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Original Article

Development and Characterization of Atenolol Based Microsponge Gel for Ophthalmic Delivery

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ABSTRACT

Background: Ocular drug delivery is hindered by a number of reasons, including nasolacrimal drainage, tear turnover and eye blinking. One of the important factors is rapid removal of drug from the eye. The fast elimination rate of drug leads to the loss of drug from the conventional dosage form like eye drop. So, to avoid this problem a novel formulation was designed in which drug will entrap in micro sponges and the micro sponges will be laden into gel. **Aim:** The basic purpose of the study is to formulate atenolol loaded micro sponge gel for the treatment of glaucoma. The microsponges were laden into a gel base to enhance the dwelling time of formulations in eye. **Materials and Methods:** Oil in oil emulsion diffusion method is used for formulating the microsponges by using polymers like Eudragit RS-100 and Eudragit RL-100. The microsponges were subjected to different analytical tools like particle size analysis, surface topography, drug entrapment efficiency, drug loading, pH determination, viscosity, *in vitro* release study and evaluated. The formulation was then laden in to the gel. The gel was then characterized for pH, viscosity and drug release study. Here, we have described a novel formulation of microsponges loaded gel of Atenolol for glaucoma with the complete characterization and *in vitro* release study. **Results:** The particle size of microsponges was found to be in the range of 7.5±0.65 to 9.2±0.5µm. The entrapment efficiencies varied from 70.12% to 80.22%. The percentage yield of the microsponges were found in the range of 75.12 to 85%. The cumulative percentage drug release varies from 60.12% to 79.32%. The microsponge loaded gel has pH in the range of 6.94±0.78 to 7.39±0.65. The viscosity of the different formulation was 220 to 287 Pa.s. **Conclusion:** Microsponges loaded gel of Atenolol for glaucoma with the complete characterization and *in vitro* release was studied. From the *in vitro* studies it can be revealed that the microsponge loaded gel may be exploited for future applications for management of glaucoma

Keywords: Microsponges, Gel, Atenolol, Glaucoma, Eudragit RS-100, Eudragit RL-100.

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INTRODUCTION

Diseases associated with the eye directly influence the vision of human beings as well as are also responsible for maintaining the worth of living. It was surprisingly found from the data that in 39 different countries about 285 million are suffering from these types of diseases.[1] The diseases associated with the eyes include the forward and subsequent portion of the eye.[2] Delivery of drug to the eyes is a very tough activity in the area of investigation and growth of a new drug product. This is because of the exceptional configuration of the organ. So, due to its unique properties, effective delivery of a drug in the eyes has always been a threat to ocular delivery.[3] In the last few years colloidal particles such as nanoparticles, microparticulate and liposome have been used.[4] The advantage of using nano and microparticulate drug delivery systems is that they could easily be installed in the eye and can be given with the ocular drops. This results in the enhancement of the dwelling time of these carriers inside the eyes.[5]

Microsponge is a microsphere that is spongy in nature. Being spongy it can entrap a large number of active ingredients. There are different methods used for the preparation of microsponges. These are emulsion and liquid-liquid suspension polymerization method. Emulsion solvent diffusion, oil-in-oil solvent diffusion and quasi-emulsion solvent diffusion method come under the category of emulsion methods.[6] The advantages of using microsponges are that it is stable over a wide pH range of 1-11 and a temperature of 130°C. These formulations are self-sterilizing because the average size of pores is around 0.25 µm where the bacteria are not able to penetrate. It also releases the drug for extended period of time in the past few years, many researchers focused on the various formulations related to ocular

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drug delivery.[7] A long-acting ophthalmic gel of Atenolol was formulated by Hassan in 2007.[8] Similarly, to target the eye the nanoparticles of Timolol Maleate (TML) consisting Fax seed gum (FX) and Chitosan (CH) were prepared for ocular delivery.[9] The mucoadhesive nanoparticles for ocular delivery were prepared by Taghe 2019.[10,22]

This research aims is to develop microsponges of atenolol by utilizing Eudragit RS-100 and Eudragit RL-100 polymers. Both the polymers are pH independent, control the release of drug. They are also compatible with ocular delivery along with magnesium stearate. These are the reasons for selection of the polymers.[11] The microsponges were subjected to determination of particle size, percent entrapment efficiency, surface morphology study and *in vitro* drug release study for period of 24 hr.

