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Original Article

Fabrication, Characterization, and *in vitro* Evaluation of Atenolol Loaded Microsponges for Ocular Delivery

Archana Dhyani[1,2,*], Ganesh Kumar[3]

[1]School of Pharmacy, Graphic Era Hill University, Dehradun, Uttarakhand, INDIA.
[2]Research Scholar, Veer Madho Singh Bhandari Uttarakhand Technical University, Dehradun, Uttarakhand, INDIA.
[3]Himalayan School of Pharmaceutical Sciences, Swami Ram Himalayan University, Dehradun, Uttarakhand, INDIA.

ABSTRACT

Aim: The purpose of the study was development and evaluation of Atenolol loaded microsponge *in situ* gel for the management of ocular hypertension, glaucoma. **Materials and Methods:** The microsponges were prepared by modified oil in oil emulsion solvent diffusion method. The polymers used for fabrication of microsponges include Ethyl Cellulose and Eudtagit RL-100. **Results:** The results of particle reveals that the particle size varies from 7.33 to 9.76µm, percentage yield ranges from 59.98 to 81.22, entrapment efficiency (%) 58.23 to 80.56 and drug content (%) varies from 54.12 to 82.89. Further, the microsponges were loaded in *in situ* gel. The *in situ* gel was fabricated by using Poloxamer 407 and HPMC K4M polymers. The microsponges loaded *in situ* gel was evaluated for different parameters like pH, viscosity, gelling capacity, gelation temperature and drug release study. The pH varies from 6.83 to 7.43, viscosity ranges from 7421 to 15623 cp, gelation temperature ranges from 37.14 to38.22°C while the drug release ranges from 62.52 to 83.32%. At last, the stability study report indicated that the developed drug loaded microsponge *in situ* gel were physically and chemically stable over a period of three months. Sterility testing was conducted in the optimized formulations as per Indian Pharmacopoeia. The studies reveal that there was no sign of growth of microorganism. **Conclusion:** Atenolol loaded microsponge loaded *in situ* gel can effectively treat Glaucoma and improve the patient compliance.

Keywords: Microsponge, Atenolol, Ethyl Cellulose, Eudragit RL-100, *in situ* gel, Glaucoma.

Correspondence:
Ms. Archana Dhyani
Associate Professor, School of Pharmacy, Graphic Era Hill University, Dehradun-248001, Uttarakhand, INDIA.
Email: archana.dhyani89@gmail.com

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INTRODUCTION

Eye is a very unique organ which is divided into two parts: frontal portal which contains parts like cornea, ciliary body, conjuctiva, pupil, iris, and lens, aqueous humor and trabecular meshwork. The posterior segment contains sclera, retina, optic nerve and vitreous humor.[1] Ophthalmic drug delivery has a number of challenges for pharmaceutical and medical sciences. There are many factors which can affects this drug delivery system like turnover of tear fluid, lachrymal drainage, the corneal epithelium –ocular barrier. All these parameters contribute to the decreased bioavailability and residence time of drug inside the eye. However direct targeting of drug in eye enhances the better bioavailability. The merits of ODDS are accurate dosing of drug, continued and controlled delivery of medicaments, better ocular bioavailability, site specific targeting to the eye, better patient compliance and improved delivery system.[2] However, the demerits of ODDS are the ocular delivery offers limited permeability to drugs in cornea which leads to poor absorption of drugs and removal of drug due to blinking of eyes results in low therapeutic effects of drugs and leads to increased dosing frequency.[3] The different approaches used to enhance the ocular bioavailability are use of viscosity enhnacers, penetration enhancers, niosomes, liopsomes, nanoparticles or nanospheres, *in situ* gel, microparticles, implants, microsponge and *in situ* gel.

Microsponges are polymeric device which consists of porous microspheres. The size of microsponges usually varies between 10-25 microns in diameter. They consist of voids of size range 5-300 µm. These are given for providing prolonged action, sustain or continuous release of drug. They are designed to reduce the dose of drug as well as dosing frequency.[4] Microsponges are generally embedded into the vehicle where they act like a microspongic carrier storing the active ingredient and thus releases the drug by triggering mechanism. The total pore density of micropores in a microsphere is 1ml/g while the length of pore is 10 feet. These microsponges can be easily incorporated inside a vehicle which may be cream, lotion, gel and powders. The active ingredient can be released in a controlled manner from the porous surface.[5]

In situ gels are the preparations which upon instillation into eye get converted into transition in eye to form a gel. By lengthening

