pharm Chemicals Co., Cairo, Egypt) and all other chemicals and reagents were Laboratory grade obtained from (Sigma-Aldrich Co. and El –Nasr Co., Cairo, Egypt).

2.2 Preparation of niosomes

LMN 0.3% w/v loaded niosomes were prepared using reverse evaporation technique. Accurately weighed quantity of surfactants and cholesterol in different molar ratios were dissolved in 20 ml chloroform – methanol mixture (2:1 v/v) into a long necked quick fit round-bottom flask (Szoka. et al., 1978).Organic mixture was slowly evaporated at 60°C under reduced pressure, using a rotary evaporator at 120 rpm such that a thin dry film of the components was formed on the inner wall of the rotating flask. The film was then redissolved with 15 ml of ether and 10 ml of phosphate buffered saline (PBS, pH7.4),accurately weighed quantity of drug was added to give a final niosomal dispersion concentration of 0.3% w/v then mixture was sonicated for 2min.,handly swirled and resonicated again for 2 min. The resultant opalescent dispersion was evaporated by rotating the flask in a water bath using a rotavapor under normal pressure in order to ensure complete disrupt of the gel formed. To ensure complete evaporation of organic mixture add 5 ml of phosphate buffered saline (PBS, pH7.4) then, evaporation continued for more 15 min, suspension was left to mature overnight at 4°C as illustrated in Table (1).

2.3 Evaluation of the prepared LMN niosomes

2.3.1 Morphology and Size of niosomes

Morphology examined by optical microscopy in magnification of 40x using (Leica Image analyzer). A drop of the formulation diluted by distilled water placed over a glass slide and fixed over the microscope, photographed and morphologically observed. (Agarwal. et al., 2001) and particle size were performed using Malvern zetasizer nanoseries, to avoid interference from particulate matter in the dispersion medium, samples were diluted with deionized double distilled water passed through a 200 nm filter.

2.3.2 Entrapment efficiency (EE%)

LMN niosomes were obtained by ultra centrifugating of the niosomal suspension at 50,000rpm for 1h using a cooling centrifuge at 4°C(Optima TLX, Beckman Coulter, Minnesota, USA).The niosomes pellets were separated from the supernatant and were washed twice, each time with 15 ml phosphate buffered saline, and recentrifuged again for 1h. The amount of entrapped lomefloxacin was determined by lysis of the separated vesicles with 5 ml of isopropanol, the volume was completed to 10ml with phosphate buffered saline and covered with parafilm to prevent evaporation.(Guinedi et al., 2005).The concentration of the drug was estimated spectrophotometrically at 281 nm (Shimadzu UV-1600 Pharma spec, Japan).

The entrapment efficiency is defined as follows

Percent of Entrapmet Efficiency = Total Drug–Diffused Drug / Total Drug×10

2.3.3-In-vitro drug release study.

The drug release study of niosomal suspension was carried out using Hanson Research device USP apparatus type I, at 37±0.5°C with stirring speed of 50 rpm using dialysis membrane of 12000- 14000 M.wt soaked for 24 hours in distilled water 1.5 mg equivalent of 0.3 % w/v of niosomal suspension was transferred to a glass cylinder having length of 10 ml and diameter of 2.5 cm fitted at its lower end with the presoaked cellulose membrane then, the glass tube was suspended in dissolution vessel containing freshly prepared phosphate buffered saline (7.4), five milliliters samples were withdrawn at specified time intervals for a total period of 24 hours. The volume withdrawn was replaced by fresh volume of dissolution medium. The filtered samples were analyzed by UV Visible spectrophotometer at 281 nm using receptor medium as a blank.

2.3.4-Stability studies

The formulation which showed best in vitro release was selected for stability studies. The accelerated stability studies were conducted according to the ICH guidelines based on Q1C for a period of 3months.

