



EMULGEL OF MOXIFLOXACIN HCL SOLID LIPID NANOPARTICLES FOR TOPICAL APPLICATION

Om Shelke^{1*} and Amol Kulkarni²

¹Faculty of Pharmacy, Pacific Academy of Higher Education and Research University, Udaipur, Rajasthan 313003, India.

²Director, Dattakala College of Pharmacy, Swami Chincholi, Maharashtra 413130, India.

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*Corresponding Author

Om Shelke

Faculty of Pharmacy,
Pacific Academy of Higher
Education and Research
University, Udaipur,
Rajasthan 313003, India.

ABSTRACT

Moxifloxacin HCl is ophthalmic antibiotic used for eye infections. An attempt has been made to formulate the Solid Lipid Nanoparticles (SLNs) and SLNs are entrapped in emulgel for controlled drug release for longer time. SLNs are formulated using cold homogenization method using Glyceryl behenate, Phospholipon 90H, Oleic acid, Palmitic acid, Polysorbate 20, Span 80, Propylene glycol and Purified water. SLNs were evaluated for particle size distribution, entrapment efficacy and in-vitro drug release. Formulated SLNs with highest entrapment efficacy and drug release were entrapped in emulgel. Emulgel were formulated using Butylated hydroxytoluene, Isopropyl Palmitate, Mineral Oil, Span 80, Polysorbate 20, Carbopol 980,

Carbopol 934, Sodium Benzoate, Sodium hydroxide and Purified Water. Emulgel formulation were characterize for physical and chemical evaluation. Low viscosity (Carbopol 934) and high viscosity (Carbopol 980) Carbomer grades were compared. Both the grade Carbopol formulation has shown good stability at accelerated and room temperature storage condition. The drug release with high viscosity grade Carbopol 980 has maintained drug release through stability study.

KEYWORDS: Moxifloxacin HCl, Solid Lipid Nanoparticles, Emulgel, Topical Application.

INTRODUCTION

Moxifloxacin HCl is a broad-spectrum antibiotic effective against gram-negative as well as gram-positive bacteria. Moxifloxacin HCl inhibits the DNA gyrase inhibitor and topoisomerase IV. Enzyme DNA gyrase is required to maintain the superhelical structure of

DNA and it is also required for DNA replication, DNA transcription, DNA repair, recombination and transposition. Moxifloxacin HCL is a new quinolone derivative and it has potential application in the treatment of bacterial infections of the skin. Moxifloxacin has significantly more antibacterial activity than the other quinolones. Moxifloxacin HCl is quite active against the majority of pathogens of human bite wounds. Moxifloxacin HCl is hydrophilic and soluble in water.^[1,2]

Topical treatment of antibiotics avoids the side effects associated with oral administration. Topical application of antibiotics increases the penetration at burned wounds at the application site and decreases antibiotic drug resistance. Application of Topical gel and ointments on the skin and mucous increases the higher rate of drug release, rapid absorption and barrier to micro-organism which helps to fast healing of wounds.^[3,4]

Solid Lipid Nanoparticles are nano-sized lipidic spheres which are made of solid lipids and ranging in size between 50 and 1000 nm. Solid Lipid Nanoparticles can be entrapped in gel or ointment formulation for topical application. SLNs are made of nontoxic and biocompatible raw materials which are generally recognized as safe (GRAS).^[5,6] An attempt has been made to Formulate Solid lipid nanoparticles of Moxifloxacin and entrapment of SLNs into gel and ointment. Entrapment of hydrophilic drugs into SLNs will retard the drug release due to hydrophobic outer layer SLNs. Controlled release formulation can be formulated by entrapping hydrophilic drug into SLNs. Formulations were evaluated for drug release.

MATERIAL AND METHOD

Materials: Moxifloxacin HCl is obtained as gift sample from Cipla. Glycerylbehenate is provided by Gattefossae. Phospholipon 90H is given by Lipoids as gift sample. Oleic acid, Palmitic acid and Propylene glycol are given by BASF.