MATERIALS AND METHODS

Materials

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

Methodology

For the preparation of microsponge oil-in-oil emulsion diffusion method is used. In this method acetone is used as solvent to dissolve both the polymers. When the polymers get dissolved, a weighed amount of atenolol is added to it. After that, a specific quantity of magnesium stearate (as anti-adherent) is added to the mixture. The whole mixture is added into 100 mL of liquid paraffin (light) at 2000 rpm for 2 hr. Once the acetone was removed, the microsponges were separated from filtration and dried in desiccators for 24 hr.[12]

The composition of microsponges was represented in Table 1.

Evaluation of Microsponges

Particle size analysis

Optical microscopy plays an important role in the determination of average particles. Usually, different methods are available for the determination of particle size. But in the laboratory scale, the particle size was determined with a help of microscope available at laboratory scale. Generally, 100 particles were counted and their average is calculated.[13]

Drug Entrapment Efficiency

For determination of Entrapment Efficiency 10 mg of microsponge was accurately weighed and dissolved in 50 mL acetone. The vortex mixing was done for 1 hr. After that, the mixture was placed for centrifugation to separate the un-dissolved drug. The supernatant layer was collected and the quantity of drug entrapped can be determined by UV spectrophotometer (Elico SL210) at 274 nm. The reading was taken three times and the standard deviation was also calculated.[14]

Percentage Yield

The practical yield was to determine and find out the efficiency of the method. It was done by determining the practical amount of microsponge to the total amount of ingredients taken.[15]

Surface topography

The surface morphology and surface topography of microsponges were determined by FESEM (Field emission scanning electron microscopy) (Zeiss, Gemini 300).[15]

Preparation of Microsponge Based Gel

The gel-loaded microsponges were prepared with Carbopol 934 polymer. For preparation of gel the weight amount of carbopol 934 (1%w/v) was soaked overnight in an aqueous media. After that, the pH was adjusted near to the ocular pH by adding drop-by-drop triethanolamine. Finally, the weighed quantity of drug loaded microsponges was added to the gel to get the final product.[15]

Characterization of Atenolol loaded microsponge gel

pH Determination

The pH plays an important role in the formulation. Any deviation or changes in the pH leads to lethal conditions. The pH of the formulation was determined by pH meter. Three readings were taken and then the mean and standard deviation were calculated.[16]

Determination of Viscosity

For determination of viscosity, Brookfield viscometer was used. The viscosity of the preparation was determined at a shear rate of 100 rpm. The procedure was conducted in triplicate and standard deviation was also calculated.[17]

In vitro release study of Microsponge loaded gel

The study of the microsponge-loaded gel was conducted in a diffusion cell. For the study, a dialysis membrane (Himedia) is used. An accurately weigh amount (1 g) of the sample was placed on the cells. The phosphate buffer pH 7.4 is used as the solvent. The temperature is set at 37°C and 50 rpm. The samples were withdrawn at a regular period for 24 hr. The samples were then analyzed spectrophotometrically at a maximum wavelength of 274 nm using UV-vis double spectrophotometer (Elico SL210).[18]

Stability Studies

The stability study was conducted as per ICH Guidelines. The microsponges were placed in a humidity chamber for three months at 40±2°C and 75±5% RH. The two parameters namely

Table 1: Formulation of Atenolol Loaded Microsponges using polymers (Eudragit RS -100 and Eudragit RL-100).

Formulation Code	Atenolol (mg)	Eudragit RS-100 (mg)	Eudragit RL-100 (mg)	Magnesium Stearate (mg)	Acetone (mL)	Light Liquid Paraffin (mL)
F1	90	-1(90)	-1(90)	5	10	200
F2	90	0(180)	-1(90)	5	10	200
F3	90	1(270)	-1(90)	5	10	200
F4	90	-1(90)	0(180)	5	10	200
F5	90	0(180)	0(180)	5	10	200
F6	90	1(270)	0(180)	5	10	200
F7	90	-1(90)	1(270)	5	10	200
F8	90	0(180)	1(270)	5	10	200
F9	90	1(270)	1(270)	5	10	200

Table 2: Results of Atenolol loaded Microsponges.