3-RESULT AND DISCUSSION

The morphology of niosomes were spherical unilamellar and homogenous in dispersion as showen in fig.1. It was obvious from Table 1 that**,** The mean particle size of formulations were in nanometer rang ranged from(537-14000 nm) the smallest PS was given by F12 which is composed of highly hydrophobic surfactant Sp60: CH at 7:6 molar ratio this might be explained by increasing cholesterol content contributes in increasing the hydrophobicity, resulting in smaller vesicles and the largest was showen by F4 composed of Span 20:CH at 1:6 molar ratio (Alsarra, et al 2005). The highest entrapment efficiency of loaded drug was observed in F12 (90.3%) containing span 60,this may be due to lower HLB of span60 (HLB 4.6) with longer alkyl chain than span 20 (HLB 8.6),regarding the effect of cholesterol molar ratio on entrapment efficiency, as the cholesterol concentration increased from 4 to 6 EE% increased and the lowest obtained with the formula F4 (39.7 %) containing span 20.The in vitro release profiles of loaded niosomes were occurred in two biphasic release processes initial (8 hr.) and slow phase (24 hr.) as showen in fig.2a,b. Results pointed to the sustained released characteristics of nisomes, where they act as reservoir for continous release of drug, the lowest drug release after 8 and 24 hours was shown by F12 (Q8 64.8 %, Q24 87.9 %). This could be explained to the long alkyl chain and low HLB of sp60 and to the high molar ratio of Cholesterol, which has the property of abolishing the gel to liquid transition of niosomes which could prevent the leakage of drug from the niosomal formulation. (Mokhtar M, et al 2008). Amount of drug released from different surfactants at different time intervals could be ranked as follow: span 20 > span 40> Span 60. The optimized formula F12 (Sp60:CH 7:6)was selected, Since it has the highest entrapment efficiency and smallest particle size when compared to all the other formulations. stability was tested for it at ICH guidelines at 40°C ± 2 °C & RH 75 % ± 5% and found to be stable with the results of (Q8 64%, Q24 86.18%) after the study period of three months.

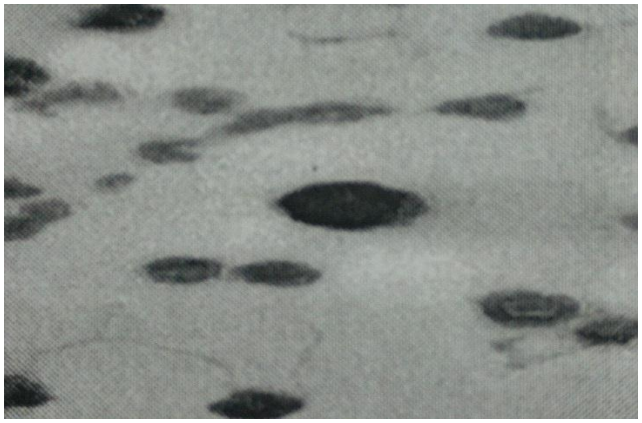

Fig 1: Photomicrograph of loaded niosomes.

Table 1: Composition and physicochemical evaluation of LMN niosomes.

Formula code Surfactant: Cholesterol. molar ratio	Particle size (µm)	EE%
F1 (Sp_{20}1:CH4)	1.22	44.5%
F2 (Sp_{40}1:CH4)	1.13	49.6%
F3 (Sp_{60}1:CH4)	1.08	53.2%
F4 (Sp_{20}1:CH6)	1.40	39.8%
F5 (Sp_{40}1:CH6)	1.18	44.3%
F6 (Sp_{60}1:CH6)	1.10	49.4%
F7 (Sp_{20}7:CH4)	0.753	64.1%
F8(Sp_{40}7:CH4)	0.621	71.6%
F9(Sp_{60}7:CH4)	0.537	75.9%
F10(Sp_{20}7:CH6)	0.612	70.4%
F11(Sp_{40}7:CH6)	0.544	86.8%
F12(Sp_{60}7:CH6)	0.537	90.3%