Method

Preparation of SLNs: Cold homogenization method is employed for the formulation of Solid Lipid Nanoparticles. Formulation composition is mentioned in Table 1. **Lipid Phase:** Melt the Solid Lipid alone or combination liquid lipid by heating in water bath at 65-70°C. **Aqueous phase:** Polysorbate 20 and Span 80 were dissolved in Purified water. Add Moxifloxacin HCl in Aqueous phase and dissolve under stirring. **Mixing:** Add aqueous phase to Lipid phase under stirring and continue stirring until it forms homogenous mixture. The

mixture is sonicated at 90w and 37°C for 5min. Add mixture of water and propylene glycol at 4°C for congealing. The mixture is homogenized for 20min at homogenization speed 12000RPM using Ultra Turrax high shear homogenizer.^[8,9]

Table. 1: Formulation composition for SLN.

Ingredients	Batch No.									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Moxifloxacin HCl	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Glycerylbehenate	70	80	90	-----	-----	-----	-----	-----	80	80
Phospolipon 90H	-----	-----	-----	70	80	90	80	80	-----	-----
Oleic acid	-----	-----	-----	-----	-----	-----	10	-----	10	-----
Palmitic acid	-----	-----	-----	-----	-----	-----	-----	10	-----	10
Polysorbate 20	3	3	3	3	3	3	3	3	3	3
Span 80	1	1	1	1	1	1	1	1	1	1
Propylene glycol	50	50	50	50	50	50	50	50	50	50
Purified water	30	30	30	30	30	30	30	30	30	30

Preparation of Emulgel: Formulation composition for emulgel formulation is Tabulated in Table 2. **Aqueous Phase:** Carbopol is dispersed in mixture of polysorbate 20 and purified water under slow stirring. **Oil Phase:** Butylatedhydroxytoluene dissolved in mixture of Isopropyl palmitate, mineral oil and sorbitan oleate under slow stirring. **Drug Phase:** SLNs containing 1% equivalent of Moxifloxacin HCl added to oil phase under stirring and mixed the phases properly. **Emulsification:** Add aqueous phase to drug phase and bulk homogenized for 20min. Dissolve Sodium benzoate and sodium hydroxide in purified water. Add this solution to emulsified bulk and homogenize the bulk for 20min. Mix the bulk under slow stirring for 30min.

Table. 2: Formulation composition for SLN containing Emulgel.

Sr. No.	Ingredients	Batch No.					
		EG01	EG02	EG03	EG04	EG05	EG06
1	SLNs Equivalent to 1% Moxifloxacin HCl	1.10	1.10	1.10	1.10	1.10	1.10
2	Butylated hydroxytoluene	0.10	0.10	0.10	0.10	0.10	0.10
3	Isopropyl Palmitate	10.00	10.00	10.00	10.00	10.00	10.00
4	Mineral Oil	15.00	15.00	15.00	15.00	15.00	15.00
5	Span 80	1.00	1.00	1.00	1.00	1.00	1.00
6	Polysorbate 20	3.00	3.00	3.00	3.00	3.00	3.00
7	Carbopol 980	0.60	0.80	1.00	-----	-----	-----
8	Carbopol 934	-----	-----	-----	0.60	0.80	1.00
9	Sodium Benzoate	0.10	0.10	0.10	0.10	0.10	0.10
10	Sodium hydroxide	QS	QS	QS	QS	QS	QS
11	Purified Water	QS	QS	QS	QS	QS	QS

Evaluation of SLNs

FTIR Spectra: Moxifloxacin API, Moxifloxacin formulation and placebo formulations were mixed in KBr separately and triturated to form uniform mixture. The samples were run for recording the IR spectra.

Particle Size Determination

The Zeta potential, polydispersity index (PDI) and average particle size were determined using a Zetasizer, Malvern Instruments. SLNs were diluted with Purified water in ratio 01:09 w/w. Purified water is filtered through 0.45 um membrane filters before use. Precautions were taken for sensitivity range of instrument for the light scattering intensity.^[10]

Entrapment efficiency (EE)

Entrapment efficiency was determined by analyzing the supernatant layer obtained after the centrifugation for 30min at high speed 16000 rpm using Remi Cooling centrifuge. The equation for calculation of EE as follows.^[11]

$$EE = \left| \frac{\text{Total Drug (assay)} - \text{Free drug}}{\text{Total Drug}} \right| \times 100$$