Formulation code	Mean particle size (µm)	Percentage Yield (%)	Encapsulation Efficiency (%)
F1	7.5±0.65	75.12±0.22	75.12±0.73
F2	7.92±0.87	76.55±0.19	78.98±0.29
F3	8.2±0.78	79.82±0.24	75.65±0.66
F4	8.54±0.91	75.23±0.36	70.12±0.45
F5	8.65±0.89	79.9±0.48	72.26±0.54
F6	8.55±0.55	82.3±0.14	80.22±0.63
F7	8.48±0.49	80.12±0.56	72.23±0.31
F8	9.2±0.58	83.21±0.45	72.34±0.89
F9	9.01±0.86	85.5±0.65	81.23±0.28

particle size and drug release study of microsponges were evaluated.

RESULTS

The microsponges were fabricated by oil in oil emulsion solvent diffusion method. The prepared microsponges were subjected to evaluation, for which the results are shown in Table 2 and Figure 1.

Particle size analysis

Particle size of different formulations is represented in Table 2 and Figure 1. The particle size of the formulation lies within the range of 7.5 ±0.65 to 9.2 ±0.5 µm.

Drug Entrapment

The percent entrapment efficiency is more than 70% for all the formulations. The highly porous nature of the microsponges was responsible for the high entrapment efficiency. The entrapment efficiencies varied from 70.12% to 80.22%. The results were represented in Table 2 and Figure 1. Percentage Yield

It helps to determine the efficiency of the method. The values of percentage yield varied from 75.12% to 85.5%. The results were shown in Table 2 and Figure 1.

Surface topography

The surface topography was determined by using FESEM (Field Emission Scanning Electron Microscopy) as shown in Figure 2.

Evaluation of Microsponges loaded *in situ* gel

For the preparation of gel, microsponges were loaded in carbopol base. The microsponges loaded gel was then subjected to different evaluation parameters like pH, viscosity and *in vitro* release study.

pH Determination

The pH varies within the range of 6.98±0.38 to7.4±0.98 which is suitable for the ocular preparation. The normal pH range was 6.5-7.6. The results of pH determination were represented in Table 3.

Table 3: **Results of Micro sponge loaded gel.**

Formulation	pH	Viscosity (Pa.s)	Cumulative Percentage Release (%)
F1	6.94±0.78	220±0.11	79.32
F2	6.98±0.38	215±0.21	68.9
F3	7.4±0.98	211±0.33	64.89
F4	7.32±0.31	216±0.56	75.45
F5	7.39±0.65	210±0.78	65.66
F6	7.26±0.98	212±0.98	62.78
F7	6.99±0.51	211±0.78	61.81
F8	7.38±0.76	210±0.87	60.88
F9	7.29±0.88	211±0.45	60.12