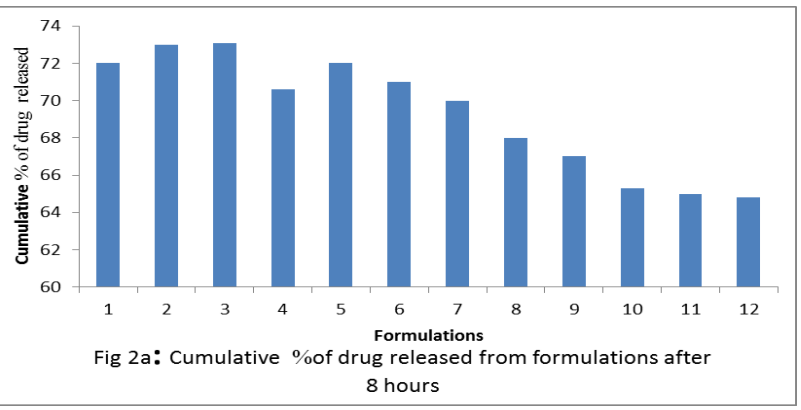

Fig 2a: Cumulative %of drug released from formulations after 8 hours

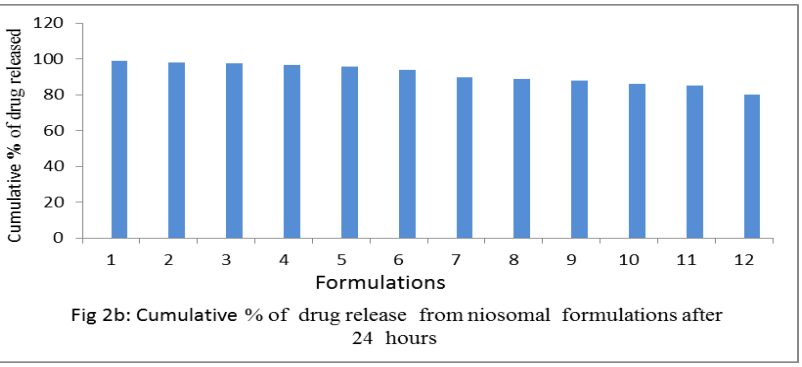

Fig 2b: Cumulative % of drug release from niosomal formulations after 24 hours

4.Formulation of niosomal *in situ* gels

The optimized formula F12 was incorporated in different insitu gel basses. Calculated amount of niosomal dispersion (equivalent to 0.3% w/w of LMN) were centrifuged at 50,000 rpm at 5°c for 60 min. The polymeric dispersion was prepared by dispersing required quantity of polymers and gums in deionized water and they were allowed to swell overnight then, the obtaind niosomal pellets incorporated into the insitu gel base by vortex and continued until a smooth homogenous niosomal gel obtained. Benzalkonium Chloride (Preservative) and Sodium chloride (Isotonocity adjusting agent) and osmolality adjusting agents were added; the gel was then sonicated to become bubble-free. The formulations were filled in amber glass vials and sealed with gray butyl rubber closures (Shivanand *et al.*, 2008). Table 2 illustrates the composition ratio of in-situ gel formulations. All glassware used during the preparation of the in situ forming gels was sterilized by autoclaving and the entire procedure (Srividya et al.,2001).

Table 2: Composition of Lomefloxacin HCl. in situ gel formulations.

Formulation code	Ingredients Concentrations (% w/v)					
	Lomefloxacin - loaded niosomes	Guar gum	Xanthan gum	HPMCk100	Sodium alginate	Carbopol 940
F1	0.3	0.2	-	0.1	0.3	-
F2	0.3	0.2	-	0.2	-	0.3
F3	0.3	0.2	-	-	0.5	0.4
F4	0.3	0.2	-	0.5	-	0.3
F5	0.3	0.2	-	-	0.3	0.4
F6	0.3	-	0.2	0.1	0.3	-
F7	0.3	-	0.2	0.2	-	0.3
F8	0.3	-	0.2	-	0.5	0.4
F9	0.3	-	0.2	0.5	-	0.3
F10	0.3	-	0.2	-	0.3	0.4
All the formulations contain : Benzylkonium chloride—0.01% W/V, Citric acid—0.2% W/V, Boric acid—0.3% W/V, Sodium chloride —0.9 % W/V, Disodium EDTA 0.0625% W/V, Sodium Metabisulfite---0.02% W/V.						