In-Vitro Drug release

In-vitro drug release study was performed using Dialysis membrane. The Dialysis membrane was kept for soaking in MiliQ water for 12hr. This dialysis membrane was mounted on the diffusion cell. SLN Suspension 2ml is placed in dialysis membrane placed on donor compartment. The receptor compartment is filled with 20ml Phosphate buffer solution of pH 7.4. The samples were withdrawn at interval of 1hr till 8 he and the samples were analyzed for drug.^[10,11]

Evaluation of Emulgel

Description

The emulgel formulations containing SLNs are evaluated for physical appearance, homogeneity, phase separation, grittiness and consistency.^[12,13]

pH

Digital pH meter was used for the determination of pH of the formulation. 10% aqueous solution of the formulation is prepared freshly, and pH is measured.^[12,3]

Viscosity

BROOKFIELD CAP 2000 plus viscometer was used for the viscosity measurement. Recipe for the viscosity measurement was 100RPM 1min using Cone Spindle 04.^[14,15]

Drug Content (Assay)

Accurately weighed 0.25g of emulgel formulation was added in 50ml volumetric flask and dissolved in 30 ml 100% methanol. Diluted further this solution to mark with 100% methanol. Further 1ml of solution diluted to 100ml with 7.4 Phosphate buffer in volumetric flask. The drug content was determined at 296 nm using UV–Vis spectrophotometer.^[16,17]

Spreadability by Texture Analyzer

Texture analyzer was used for the determination of the spreadability. Spreadability is measured in terms of firmness and peak negative force in instruments texture analyzer. All the formulations were analyzed for texture analyzer.

Extrudability

The amount of formulation extruded from Laminated Tube on application of weight (in gm) required to extrude at least 0.5 cm ribbon of formulation in 10s was determined.^[29-31]

$$\text{Extrudability} = \frac{\text{Applied weight to extrude formulation from tube}}{\text{Area (cm}^2\text{)}}$$

In-vitro Drug release

Dialysis membrane was used to carry out the in-vitro drug release study. The dialysis membrane was cut to suitable size to fix on Franz diffusion cell. First dialysis membrane was boiled in distilled water for 1 hr and in absolute alcohol for next 1 hr. Dialysis membrane was soaked in pH 7.4 phosphate buffer saline for 24 hr. *In vitro* drug release studies were carried out by taking 500mg of emulgel formulation on the dialysis membrane. Dialysis membrane along with formulation was mounted on the Franz diffusion cell. The receptor medium with pH 7.4 phosphate buffer saline was maintained at constant temperature of 35°C by circulating water bath.^[18,19]

Ex-vivo Studies

Ex- Vivo skin permeation was performed by Franz Diffusion cell with effective skin diffusion area of 3.56 cm². The Pig Ear Skin of suitable size was mounted between donor and acceptor compartment with the help of clamp. The skin (Dorsal side) should be mounted such that the stratum corneum facing the donor compartment. Than fixed quantity of emulgel

containing 1.0% Moxifloxacin was applied on donor compartment. The receptor compartment was filled with phosphate buffer pH 7.4 was maintained at temperature 35°C with stirring at 100rpm. At predetermined intervals 1hr, 1ml was withdrawn and the same volume of the same medium was added immediately into receptor compartment. The procedure was repeated up to 6hrs. The samples were analyzed by UV spectrophotometer at 296 nm using blank as phosphate buffer pH 7.4.^[19,20]

Stability studies of the optimized formulation

The Optimized formulations EG02 and EG05 were packed in High barrier laminated collapsible tubes. Stability study was carried out for 3 Months by keeping at 25°C±2°C/60%±5% RH and 40°C±2°C/75%±5% RH. Samples were withdrawn at time point 1M, 2M and 3M. Withdrawn stability samples were evaluated for physical appearance, viscosity, drug content, pH and *in vitro* studies through dialysis membrane.^[21,22]

RESULTS AND DISCUSSION

FTIR Spectra

FTIR spectra of moxifloxacin HCl, Formulation and placebo formulation has shown characteristics peaks of Moxifloxacin HCl are intact in final formulation. FTIR spectra of moxifloxacin HCl, Formulation and placebo formulation are shown in figure 1. Hence, Moxifloxacin has good compatibility with the used excipients in formulation.