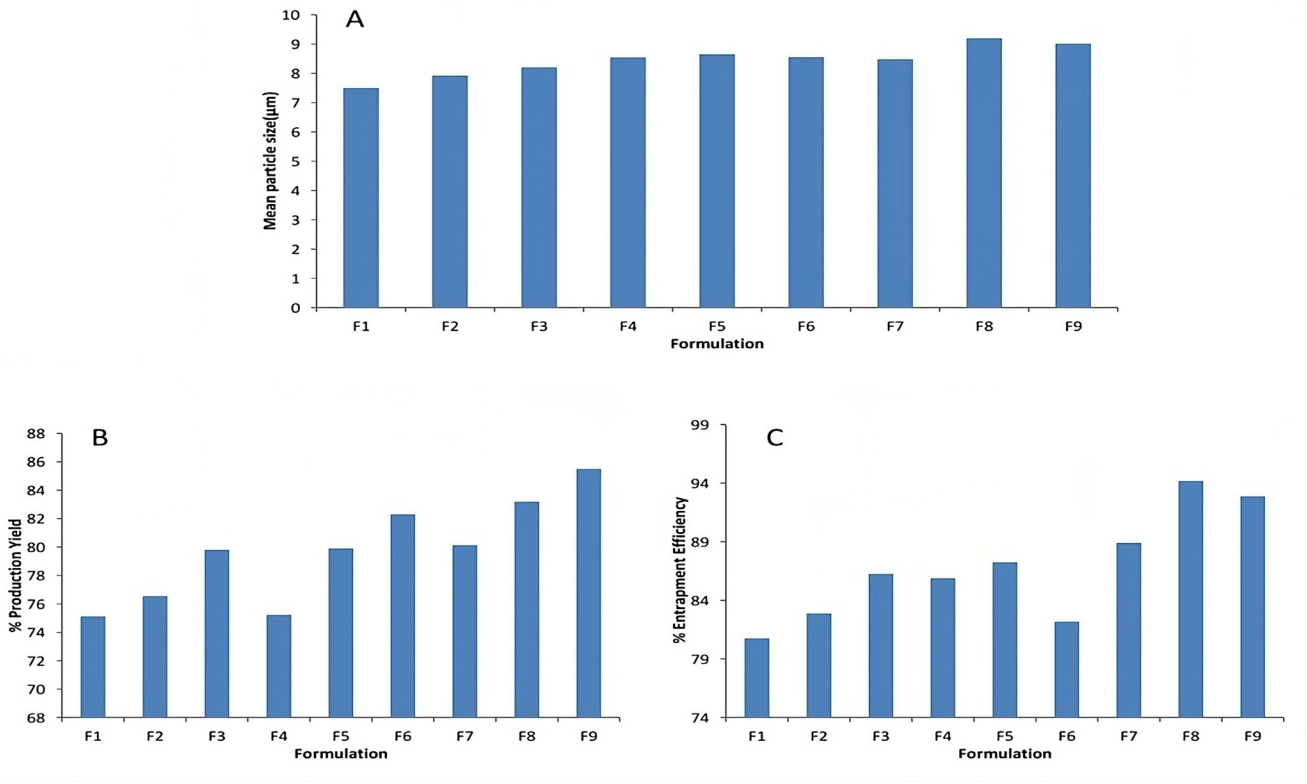

Figure 1: Evaluation of Microsponge, A.: Mean particle size of F1-F9 formulations, B: Percent Production Yield of F1-F9 Formulation, C: Percent Entrapment Efficiency of F1-F9.

Viscosity

The viscosity of the formulation varies between 220 to 287 Pa.s. This viscosity of preparation is suitable for the ocular products to remain inside the eye and to increase the residence time in the eyes.

In vitro release study

The *in vitro* release study was carried out for 24 hr. The release study was conducted in pH 7.4 phosphate buffer. The results of release study were shown in Table 3. The data from *in vitro* release study were put into mathematical model like zero order, first order, Higuchi and Korsmeyers Peppas model. The results of R^2 value of zero, first, Higuchi's and Korsmeyers Peppas were shown in Table 4 and Figure 3.

Stability Studies

The stability studies for all the formulation was conducted as per ICH guidelines. The mean particle size and cumulative percent drug release of all formulations were calculated after three months. The results were represented in Table 5.

DISCUSSION

Atenolol loaded microsponges were successfully formulated by oil-in-oil emulsion solvent diffusion method. The role of magnesium stearate was as an anti-adherent agent. It prevented

Table 4: Results of Kinetic modeling of Micro sponges loaded gel.

Formulation	Zero Order	First Order	Higuchi's	Kerseymeres Pappas
F1	0.994	0.993	0.872	0.958
F2	0.995	0.995	0.866	0.975
F3	0.988	0.994	0.830	0.901
F4	0.997	0.994	0.842	0,966
F5	0.995	0.988	0.846	0.980
F6	0.988	0.988	0.821	0.976
F7	0.982	0.82	0.805	0.964
F8	0.975	0.979	0.791	0.964
F9	0.976	0.975	0.776	0.941

Table 5: Stability studies of formulations after three months.

Formulation Code	Mean Particle Size (µm)	Cumulative % drug release
F1	7.55±0.75	78.2
F2	7.99±0.89	67.56
F3	8.42±0.88	62.12
F4	8.55±0.91	72.29
F5	8.65±0.69	61.88
F6	8.56±0.95	60.22
F7	8.5±0.39	59.19
F8	9.27±0.58	58.68
F9	9.11±0.86	57.67

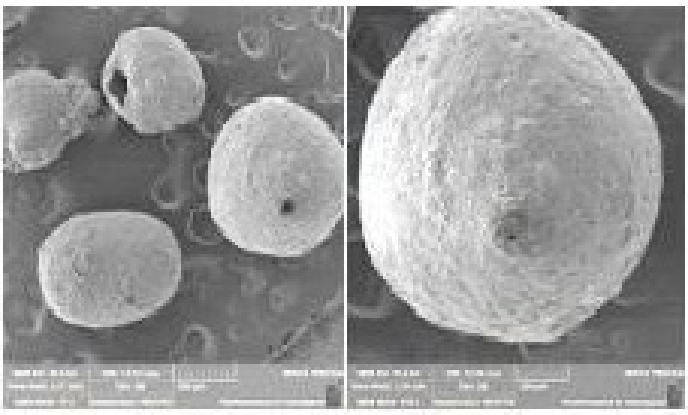

Figure 2: FESEM of Micro sponges.