4.1 Evaluation of prepared in-situ gel formulations

4.1.1 Determination of physical appearance and clarity

The formulations were visually observed for color and presence of suspended particulate matter under florescent light against a white and black background.

4.1.2 Determination of pH values of the formulations

The pH of each prepared formulation was recorded by using previously calibrated digital pH meter (Jenway 3510, Camlab, UK).The values were determined by bringing electrode of the

pH meter in contact with the surface of the formulation and allowing it to equilibrate for 1 min. The experiment was run immediately after preparation and after storage for 24hr at room temperature.

4.1.3. Entrapment efficiency (EE%)

An aliquot of each formulation was diluted up to 100 ml of phosphate buffered saline (pH 7.4) and centrifuged at 50,000 rpm at 5° c for 60 minutes to separate the free drug leaked out of noisome.The obtaind niosomal pellets washed twice with PBS (pH 7.4) and centrifuged again for 60 min. then isopropyl alcohol was used to break niosomes and release the entrapped drug. The absorbance was estimated spectrophotometrically at 281 nm using PBS (pH 7.4) as blank. The results were the mean value of three replicates.

EE% = Entrapped drug / Total drug × 100

4.1.4 Measurement of Spreadability

The delivery of the correct dose of the drug depends highly on the spreadability of the formulation it was measured by using modified glass assembly in which warm water (37 °C ± 3°C) was filled. The slope of assembly was 45° and the phosphate buffered saline (pH 7.4) presoaked membrane was pasted on the assembly and then 100-200 µl of formulations were dropped on the membrane. The distance(length of external ear is 1.5 cm to reach tympanic membrane) travelled by each individual formulation before gelling was measured.(Mali et al., 2011).

4.1.5 Gelling time

The prepared in situ gelling system was evaluated for gelling time in order to identify the composition suitable for use as in situ gelling system, it is the time for first detection of gelation, it was measured by using glass tube containing 2ml of freshly prepared phosphate buffered saline (pH 7.4) and maintained at 37ºC±0.5ºC, 100-200µL from each prepared formulation was dropped on the glass tube and gelling time was measured.

4.1.6-Rheological studies

This is an important parameter for the in situ gel, to be evaluated. From the literature, it is evident that in the solution form, the formulations is needed to have a viscosity of 5 to 1500c. Further, after gel formation, it is needed to have a viscosity of about 50-50,000cps (Giuseppina et al., 2006). The viscosity and rheological behavior of the prepared gelling

systems was measured at the angular velocity of 20, 30, 50, 60, 100, 200 using (Brookfield DVIII Viscometer) fitted with spindle 52 cone and plate spindle.

A. viscosity determination of solutions

A 0.5 ml of prepared solution were poured into the adapter of the viscometer and water at 25°C was circulated through jacket of the adaptor at pH5 (non-physiological condition) and the viscosity values were recorded.

B. viscosity determination of in situ gels

The gel formulations were made by adding phosphate buffered saline solution to formulations at thermostated 37°C ±0.5°C by a circulating bath connected to the viscometer adaptor (physiological condition).

