International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 13, Issue 1, 2021

Original Article

DRUG RELEASE CONTROL AND ENHANCEMENT USING CARRIERS WITH DIFFERENT CONCENTRATIONS OF CAPMUL® MCM C8

MOHAMMAD F. BAYAN

Faculty of Pharmacy, Philadelphia University, Amman, Jordan
Email: mbayan01@qub.ac.uk

Received: 15 Sep 2020, Revised and Accepted: 21 Oct 2020

ABSTRACT

Objective: The main aim of this study was to design a drug carrier capable to control and enhance the release of poorly water soluble drugs.

Methods: Three polymeric formulations, based on poly (2-hydroxyethyl methacrylate) and loaded with different Capmul® MCM C8 concentrations (0, 10 and 20 % w/w), were prepared. Felodipine, which is a poorly soluble substance, was selected as a model drug. The effect of Capmul® MCM C8 on swelling behavior and *in vitro* release profile of the prepared polymer was investigated in PBS.

Results: The swelling profiles of all formulations were statistically similar, which indicated the non-significant effect of added Capmul® MCM C8 on polymer's swelling behavior. All formulations showed a delayed drug release. Formulation-F3, which is loaded with 20% w/w Capmul® MCM C8 displayed a significant higher release compared to the other formulations.

Conclusion: Capmul® MCM products, which are widely used in food industries, can be used to improve the oral delivery of poorly soluble substances. The optimized formulation exhibited the ability to control and enhance the release of the model drug.

Keywords: Capmul® MCM C8, Drug delivery, Free radical polymerization, Bioavailability enhancement

DOI: http://dx.doi.org/10.22159/ijap.2021v13i1.39742. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

An ideal drug delivery system aims to deliver the drug, selectively and effectively, to the site of action in the body. Such system should be capable to prevent and retard the drug release until reaching the target site; thus improving the drug availability and therapeutic efficacy and reducing potential side effects. The poor bioavailability represents a major issue for new drug entities as around 60% of these new drugs are reported to have bioavailability issue due to solubility problems. This has increased the attention towards the continuous development and improvement of drug delivery systems, capable to enhance the solubility of poorly soluble drugs; thus enhancing the drug bioavailability and therapeutic efficacy [1]. Various methods and technologies have been reported to improve the bioavailability of poorly soluble drugs, such as mesoporous silica based systems, solid dispersion technology, nanocrystals technology, liposomes, supercritical fluid technology, self-emulsifying systems and melt extrusion [2-8]. The crystalline drug form might be converted to the more soluble amorphous form (no energy is required to break the intermolecular forces of the crystal lattice) in these approaches. Capmul® MCM products have been widely employed in skin care products and food industries such as; ice creams, bakery, beverages, chewing gums and confectionery. They are obtained via direct esterification of glycerin with vegetable sourced octanoic and decanoic acids. They can enhance the solubility and or absorption of poorly soluble/absorbed drugs [9-11]. Shailendrakumar *et al.* [12] incorporated Capmul® MCM in the development of a promising controlled delivery system to enhance the oral bioavailability of pentoxifylline. In another study, Meola *et al.* [13] used Capmul® MCM in the preparation of silica-lipid hybrid microparticles to improve the dissolution and oral delivery of simvastatin. 2-hydroxyethyl methacrylate (HEMA) represents one of the most commonly used synthetic monomers for the preparation of crosslinked polymers and it has been widely used in many pharmaceutical applications such as soft contact lenses [14] and drug carriers [15]. The easiness of preparation, the flexibility in modifying the polymer structure, the ability to control the drug release and protect it from degradation as well as the polymer swelling behaviour are all features encouraged its use in many biomedical and drug delivery applications. The chemical and thermal stability as well as biodegradability and biocompatibility of poly (2-hydroxyethyl methacrylate) based polymers have also made them attractive for many pharmaceutical and biomedical applications [16-20]. Mangiacotte *et al.* [21] used HEMA in the development of polymeric mucoadhesive nanoparticles, as a potential ophthalmic drug delivery system. Rashid et al. [22] have also used HEMA in the synthesis of polymeric microgels designed for the controlled delivery of acid labile therapeutic agents. The synthesized carrier was loaded with esomeprazole as a model drug. The in vitro and in vivo studies had shown that the carrier was able to retard the drug release in the stomach; while trigger the release in the intestinal environment. The main objective of this study was to develop a drug delivery system, based on poly (2-hydroxyethyl methacrylate) polymer with different concentrations of Capmul® MCM C8, prepared using a free radical polymerization method as a promising system to control and enhance the release of poorly water soluble drugs. Felodipine was selected as a model drug to be loaded in the prepared carriers; since it is classified as a BCS class II drug according to the biopharmaceutics Classification System (low solubility, high permeability) [23-25]. Swelling studies were performed for the produced carriers and in vitro release studies were also performed to study the effect of changing the concentration of Capmul® MCM C8 on the release profiles of the model drug.