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the formulation's duration in the eye, the *in situ* gel increases the drug's ocular bioavailability and hence increases patient acceptability. Temperature, pH, and ionic strength are the variables in charge of phase change.[6,7] *In situ* gels can be used for buccal, nasal, ocular intraperitoneal, transdermal, and vaginal routes. Natural as well as synthetic or semi-synthetic polymers are used for fabrication of *in situ* gel. Examples of natural polymers includes chitosan, guargum, tragacanth, pectin, carageenan, xanthan gum while examples of synthetic or semi-synthetic polymers includes methyl cellulose, poloxamer, PLGA, HPMC, carbopol, Pluronics.[8] The *in situ* gels were subjected to evaluation parameters like physical appearance, gelling capacity, determination of pH, rheological measurement, drug content and sterility testing.

MATERIALS AND METHODS

Materials

Atenolol was procured from Mepromax Ltd., Dehradun (Uttarakhand). Eudragit RL-100 was purchased from Evonik India Ltd., Ethyl cellulose, Magnesium stearate, acetone and other chemicals were procured from Central Drug House ltd, New Delhi.

Methods

Microsponges were made using O/O ESDM. The necessary quantity of polymers was dissolved in acetone in the first stage. Further, magnesium stearate (5%w/v) was added to the Atenolol.

This combination was sonicated for 5 min at 3000 rpm. For 3 hr at a speed of 4000 rpm, mixture was added to light liquid paraffin (200 mL). The solvent acetone was fully eliminated during this time. Microsponges were created as a result. The following stage involved washing the created microsponge with n-hexane and drying it for 12 hr at room temperature. Eventually kept in desiccators.[9] The composition of Atenolol Loaded microsponges using Ethyl Cellulose and Eudragit RL-100 were shown in Table 1.

Evaluation of Microsponges

Particle size by optical microscopy

Optical microscopy plays an important role in determination of average particle. Sample was mounted on a glass slide and it was observed through a microscope. Around 300 particles were counted and the mean particle size was calculated.[10]

Product yield[10]

Product yield helps to determine the efficiency of the method. It was calculated using formula:

$$\text{Production Yield (\%)} = \frac{\text{Practical mass}}{\text{Theoretical yield}} \times 100$$

Drug content (DC) and entrapment efficiency (EE)

Accurately weigh 50 mg drug loaded microsponges. Dissolve it in acetone 5 mL. The sample was centrifuged at 4500 rpm for 10 min. A sample of the supernatant layer was taken for analysis at 274 nm. The DC and EE efficiency was determined.[11]

Micro sponges surface morphology

Determined the surface topography of micro sponges using field emission scanning electron microscopy.[12]

Formulation of Atenolol loaded microsponge *in situ* gels

Poloxamer 407 and HPMC K4M were weighed out and mixed with distilled water. The mixture was refrigerated overnight at 4°C so that the entire polymer swells. The weighed quantity of microsponge (0.1%w/v) was added to the solution once a clear, viscous solution had formed. The solution was then sonicated at 2000 rpm for 1min in order to form gel.[13] The formulation chart was represented in Table 2.

Evaluation of prepared mirosponges gel

Determination of the pH

pH meter was used for determination of pH. The average of three readings was taken and recorded.[14]

Rheological behavior of gels

Rheological property of gel was used to determine viscosity of the formulation. Brookfield viscometer was used for the study. The viscosity was determined at 50 rpm. The readings were taken in triplicates.[15]

In vitro gelling capability

The method involves a drop of gel which is placed in a vial containing PBS pH 7.4 (2 mL) at 37°C. The gelation time was recorded. According to gelling capacity, different grades were given.[15]

In vitro drug diffusion study

Franz Diffusion cell was used to carry out *in vitro* diffusion test in PBS pH 7.4(50 ml). For study a semi permeable membrane (Molecular weight > 10, 000 Himedia) was used. Weigh 0.5 g of microsponge gel and placed it on cell for the study. The study was conducted for 24 hr. The samples were analyzed at 274 nm.[16]

Kinetic Modeling

The data of an *in vitro* drug release investigation on microsponge were fitted in kinetic equations, including Higuchi's model, first order and zero order. R^2 and K values were determined for the regression analysis's linear curve.[16]

Table 1: Composition of Atenolol Loaded Microsponges using Ethyl Cellulose and Eudragit RL -100.