4.1.7 In vitro drug release studies.

The drug release study of in situ gel solution was carried out by using Franz diffusion cell. The formulation containing 3mg/ml concentration of lomefloxacin Hcl was placed in donor compartment and freshly prepared phosphate buffered saline (7.4) in receptor compartment, constantly stirred with a small magnetic bar at a speed of 50 rpm during the experiments to confirm homogeneity, temperature was maintained at 37 ±0.5°C by circulating hot water through the jacket of Franz-diffusion cell, between donor and receptor compartment dialysis membrane is placed (0.2 µm pore size), the cellophane membrane was soaked overnight in the receptor medium. The drug samples (1 ml) were withdrawn at predetermined regular time intervals of 1, 2, 3, 4, 5, 6and 7hr and replaced by same volume of phosphate buffered saline (Padma et al. 2010; Mali., et al. 2011). The samples were diluted with appropriate receptor medium and analyzed by a UV-Visible spectrophotometer at 281 nm using receptor medium as a blank then, the release of selected in situ gelling system was compared with that of marketed drops.

4.1.8-Accelerated Stabilities Studies

Optimized sterile formulations was subjected to stability testing according to International Conference on Harmonization (ICH) guidelines. Sterile optimized formulations was filled in previously sterilized glass vials, closed with gray butyl rubber closures and sealed with an aluminum caps. The vials contain optimized formulations were kept in stability chamber, maintained at 40 ± 2°C and 75 ± 5 % RH for 3 months. Samples were withdrawn monthly

and estimated for drug content, pH, visual appearance, gelling capacity, *in vitro* drug release and drug content during the study period (Doijad et al., 2006).

4.1.9-Antimicrobial efficacy studies of the formulations

Antimicrobial efficacy was checked out to ascertain the biological activities of the optimized formulations. These were determine by agar diffusion test employing Cup-Plate method. Sterile solutions of Lomefloxacin Hcl (standard solution) and the optimized formulations were placed into cups of the media previously seeded with Staphylococcus aureus, Pseudomonas aeruginosa as the test organisms. After allowing diffusion of the solutions for 2 hours, the agar plates were incubated at 37^{o}C for 24hrs.The zone of inhibition measured around each cup was compared with that of control. The entire operation except the incubation was carried out in a laminar airflow unit.(Mitan et al., 2007).

5. RESULTS AND DISCUSSION

5.1- Determination of visual appearance, clarity and pH of formulations

All formulations were faint yellow in color, translucent and free from suspended particulate matter. The pH of all formulations were in the acceptable range (6.10-6.79),indicating that the pH of the formulations was suitable for administration in the ear as illustrated in table 3.

5.2- Entrapment efficiency (EE%)

As seen in table 3, EE% of all formulations was found to be in the range of 96.24% to.99.83%.

5.3-Measurement of Spreadability

It was obvious from table 3 that, all formulations showed sufficient spreadability (more than 1.5cm) to reach tympanic membrane as the length of external ear is 1.5 cm.

5.4- Gelling time

It was evident from table 3 that, the optimized formulations were selected on the basis of gelling time and viscosity, the reason behind this is that the formulation applied as solution should form gel between 30 to 90 sec. in ear, If formulation gels in less than 30 sec.it may form gel before reaching tympanic membrane. On the other hand when the formulation takes more than 90 sec. to form gel then the patient needs to keep head inclined for longer time. The score (+)was assigned to formula F4 which showed the lowest gelling time(less than 30 sec.), it may form gel before reaching tympanic membrane. The score of (++) was assigned to

the Formulations F1, F2, F3, F5, F8 and F10 which exhibited phase transition between 30 to 90 sec., hence can be considered as effective in-situ gelling systems, the reason behind this is that the formulation applied as solution and form gel between 30 to 90 sec. in ear which were taken for further study. The score of (+++) was assigned to the relatively Longer gelling time(only after 90 sec) seen in F6, F7and F9.

Table 3: physicochemical characters of the prepared formulations.