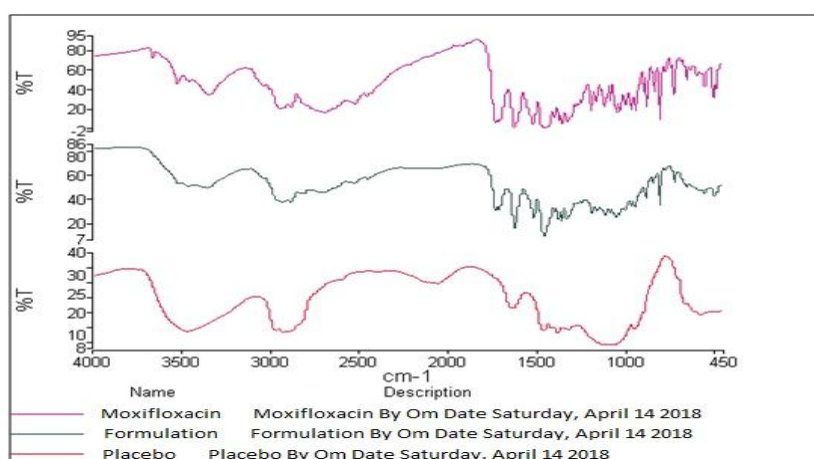


Figure. 1: FTIR spectra of moxifloxacin HCl, Formulation and placebo formulation.

Particle Size Distribution: All the results for Zeta potential, PDI, average particle size is compiled in Table No. 3. Results for zeta potential and PDI are satisfactory and acceptable range. Particle size distribution of all the batches were found in range 207nm to 299nm.

Table 3: Results for Zeta potential, PDI, average particle size, and entrapment efficacy.

Batch No.	Zeta Potential (mv)	PDI	Avg. Particle Size (nm)	Entrapment efficacy %
F1	-23.35±0.9	0.212±0.9	299±2.2	65.43
F2	-24.29±2.4	0.221±1.1	278±2.7	70.67
F3	-21.29±1.8	0.231±1.2	258±3.4	75.49
F4	-23.81±1.3	0.210±0.8	289±2.5	70.34
F5	-19.31±1.0	0.229±0.7	273±2.3	78.65
F6	-25.29±1.3	0.215±1.3	212±3.4	86.12
F7	-30.12±1.4	0.231±0.6	207±1.1	91.23
F8	-28.34±2.3	0.221±0.8	210±1.9	88.34
F9	-26.45±3.1	0.211±1.2	220±1.2	78.78
F10	-25.92±2.1	0.209±0.9	230±1.9	76.45

The increase in the concentration of lipid concentration the particle size of the SLN are decreased significantly. The combination of Lipids gives further reduced size of the particle size of SLN.

Entrapment Efficacy

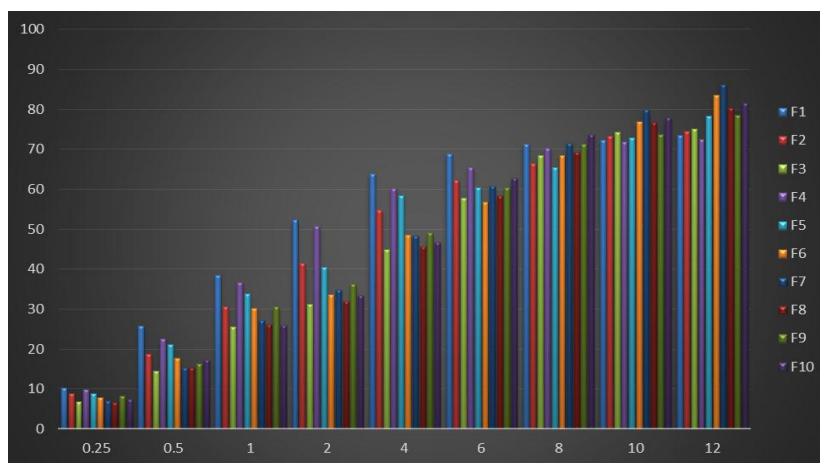
Entrapment efficacy of all the formulations were in acceptable range 65% to 91%. All the results are compiled in Table 3. The increase in the concentration of Lipids, the entrapment efficacy of the formulation increases significantly. Formulation F7 is selected for the further study and entrapment into the emulgel for constant drug release for 24hrs.