the agglomeration of the microsponges. The polymers used for the study were Eudragit RS-100 and Eudragit RL-100. The selection of the polymers was based on its pH independent property, control release of drug and compatibility with eye. The concentration of polymers is represented by three different levels -1,0,1 where -1 represents the lowest concentration, 0 (zero) represents medium concentration and 1 represents the highest concentration of polymers. The formed microsponges were subjected to different evaluation parameters like particle size, percentage yield and encapsulation efficiency. The particle size of the formulation lies within the range of 7.5 ±0.65 to 9.2 ±0.5 µm. The size of microsponges for ocular delivery should not exceed 10 µm. The size above 10 µm can cause irritation to the eyes. All the formulated microsponges had a size below 10 µm and were thus suitable for ocular delivery. It was observed from the results that particle size has increased with the increase in the concentration of the polymer.[10] Similar types of results related to the particle size of microsponges were obtained by Gupta *et al.*, 2013[19] where the rise in the concentration of polymer results in an increase in particle size. The entrapment efficiencies of all formulation vary from 70.12% to 80.22%. The drug entrapment efficiency depends upon the concentration or amount of polymers. Entrapment efficiency greatly increased with the increase in polymer concentration.[20] The results related to entrapment efficiency are in agreement with the earlier research conducted by Taghe and Mirzaeei *et al.*, 2018.[10] The percentage yield was ranges from 75.12% to 85.5%. It was found as the polymer concentration was increased, the yield of microsponges also increased. The high percentage yield determined the efficiency of the method to prepare microsponges. The surface topography was determined by using FESEM. The images of FESEM revealed that the microsponges thus formed were round and spherical. The FESEM also revealed the pores on the surface of the microsponges. The microsponges had a smooth regular surface. These results were in correlation with the work done by Shahzad *et al.*, 2018.[21] Thus, it can be quoted that the method used for the preparation of microsponges was capable of producing microsponges with desired features. In another study done by Dhyani and Kumar, it was found that microsponges of Ethyl cellulose and Eudragit RS-100 was easily fabricated by o/o emulsion solvent diffusion method. The obtained microsponge was regular and smooth in surface with particle size less than 10 µm.[22]

Once microsponges were evaluated they were incorporated into a gel base. After that, it was evaluated for pH determination, viscosity and *in vitro* release study. The pH of all formulation varies within the range of 6.98±0.38 to7.4±0.98 which is suitable for the ocular preparation. Usually, the ocular preparations must have a pH value of 7.4. This value of pH is best suited for an