Formulation Code	Atenolol (mg)	Ethyl Cellulose (mg)	Eudragit RL -100 (mg)	Magnesium Stearate (mg)	Acetone (mL)	Light Liquid Paraff (mL)
FE1	90	90	90	5	10	200
FE2	90	90	180	5	10	200
FE3	90	90	270	5	10	200
FE4	90	180	90	5	10	200
FE5	90	180	180	5	10	200
FE6	90	180	270	5	10	200
FE7	90	270	90	5	10	200
FE8	90	270	180	5	10	200
FE9	90	270	270	5	10	200

Table 2: Composition of Atenolol Loaded Microsponges *in situ* gel

Formulation Code	Composition (%w/v)			
	% capacity concentration of Poloxamer 407	% Concentration of HPMC K4M	Sodium chloride	Benzalkonium chloride
FE1	14	0.5	0.85	0.01
FE2	14	0.75	0.85	0.01
FE3	14	1	0.85	0.01
FE4	16	0.5	0.85	0.01
FE5	16	0.75	0.85	0.01
FE6	16	1	0.85	0.01
FE7	18	0.5	0.85	0.01
FE8	18	0.75	0.85	0.01
FE9	18	1	0.85	0.01

Stability Study

For stability studies the sample of microsponges was stored for three months at 40°C and 75% RH. The parameters like mean particle size and % EE were evaluated.[17]

Sterility Testing

As per IP sterility testing of the formulation was conducted by direct inoculation method. It can be done by incubating formulation in alternate thioglycolate medium at 30-35°C and soyabean casein digest medium at 20-25°C for not less than 14 days to find out the growth of bacteria and fungi respectively.[18]

RESULTS

Particle size by optical microscopy

The particle size of all formulation varies from 7.33±0.27 µm to 9.76±0.61 µm. Formulation FE9 has the largest particle size while the formulation FE1 has lowest particle size. The results were shown in Table 3 and in Figure 1 (A).

Percentage yield

The results of percentage yield was represented in Table 3 and Figure 1(B). The maximum percentage yield was found for 59.98% for formulation FE1 while maximum yield of 81.22% was found for formulation FE9.

Drug Content (DC)

DC varies from 54.12% to 82.89% from FE1 to FE9.The maximum DC was found for FE8 formulation 82.89% while minimum DC for FE1 which is 54.12%. However, Table 3 represents the results of % DC.

Percentage Entrapment Efficiency (%EE)

For formulations FE1–FE9, the EE varies from 58.23% to 81.87%. The drug to polymer concentration affects the EE percentage. The porous design of microsponge can be linked to EE. Microsponges' porous structure encourages great entrapment efficiency. The results were shown in Figure 1(C) and Table 3.

Microsponges surface morphology

The surface morphology of FE9 formulation was determined by FESEM study. FESEM shows that the microsponges were uniform and round in shape with spongy surface as shown in Figure 2.

Evaluation of Gel loaded Microsponges

For gel loaded microsponges, the various characteristics, such as pH, rheological behavior, gelling capacity, gelling temperature, cumulative percentage drug release, and stability tests, were assessed. The results are represented in Table 4.