In-vitro drug release

Amount of drug released from the Solid lipid particles are in the range 72-86% after 12 hrs. Results are tabulated in Table 4 and graphically represented in figure 2. All the SLNs are showing drug release in acceptable range. The drug release is dependent upon the concentration of lipid present in formulation, higher the concentration of lipid lowers the drug release. The lower lipid concentration shows initial higher drug release and then release declined with time. The combination of two lipids shows constant drug release for longer time than the higher lipid concentration of single lipid. The maximum drug release is found with the combination of lipids Phospholipon 90H and Oleic acid.

Table. 4: In-vitro drug release from SLNs.

Time	Batch No.									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
15 min	10.32	8.89	6.76	9.88	8.80	7.78	7.10	6.68	8.32	7.47
30 min	25.67	18.65	14.45	22.59	21.08	17.78	15.23	15.29	16.34	17.39
1 hr	38.45	30.63	25.54	36.72	33.74	30.28	27.21	26.18	30.53	25.97
2 hr	52.34	41.44	31.25	50.68	40.51	33.56	34.88	31.93	36.22	33.48
4 hr	63.74	54.76	44.91	60.23	58.45	48.45	48.35	45.73	49.11	46.67
6 hr	68.89	62.29	57.74	65.34	60.45	56.78	60.71	58.30	60.49	62.77
8 hr	71.29	66.45	68.56	70.37	65.48	68.56	71.56	69.35	71.24	73.69
10 hr	72.37	73.23	74.34	71.86	72.92	76.83	79.88	76.72	73.69	77.88
12 hr	73.54	74.48	75.02	72.55	78.26	83.56	86.22	80.35	78.48	81.47

**Figure. 2: In-vitro drug release from SLNs.**

Evaluation of Emulgel

Description: Appearance of all the formulation is white smooth cream. Homogeneity of the formulation is fair, good and excellent. Phase separation is not found among all the formulation.

Table. 5: Results for descriptions.

B. No.	Appearance	Homogeneity	Phase Separation	Grittiness	Consistency
EG01	White Smooth Emulgel	Fair	No	Not found	Low
EG02	White Smooth Emulgel	Good	No	Not found	Medium
EG03	White Smooth Emulgel	Excellent	No	Not found	High
EG04	White Smooth Emulgel	Fair	No	Not found	Low
EG05	White Smooth Emulgel	Good	No	Not found	Medium
EG06	White Smooth Emulgel	Excellent	No	Not found	High

pH: pH of the formulated formulation was in range 4.5 to 4.8. Results are tabulated in Table 6. Although the pH of the formulation adjusted during manufacturing, the pH of the formulation is dependent on the concentration of the Carbopol level in formulation. The

higher the concentration of the Carbopol in formulation, lower will be the pH of formulation due to acidic nature of Carbopol.

Viscosity: Viscosity of the formulations was found in range 3.4 to 3.6 Poise. Results are tabulated in Table 6. Viscosity is dependent on the concentration of the Carbopol and pH of the formulation.

Drug Content (%)

The drug content of all the formulation was found in acceptable range 96.6 to 100.9%. Results are tabulated in Table 6.

Spreadability: Spreadability of the formulation was found in the range 12-14. Results are tabulated in Table 6. Spreadability is dependent on the viscosity of the formulation, higher the viscosity of the formulation lower will be the spreadability of the formulation.

Extrudability: Extrudability of the formulation was found in the range 14.9 to 17.6 gm/cm². Results are tabulated in Table 6. Extrudability is ease of formulation will come out from tube after pressing the tube. Extrudability is affected by the viscosity of the formulation. Higher the viscosity of the formulation lower will be the extrudability.