FORMULATION CODE	pH	Gelling time	Entrapment efficiency (EE%).	Spreadability [Distance travelled before gelling (cm)]
F1	6.14	++	98.91	2.3
F2	6.33	++	97.78	2.6
F3	6.79	++	99.34	2.2
F4	6.12	+	97.01	2.3
F5	6.67	++	99.03	2.4
F6	6.66	+++	98.78	2.6
F7	6.74	+++	99.09	2.5
F8	6.43	++	99.83	2.3
F9	6.10	+++	97.44	2.1
F10	6.32	++	96.24	2.1

+ gelling time less than 30 sec, dissolves rapidly, ++ gelling time 30-90 sec and remains for few hour, +++. shows gelation time 90-300 sec. and remains for extended period.

5.5-Rheological studies

As depicted in Fig.3 a, b that, all the formulations exhibited newtonian and pseudoplastic flow characteristics (shear thinning and the decrease in viscosity with the increase in angular velocity) before and after gelling in phosphate buffered saline (PBS) respectively, F3 and F 8 was selected as they showed the required viscosity range with a remarkable increase in the viscosity after gelling this confirms the occurrence of phase transition process hence, formulations were taken for further study.

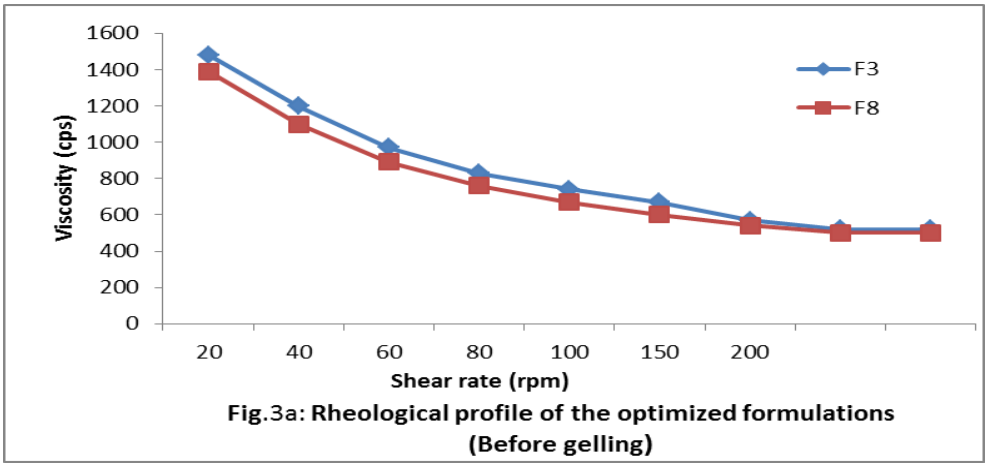

Fig.3a: Rheological profile of the optimized formulations (Before gelling)

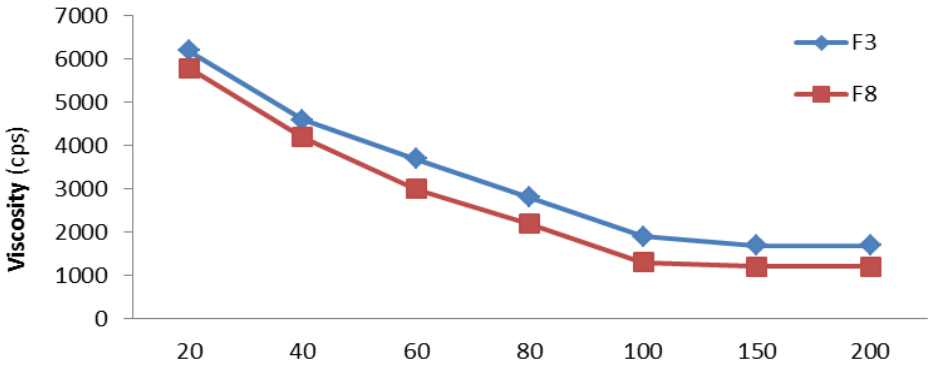

FIg.3b : Rheological profile of the optimized formulations (After gelling)

5.6-In vitro drug release studies

The results illustrated in Fig.4 indicated that, amongst all the formulations the slowest rate of drug release was obtained from the formulation F3 containing (0.2% GG, 0.4% CP, 0.5% SA) with drug release 53.2% at 7hrs, whereas formulation F8 containing (0.2% XG, 0.4% CP and 0.5% SA) showed drug release 58.20 % at 7hrs and 100% for market product 0.3% at 5 hrs. The results clearly shows that, the formulations have the ability to retain drug release and premature release will not occur which may be attributed to the optimum concentration of polymers.