MATERIALS AND METHODS

Materials

2-Hydroxyethyl methacrylate, ethylene glycol dimethacrylate, 2,2′-Azobis(2-methylpropionitrile), sodium chloride, sodium phosphate dibasic dodecahydrate, sodium dodecyl sulphate (SDS), potassium chloride and felodipine were supplied by Sigma-Aldrich, USA. Sodium hydroxide and potassium phosphate monobasic were supplied by Scharlau Chemie, Spain. Capmul® MCM C8 was supplied by ABITEC, UK. Hydrochloric acid (37%) was supplied by Biosolve Chimie, France. Water used in all experiments was HPLC grade water. All chemicals were used as supplied without any modification.

Methods

Preparation of polymeric films with different concentrations of Capmul® MCM C8

A free radical polymerization method was used to prepare Six polymeric films (P1-P3 and F1-F3) using the quantities described in table 1 by dissolving the ingredients of each formula together at room temperature with stirring. After that medical syringes (10 ml) with needles were used to pour the prepared solutions into designed molds. A release liner was placed over two glass plates and a medical grade silicone tubing was placed in a hemispherical shape over one of the plates to draw the borders of the mold. The two plate were held together vertically using foldback clips. After pouring the solutions, the molds were placed in the oven allow polymerization at 60 °C for 18 h. After polymerization, the films were then taken out the molds and placed in HPLC grade water and replaced daily to remove any unreacted species, which was confirmed using a UV/VIS spectrophotometer (Spectroscan 80 D, Biotech Engineering Ltd., UK). A cork borer no. 2 (6.25 mm in diameter) was used to cut the swollen polymers into small discs. Finally, these discs were dried until a constant weight was reached.

Table 1: The Prepared polymeric films

Formula	2-Hydroxyethyl methacrylate (grams)	Capmul® MCM C8 (grams)	Ethylene glycol dimethacrylate (grams)	2,2′-Azobis(2-methylpropionitrile) (grams)	Felodipine (grams)
P1	9.8	-	0.1	0.1	-
P2	8.8	1.0	0.1	0.1	-
P3	7.8	2.0	0.1	0.1	-
F1	9.3	-	0.1	0.1	0.5
F2	8.3	1.0	0.1	0.1	0.5
F3	7.3	2.0	0.1	0.1	0.5

Swelling studies

The effect of Capmul®MCM C8 concentration on the swelling ration of the produced discs was investigated in Phosphate Buffered Saline (PBS) at 37 °C. The dried polymeric were weighed and then placed in a McCartney bottle containing 5 ml PBS. The discs were removed from the swelling media at predetermined time points. The removed samples were weighed after being dried superficially using a medical tissue paper and then returned back to the swelling medium. The swelling behavior of the prepared discs was studied via calculating the swelling ratio, using Equation 1, at each time point. The obtained data were analyzed statistically (GraphPad Prism 8 software) using a two-way analysis of variance, followed by Tukey's multiple comparisons test (n=5, p<0.05).

$$\text{Swelling ratio (\%)} = \left[\frac{\text{Weight of the swollen disc} - \text{Weight of the dried disc}}{\text{Weight of the swollen disc}}\right] \times 100\%$$

…. (Equation 1)

***In vitro* drug release studies**

The *in vitro* release of the model drug was investigated in PBS (pH 7.4), containing 1% w/v SDS, using a modified method of Heelan and Corrigan [26-28]. The prepared formulations were immersed in 20 ml PBS (previously maintained at 37 °C) inside a sealed McCartney bottle. The bottle was stirred in a shaking water bath at 37 °C and 100 cycles/min. At predetermined time points, 0.5 ml samples were removed from the bottles and replaced with the same volume of fresh PBS (previously maintained at 37 °C). The withdrawn samples were filtered and analyzed spectro-photometrically (Spectroscan 80 D, Biotech Engineering Ltd., UK) at 364 nm. A calibration curve was constructed at 364 nm and the method was fully validated. The obtained data were analyzed statistically (GraphPad Prism 8 software) using a two-way analysis of variance, followed by Tukey's multiple comparisons test (n=3, p<0.05).

RESULTS AND DISCUSSION

Preparation of polymeric films with different concentrations of Capmul® MCM C8

Six polymeric films loaded with different concentrations (0, 10 and 20% w/w) of the bioavailability enhancer (Capmul® MCM C8), based on 2-Hydroxyethyl methacrylate as a monomer and ethylene glycol dimethacrylate as a crosslinker, were synthesised successfully using a thermal bulk polymerization method. Theses formulations were developed as promising controlled delivery systems and loaded with Capmul® MCM C8 for the potential enhancement of release and bioavailability of poorly water soluble drug. Patel *et al.* have employed Capmul® MCM C8 as a bioavailability enhancer in pellets designed for improved oral drug delivery of gliclazide [29]. The prepared formulations were loaded with 5% w/w of the antihypertensive agent, felodipine, as a model drug.