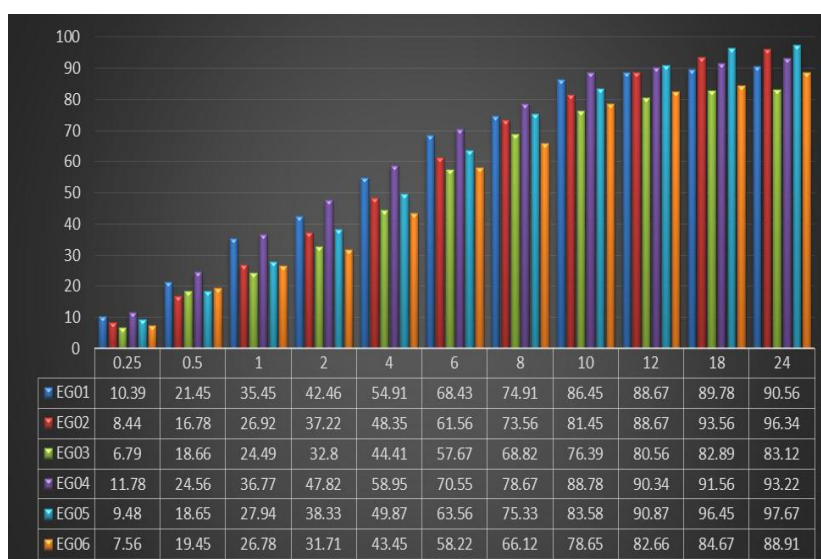
Table. 6: Results for pH, Viscosity, Drug Content, spreadability and extrudability.

Batch No.	pH	Viscosity	Drug Content (%)	Spreadability	Extrudability
EG01	4.64	3.55	98.4	15.78	17.67
EG02	4.72	3.67	99.7	14.45	16.12
EG03	4.80	3.73	99.6	12.56	14.98
EG04	4.56	3.46	96.6	16.38	17.27
EG05	4.68	3.54	99.8	15.12	15.67
EG06	4.75	3.68	100.9	14.28	14.35

In-vitro Drug release: Drug release from the emulgel formulation was found in range 83.1 to 97.6 %. Results are tabulated in Table 7 and graphically represented in Figure 3. Formulations with the similar concentration of Carbopol although the grades are different are showing the similar release profile. This may be due to different viscosity grades of Carbopol. Viscosity of the formulation affects the drug release from the formulation. Low viscosity grade Carbopol 934 is showing higher drug release and high viscosity grade Carbopol 980 is showing less drug release with the same polymer concentration. The concentration of Carbopol within the same grade has concentration dependent impact on drug release. The highest drug was found with the batch no. EG02 and EG 05.

Table. 7: In-vitro drug release from SLNs containing Emulgel.

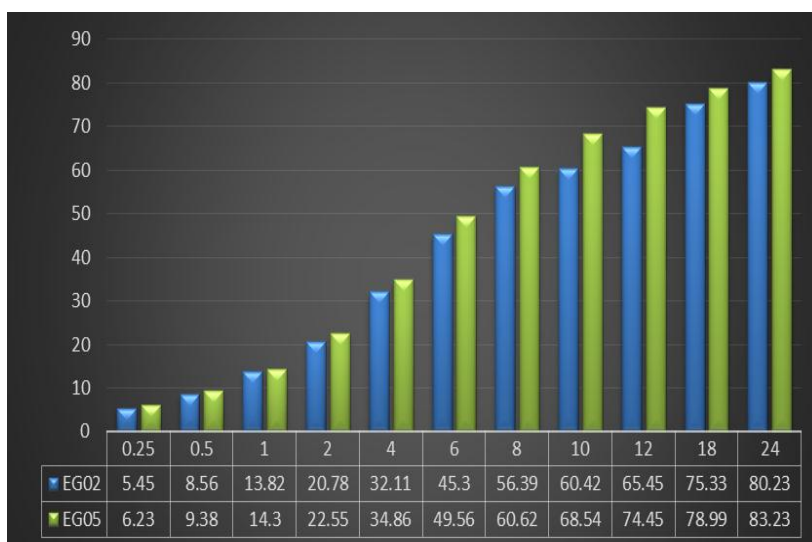
Time	Formulation Code					
	EG01	EG02	EG03	EG04	EG05	EG06
15 min	10.39	8.44	6.79	11.78	9.48	7.56
30 min	21.45	16.78	18.66	24.56	18.65	19.45
1 hr	35.45	26.92	24.49	36.77	27.94	26.78
2 hr	42.46	37.22	32.80	47.82	38.33	31.71
4 hr	54.91	48.35	44.41	58.95	49.87	43.45
6 hr	68.43	61.56	57.67	70.55	63.56	58.22
8 hr	74.91	73.56	68.82	78.67	75.33	66.12
10 hr	86.45	81.45	76.39	88.78	83.58	78.65
12 hr	88.67	88.67	80.56	90.34	90.87	82.66
18 hr	89.78	93.56	82.89	91.56	96.45	84.67
24 hr	90.56	96.34	83.12	93.22	97.67	88.91