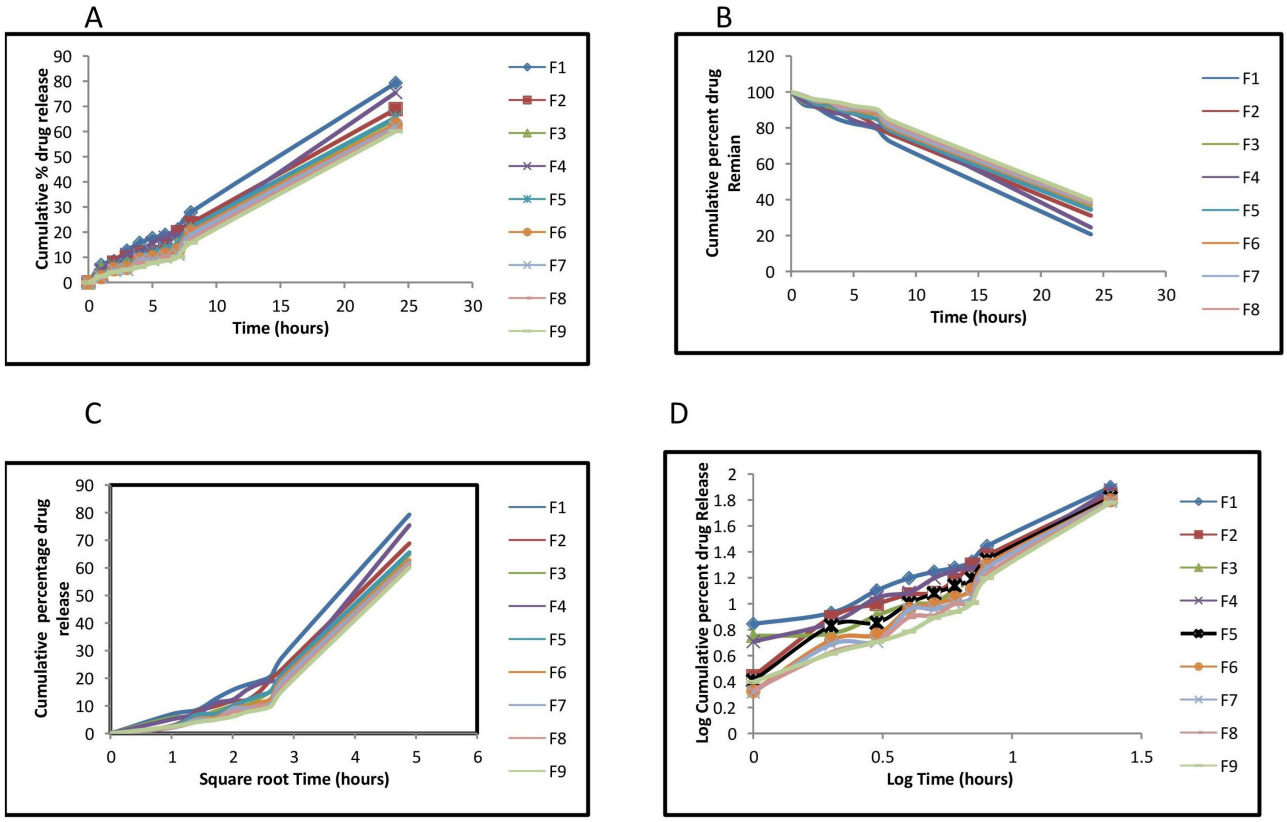

Figure 3: Release study of Micro sponges, a: Zero Order Release of F1-F9, B: First Order Release of F1-F9, C: Higuchi Plot of F1-F9, D: Nordmeyer Pappas Plot of F1-F9 formulation.

ocular product. The viscosity of all formulations lies between 220 to 287Pa.s. This viscosity of preparation is suitable for the ocular products to remain inside the eye and to increase the residence time in the eyes. The *in vitro* release study was conducted in pH 7.4 phosphate buffer. The study revealed that as the polymer concentration was enhanced, the drug release was reduced and as the concentration of polymer increased the percent entrapment efficiency increased. The percentage of drug release varies from 60.12 to 79.32%. A high concentration of Eudragit RS -100 slows the release of the drug in comparison to Eudragit RL-100.This is because Eudragit RS-100 has low permeability than Eudragit RS-100 formulations. The data of the release profile was put in zero order, first order, Higuchi, KorsmeyerPeppas models. From the values of R^2 it can be concluded that the formulations follow zero-order release kinetics. Since the value of R^2 for the Higuchi equation is less than 0.9, therefore, the microsponges do not follow diffusion mechanism. Higher values of KorsmeyerPeppas reveal that the formulations themselves follow the supercase-II transport mechanism. At last, the stability study of all formulation was conducted for three months as per ICH guidelines. From the results, it was concluded that there was no noteworthy change in particle size and drug release after three months. Thus, all the formulations were found to be stable after three months.[23-25]

CONCLUSION

In this article, the Atenolol loaded microsponge gel was successfully prepared. The formulations were characterized and its release profile was also observed up to a period of 24 hr. This study further provides an opportunity to use microsponge gel for future generations for the treatment of glaucoma. It also opens the door for various researchers to formulate this kind of preparation for the overcoming generation which provides maximum patient benefits with minimum side effects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

FESEM: Field Emission Scanning Electron Microscopy; **PBS:** Phosphate buffer saline; **ICH:** International Council for Harmonization; **Rpm:** Revolution per minute.

SUMMARY

The aim of present study was to develop and evaluate a microsponge gel of Atenolol for ocular delivery. Initially, microsponges were fabricated by oil in oil solvent diffusion method. After that, the formulated microsponges were incorporated into a carbopol gel. The gel-loaded microsponges were evaluated for viscosity, pH and drug release. The result shows that microsponge gel was suitable for ocular delivery.

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