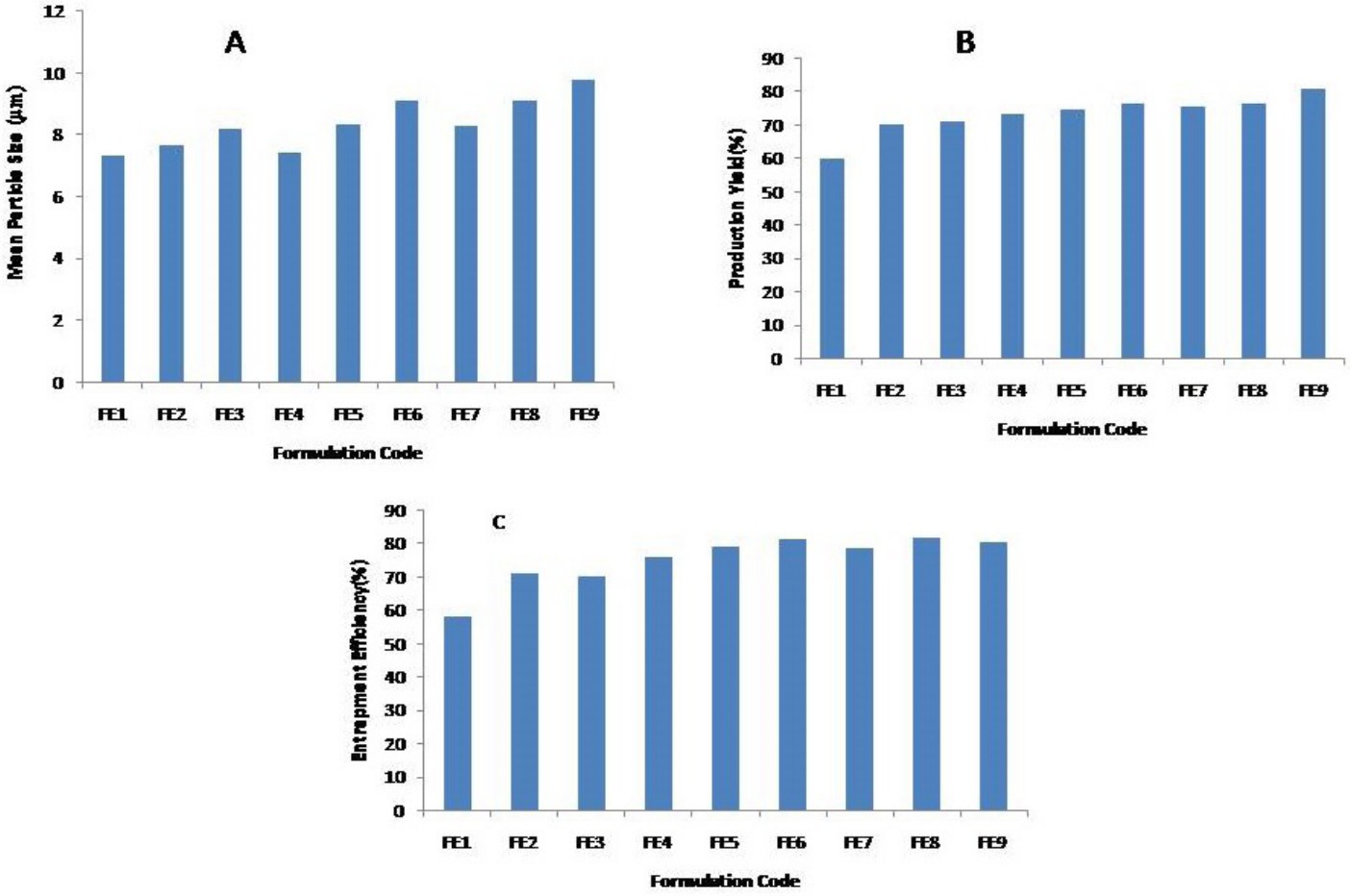

Figure 1: Results of different evaluation parameters of microsponges.

A) Mean particle size of microsponges, B) Production yield of microsponges C) Entrapment Efficiency of microsponges.

Table 3: Results of formulation FE1-FE9.

Formulation code	Mean particle size (µm)	Percentage Yield (%)	Encapsulation Efficiency (%)	Drug Content (%)
FE1	7.33±0.27	59.98	58.23	54.12
FE2	7.68±0.91	70.11	71.22	66.23
FE3	8.21±0.29	71.38	70.43	68.98
FE4	7.43±0.36	73.23	75.98	63.23
FE5	8.32±0.49	74.87	79.32	69.87
FE6	9.09±0.28	76.45	81.33	71.23
FE7	8.29±0.99	75.89	78.88	72.45
FE8	9.11±0.76	76.38	81.87	82.89
FE9	9.76±0.61	81.22	80.56	79.09

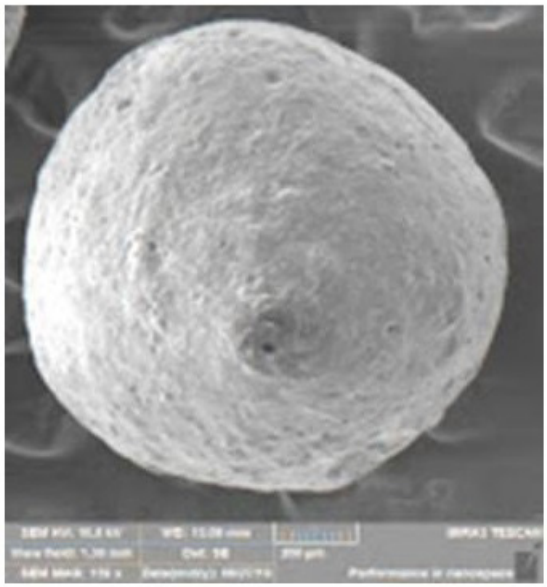

Figure 2: FESEM of FE9 microsponge.

pH

The pH of formulations FE1-FE9 lies within the range of 6.83 to 7.43 which is suitable for the ocular preparation. Table 4 and Figure 3(A) represents the results of different formulations.