**Figure. 3: In-vitro drug release from SLNs containing Emulgel.****Ex-vivo drug release**

The drug release found in the range 80-83% after 24 hrs. The results are tabulated in table 8 and graphically represented in figure 4. The drug release of selected formulation ex-vivo has shown similar pattern of drug release but less drug release compared to the in-vitro drug release data. The highest and constant drug release found with the both the formulations. Low viscosity Carbopol grade has higher drug release than high viscosity Carbopol grade.

Table. 8: Ex-vivo drug release from SLNs containing Emulgel.

Time	Batch No.	
	EG02	EG05
0.25	5.45	6.23
0.5	8.56	9.38
1	13.82	14.3
2	20.78	22.55
4	32.11	34.86
6	45.30	49.56
8	56.39	60.62
10	60.42	68.54
12	65.45	74.45
18	75.33	78.99
24	80.23	83.23

**Figure. 4: Ex-vivo drug release from SLNs containing Emulgel.**

Stability Study

Stability results are tabulated in Table 9 for physical and chemical parameters. Description of the formulation is same throughout the stability study. The pH and viscosity of the formulation has not shown any changes initial results versus stability results. Drug content is same at 3M 25°C/60%RH when compared to the initial samples but drug content at 40°C/75%RH has dropped slightly. This may be due to minor degradation of active at accelerated storage condition. Spreadability of the formulation has not shown any significant changes.

Table. 9: Results of Stability study samples of EG02 and EG 05.

Batch No.	Storage Condition	Time Point	Description	pH	Viscosity	Drug Content %	Spreadability	
EG02	Initial	0M	White Emulgel	4.63	3.67	99.7	14.45	
		40°C/75%RH	1M	White Emulgel	4.51	3.63	99.5	15.56
			2M	White Emulgel	4.48	3.61	99.1	16.298
	25°C/60%RH	3M	White Emulgel	4.41	3.58	98.7	16.583	
		1M	White Emulgel	4.61	3.66	99.6	15.182	
		2M	White Emulgel	4.58	3.69	99.5	15.221	
	EG05	40°C/75%RH	3M	White Emulgel	4.69	3.64	99.3	14.969
			Initial	White Emulgel	4.63	3.54	99.8	15.12
			1M	White Emulgel	4.51	3.50	99.4	16.451
25°C/60%RH		2M	White Emulgel	4.48	3.47	98.9	16.782	
		3M	White Emulgel	4.41	3.44	98.4	16.989	
		1M	White Emulgel	4.61	3.56	99.6	15.345	
EG05	25°C/60%RH	2M	White Emulgel	4.58	3.58	99.5	15.678	
		3M	White Emulgel	4.69	3.53	99.3	15.189	

Drug release profile of initial versus 3M stability samples were compared with the same batch. Results are tabulated in Table 10 and graphically represented in figure 5 & 6. The batch EG02 has shown similar drug release profile initial versus 3M stability sample of accelerated and room temperature storage condition. The batch EG05 has shown slightly different drug release profile at accelerated and room temperature storage condition when compared with initial sample. The release profile of high viscosity Carbopol grade has shown similar drug release profile to that of initial sample while drug release profile of low viscosity Carbopol has changed significantly.

Table. 10: In-vitro release of EG 02 & EG 05 initial vs 3M Stability samples.