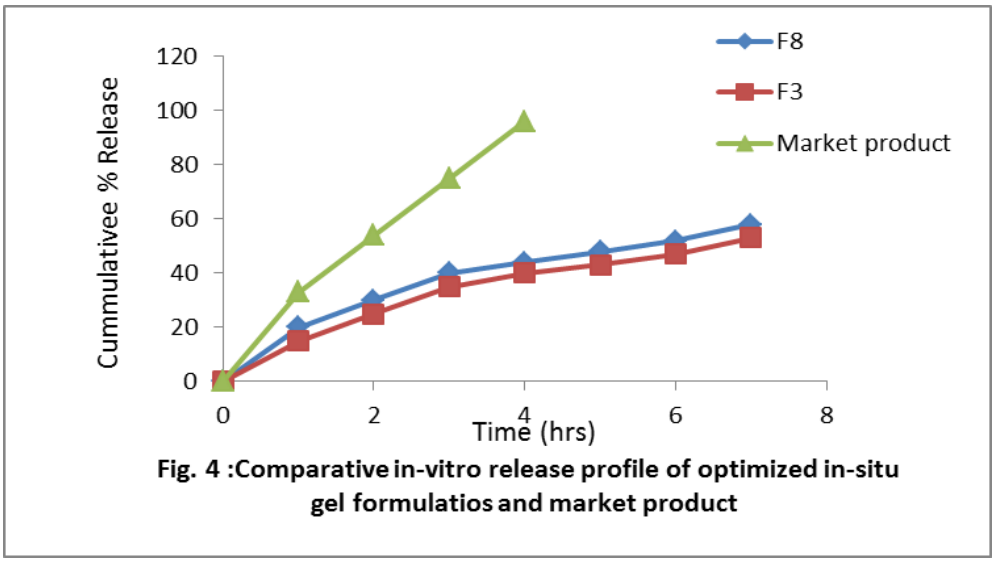

Fig. 4 :Comparative in-vitro release profile of optimized in-situ gel formulatios and market product

5.7 Accelerated Stabilities Studies

The optimized Formulations were analyzed for Visual appearance, Clarity, pH, drug content, viscosity, in vitro release and gelling time. Studies revealed that there were no changes

observed in visual appearance and Clarity furthermore, it was observed that The formulations showed slight changes in pH, but it were in acceptable limits (± 0.5).Study of drug content, viscosity, in vitro release and gelling time showed that no definite changes was observed (deviation not more than one percent).

5.8 Antimicrobial studies

As depicted in table 4 results indicated that, LMN retained its antimicrobial efficacy when formulated as niosomal in-situ gelling system may be due to constant release of drug from the polymer drug reservoir complex.

Table 4: Antimicrobial activity of Lomefloxacin in situ gels.

Formulation	Pseudomonas Aeruginosa	Staphylococcus Aureus
	Zone of inhibition (mm)	
F3	68	46
F8	66	47
Standard	70	48

6. CONCLUSION

In conclusion, the results of the present study demonstrated that LMN broad spectrum antibacterial agent used in the treatment of otic infections, was successfully formulated as *niosomal in-situ* gel system for ear drops. The formula F3 (0.2% GG, 0.4% CP, 0.5% SA) showed prolonged drug release over a period of 7 hours and was stable with no adverse effect of temperature and humidity during the storage over three months, thus making it a viable alternative to conventional ear drops resulting in high drug concentration in local area causing less frequency of administration, as the formula is applied in the form of solution, phase transition from solution to gel within 30 -90 sec. occurs, improving the patient acceptability.

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