Rheological behavior

The viscosity was determined with Brookfield viscometer. The viscosity was found to be 7421 to 15623 cp. Results were shown in Table 4 and Figure 3(B).

Gelling temperature

The gelling temperature varies from 37.14 to 38.22°C for different formulations FE1-FE9 The results reveal that the formulation converts into gel in body temperature. Results were represented in Table 5 and Figure 4. A) pH of FE1-FE9 B) Viscosity of formulation FE1-FE9 C) Gelation temperature of FE1-FE9.

Release study of Microsponge *in situ* gel Franz diffusion cell was used for *in vitro* release study. The data were then put into various mathematical models in order to find the release mechanism. The results obtained for each formulation were displayed in the Table

Table 4: Results of microsponge loaded *in situ* gel FE1-FE9.

Formulation	pH	Viscosity (cP)	Gelling capacity	Gelation temp. (°C)	Cumulative % drug release after 24 hr
FE1	6.83±0.62	7421	++	37.14±0.45	83.32
FE2	6.78±0.11	8520	++	37.95±0.12	75.76
FE3	7.25±0.42	8999	+++	36.33±0.21	71.19
FE4	7.29±0.47	10550	+++	37.99±0.42	79.85
FE5	7.04±0.12	12345	+++	37.67±0.49	70.66
FE6	7.62±0.72	12665	+++	38.12±0.86	68.79
FE7	6.99±0.87	13190	+++	37.54±0.79	65.87
FE8	7.37±0.99	14349	+++	38.21±0.98	64.89
FE9	7.43±0.19	15623	+++	38.22±0.99	62.52

Table 5: Kinetic modeling of Microsponges *in situ* gel.

Formulation	Zero Order	First Order	Higuchi's	Korsmeyers Peppas		Best fit model	Release Mechanism
R^2	R^2	R^2	R^2	R^2	n		
FE1	0.994	0.992	0.893	0.969	0.749	Zero order	Anomalous
FE2	0.971	0.970	0.946	0.955	0.833	Zero order	Anomalous
FE3	0.989	0.977	0.947	0.987	0.731	Zero order	Anomalous
FE4	0.983	0.982	0.937	0.969	0.709	Zero order	Anomalous
FE5	0.989	0.978	0.9.43	0.987	0.731	Zero order	Anomalous
FE6	0.981	0.970	0.935	0.98	0.942	Zero order	Anomalous
FE7	0.988	0.985	0.823	0.968	0.928	Zero order	Anomalous
FE8	0.994	0.993	0.837	0.962	0.952	Zero order	Anomalous
FE9	0.993	0.992	0.0823	0.973	0904	Zero order	Anomalous