Batch No.	EG 02			EG 05		
	Initial	3M 25°C/60%	3M 40°C/75%	Initial	3M 25°C/60%	3M 40°C/75%
0.25	8.44	8.11	8.98	9.48	10.34	11.23
0.5	16.78	15.89	16.99	18.65	19.86	16.67
1	26.92	24.36	25.66	27.94	28.48	30.46
2	37.22	36.12	37.78	38.33	40.33	43.45
4	48.35	46.45	47.67	49.87	51.27	56.73
6	61.56	60.38	61.78	63.56	65.67	68.98
8	73.56	72.88	73.92	75.33	79.45	81.34
10	81.45	80.72	82.22	83.58	85.91	86.89
12	88.67	88.01	89.81	90.87	93.56	96.56
18	93.56	93.28	94.58	96.45	94.45	96.87
24	96.34	95.97	96.57	97.67	95.17	96.94

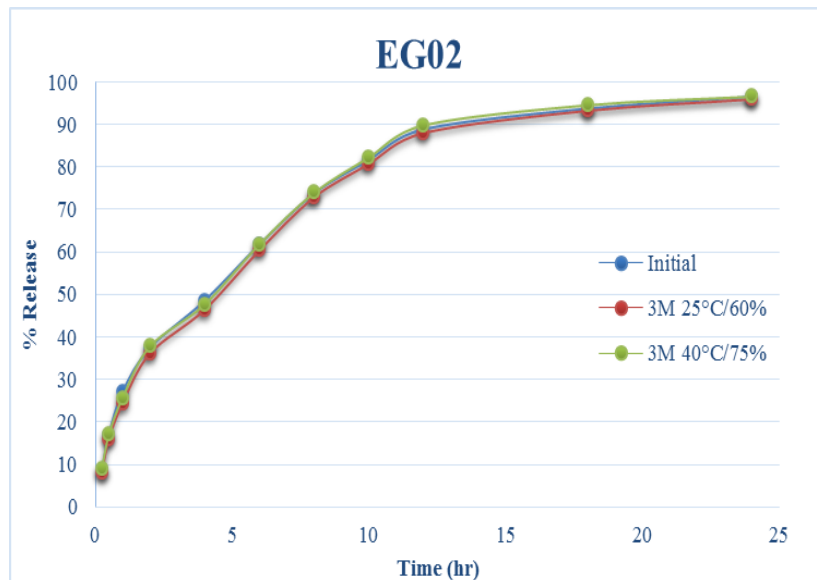


Figure 5: In-vitro release of EG 02 initial vs 3M Stability samples.

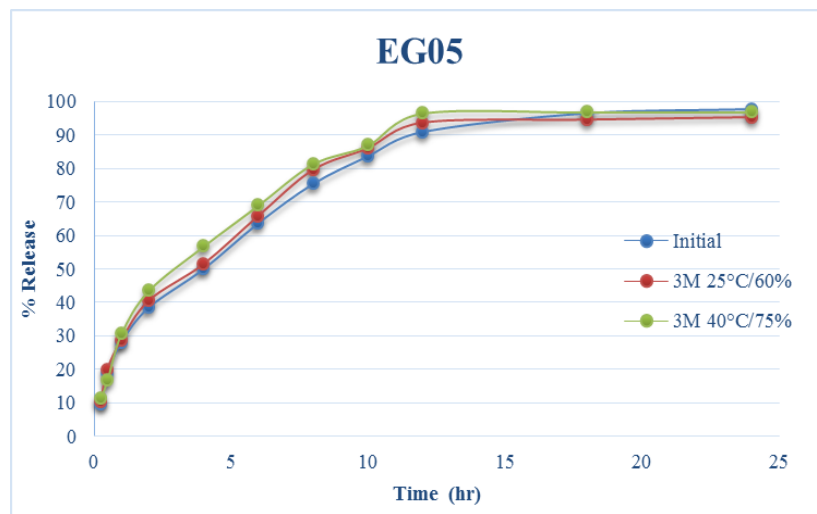


Figure. 6: In-vitro release of EG 05 initial vs 3M Stability samples.

CONCLUSION

The SLNs of water-soluble drug moxifloxacin HCl can be formulated. SLNs in combination with Phospholipon 90 H and Oleic acid has shown good stability and better drug release than the single lipid Phospholipon 90H. The combination of two lipids gives greater stability and drug release to SLN than the single lipid. Moxifloxacin has good compatibility with all the ingredients. The concentration of polymer and grade of polymer in formulation has major impact on the drug release from the formulation. The stable formulation composition can be formulated with the mentioned ingredients. The viscosity Carbopol grade is more suitable for the formulation than the low viscosity grade Carbopol. The formulated formulation is stable for 3M accelerated and room temperature storage condition.

CONFLICT OF INTERESTS

Declare none.

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