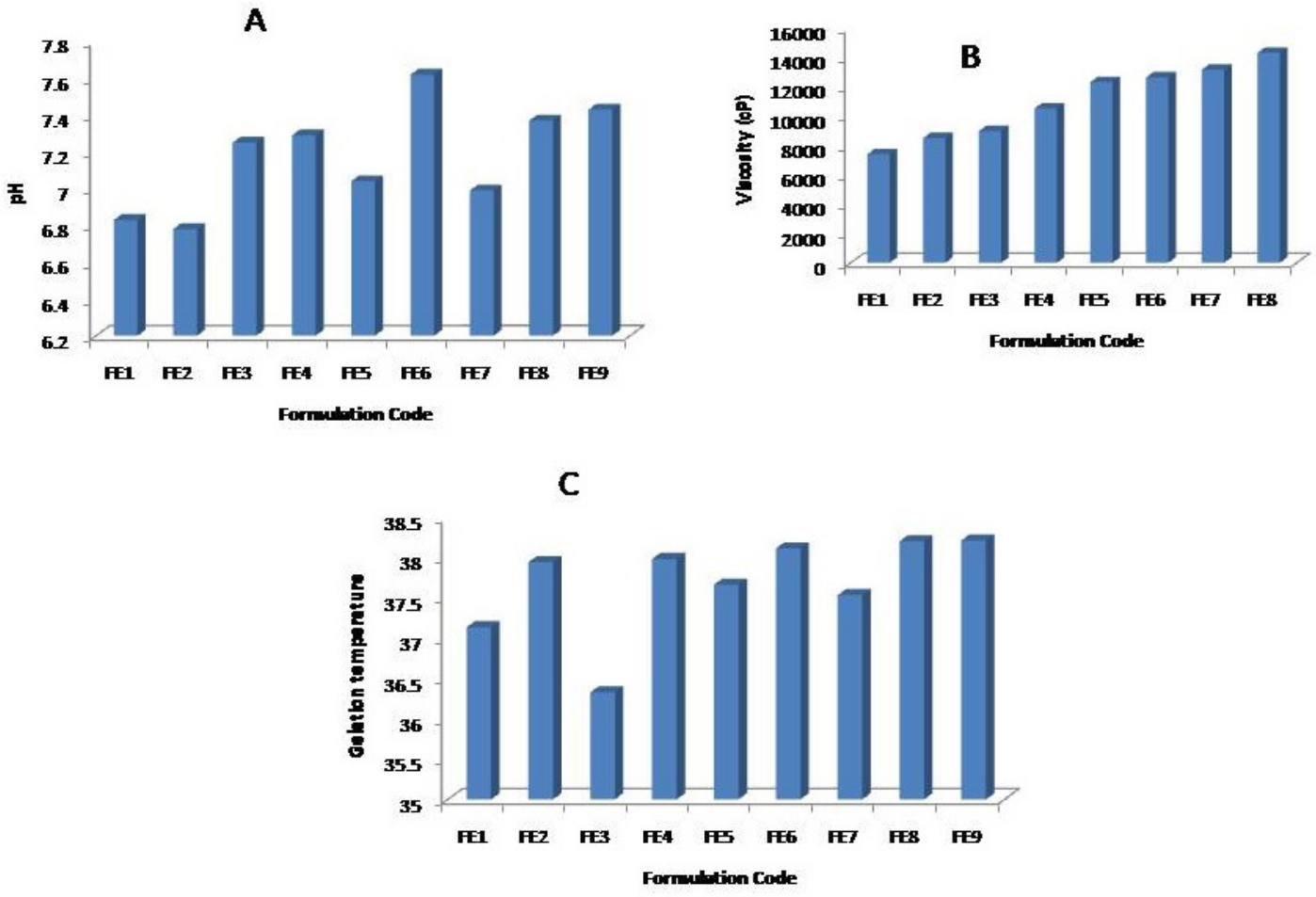

Figure 3: Results of Evaluation parametersmicrosponge loaded *in situ* gel.

A) pH, B) Viscosity, C) Gelation temperature of different formulations.

Table 6: Stability studies of formulations after three months. (FE1-FE9).

Formulation Code	Mean Particle Size (µm)	Cumulative % drug release
FE1	7.55±0.75	78.2
FE2	7.99±0.89	67.56
FE3	8.42±0.88	62.12
FE4	8.55±0.91	72.29
FE5	8.65±0.69	61.88
FE6	8.56±0.95	60.22
FE7	8.5±0.39	59.19
FE8	9.27±0.58	58.68
FE9	9.11±0.86	57.67

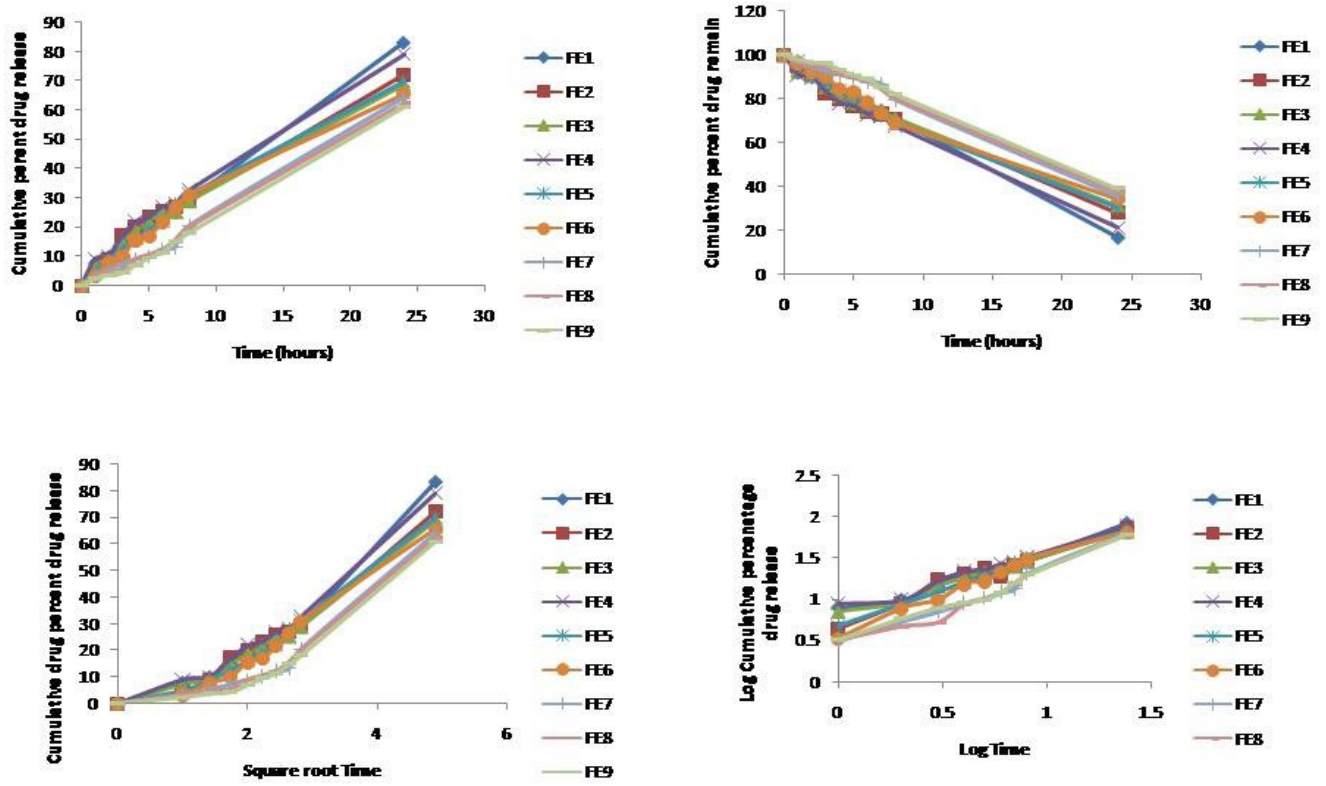

Figure 4: Release Profile of different formulation (FE1-FE9).

A) Zero Order plot, B) First order plot, C) Higuchi's plot, D) Korsmeyer's Peppas Plot.

5 and Figure 4. A) Zero order plot B) First order plot C) Higuch's Plot D) Korsmeyer's Peppas Plot.

Stability studies

The results of the study are shown in Table 6. According to the studies, there were no changes in the formulations' particle size and EE during the storage period.

Sterility Testing

Sterility testing was conducted in the optimized formulation (FE9) as per Indian Pharmacopoeia. The studies reveal that there was no sign of growth of microorganism.

DISCUSSION

The microsponges were successfully prepared O/O ESDM. The microsponges were fabricated by using polymers Ethyl Cellulose and Eudragit RL-100. The amount of polymers were kept at three different levels which is low (-1), intermediate (0) and high (1). The O/O ESDM involves two phases (internal and external phase). The internal phase contains drug and polymers in solvent acetone. Acetone acts as a bridging liquid for atenolol and also behaves as good solvent for drug. The external phase consists of liquid paraffin. The method involves the slow addition of internal phase into external phase with constant stirring at 2000 rpm for 2 hr. The microsponges were assessed for particle size, production yield, entrapment efficiency, drug content. The mirosponges were further incorporated into *in situ* gel and then microsponge loaded gel was evaluated for other evaluation parameters. For fabrication of *in situ* gel different concentration of Poloxamer 407 (14,16 and 18%) and HPMC k4M (0.5, 0.75 and 1%) was used. Benzalkonium chloride was added as a preservative while sodium chloride was added to maintain the tonicity of the formulation.

The results reveal that the size varies from 7.33 to 9.76 µm. The study suggests that as the concentration of polymers were amplified, the particle size also increases. The particle size was maximum when the ratio of both the polymers was at maximum level. The size of all formulations was found to below 10 µm. The particle having size below 10 µm do not cause any sign of irritation to the eye and thus easily suited for ocular delivery.[11] The percentage yield ranges from 59.98 to 81.22. The maximum percentage yield was found for formulation FE9 having high amount of polymers while the low percentage yield was observed for FE1 formulation which contains low amount of polymers. The study suggests that as the concentration of polymer was raised,

the yield of microsponges also gets amplified. The results of drug content (%) ranges from 54.12 to 82.89 for formulation FE1 and FE9. The basic reason behind high DC was the spongy nature of formulation which can accommodate high drug load. The results were in co-relation with the work done by Pethe *et al.*; 2023.[19] The results of EE vary from 58.23% to 81.87%. Among all the formulations, the maximum entrapment efficiency was found for FE8 (82.81%) while minimum entrapment efficiency was FE1 (58.23%) formulation. The drug to polymer concentration affects the EE percentage. High drug content and effective entrapment are favored by higher drug to polymer ratio values. This is consistent with the findings cited by Obiedallah *et al.* in 2018.[11] The surface morphology of FE9 formulation was determined by FESEM study. FESEM shows that the microsponges were round and uniform with spongy surface. A closer look at a microsponge reveals the surface has distinctive interior pores. The microsponges that had been created were homogeneous and spherical in shape. Further, the porous nature of microsponges was also analyzed from the study. The results of FESEM were similar to the finding done by Kshirasagar *et al.*; 2023.[20] The FESEM also revealed the pores on the surface of the microsponges and had a smooth regular surface. Thus, it can be quoted that the method of preparation of microsponges was capable of producing microsponges of desired features.

Once the microsponges were fabricated it was loaded in *in situ* gel and various characteristics, such as pH, rheological behavior, gelling capacity, gelling temperature, cumulative percentage drug release, and stability tests, were assessed. For an ophthalmic product, a pH of 7.4 is appropriate. All formulations' pH values were determined to be within 6-7, indicating that they are all appropriate for ocular administration. The pH of the formulations varies from 6.83 to 7.43 indicating the suitability for formulation for ocular delivery. The results can be co-related with the work done by Vyas *et al.*[21] The viscosity of all formulation was determined with Brookfield viscometer. The viscosity of the microsponges loaded gel was found to be 7421 to 15623 cp. The viscosity helps to enhance the residence time of formulation in eye. The developed formulation was found to have suitable viscosity for ocular delivery. The study shows that the gelling temperature varies from 37.14 to 38.22°C. The results reveal that the formulation converts into gel in body temperature. Finally, it was also found that all the formulations have good gelatin capacity.

The *in vitro* release investigation of microsponge loaded *in situ gel* was conducted in a Franz Diffusion cell. The release data for each formulation was calculated. According to the study, the formulations FE9 release drugs at the slowest rates because of their high polymer concentrations. For release mechanism, various mathematical models were used. The data was exposed to kinetic models such as zero order, first order, Higuchi's, and Korsmeyer Peppas. The data reveals that all preparations follow zero order drug release. In zero order plot, R^2 >0.9 for all formulations. In Kerseymeres Pappas plot the value of n < 0.89 shows the anomalous transport mechanism while n>0.89 which shows that case II transport mechanism. The results of stability studies indicates that the there were no changes in the formulations' particle size and EE during the storage period. Sterility testing was conducted in the optimized formulation (FE9) as per Indian Pharmacopoeia. The studies reveal that there was no sign of growth of micro-organism.

CONCLUSION

The aim of research is development and evaluation of Microsponge loaded *in situ* gel of Atenolol for ocular drug delivery. For this combination two different polymers like ethyl cellulose, and Eudragit RL-100 was used for manufacturing of microsponges. The method used for fabrication of microsponges was modified oil in oil emulsion solvent diffusion method (O/O ESDM). The studies reveal that *in situ* gel were physically and chemically stable and retain their pharmaceutical properties at various environmental conditions over a period of three months. Sterility testing was conducted in three optimized formulation as per Indian Pharmacopoeia. The studies reveal that there was no sign of growth of micro-organism was observed. Further, there was no appearance of turbidity in the formulation was found. The results of the study reveal that the formulation was non-irritating to the eyes. From the above report following points can be concluded that ethyl cellulose, and Eudragit RL-100 are safe, biodegradable, and poses releases retardant properties. Modified oil in oil emulsion solvent diffusion method successfully produces microsponges formulation with desired characteristics. Microsponge loaded *in situ* gel is an unique carrier to deliver the drug at a target site. Atenolol loaded microsponge loaded *in situ* gel can effectively treat Glaucoma and improve the patient compliance.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DSC: Differential Scanning calorimetry; **FTIR:** Fourier transform Infrared Spectroscopy; **SEM:** Scanning electron microscopy; **O/OESDM:** Oil in oil emulsion solvent diffusion method; **Rpm:** Revolutions per minute; **µm:** Micrometer; **Cps:** Centripoise; **DC:** Drug Content; **EE:** Entrapment Efficiency; **PBS:** Phosphate buffer saline.

SUMMARY

The main purpose of the current research was to develop Atenolol loaded mirosponge using Ethyl cellulose and Eudragit RL-100 by oil in oil solvent emulsion diffusion method. The created microsponges were then incorporated into *in situ* gel which was fabricated by using Poloxamer 407 and HPMC K4M. From the study the FE9 was found to be most optimized formulation which shows good results. The study was done to provide sustained or controlled release of drug, increasing the residence time of preparation, improved patient compliance and bioavailability of the formulations.

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