Swelling studies

A quantitative method was used to evaluate the swelling behaviour of the prepared non-drug loaded formulations (P1-P3) in PBS [30]. The swelling ratio of a polymer in aqueous medium is mainly controlled by the polymer-polymer and polymer-medium interactions and the equilibrium swelling ratio is obtained when a balance occurs between these two interactions [31]. Fig. 1-2 shows the effect of Capmul® MCM C8 concentration on the polymer's swelling behaviour. The three formulations showed statistically similar profiles with an equilibrium swelling ratio of 35% obtained within 24 h. This indicates the non-significant effect of the used Capmul® MCM C8 concentrations on the polymer's swelling profile.

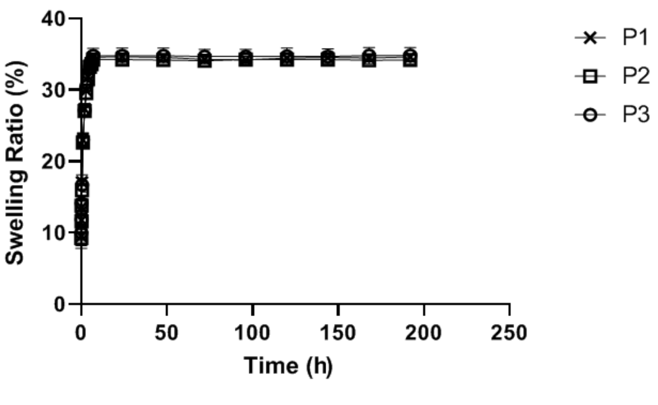

Fig. 1: Time-dependent swelling ratio (mean±SD, n=5) of P1, P2 and P3 in PBS

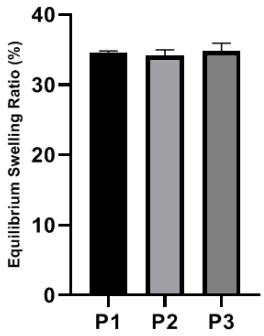

Fig. 2: Equilibrium swelling ratio (mean±SD, n=5) of P1, P2 and P3 in PBS

In vitro drug release studies

The release profiles and release rate constants (K_m) of felodipine from the prepared formulations (F1-F3) are presented in fig. 3 and table 2. It can be observed that all profiles exhibited a delayed-controlled release for the model drug. The effect of Capmul® MCM C8 concentration one the release profiles of the model drug was also investigated. Increasing Capmul® MCM C8 concentration from 0 to 10% w/w had no significant effect on the drug release profile, while increasing it to 20% w/w (F3) resulted in a significant higher drug release. This improved release can be explained by the formation of micelles by Capmul® MCM C8 within the polymeric network [32-34]. This result was also confirmed by the release rate constants obtained in table 2. The mechanisms of drug release from a polymeric network can be diffusion controlled, swelling-controlled and/or chemically controlled such as the enzymatic cleavage of the polymeric chains [35-37]. The first 60% of all release data were fitted to the Korsmeyer Peppas release model (R^2 ranged from 0.95 to 0.99), to investigate the release mechanisms and release rate constants. This model (Equation 2) is based on a plain exponential equation relates the drug release with time. It is commonly used in polymeric drug delivery systems and particularly when the drug has more than one release mechanism and/or it is not clear [28, 38-40]. In this equation, Q refers to the ratio of substance release at specific time (in hours) point (t), K_m to the release rate constant and n to the diffusion or release exponent. A linear regression of log Q versus log t was performed for the three formulations to find K_m and n value, which gives an indication about the release mechanism. A Fickian diffusion mechanism is indicated when n value≤ 0.5, A n anomalous mechanism (the release is controlled by both diffusion and relaxation of the polymeric chain) when 0.5 < n value < 1.0, case 2 transport (release is controlled by relaxation of the polymeric chain) when n value = 1 and super case 2 transport (the release is controlled by both diffusion and relaxation of the polymeric chain) when n value>1.0 [41-43]. The estimated n value was between 0.5 and 1.0 for the three prepared formulations, which indicates an anomalous release mechanism.

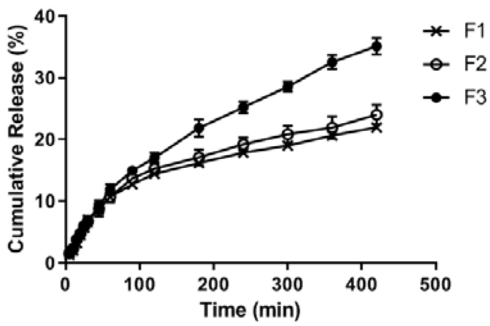

Fig. 3: The release profiles of Felodipine from the prepared formulations [F1, F2 and F3] (mean±SD, n=3) at pH 7.4

$$Q = K_m t^n \text{ ...... (Equation 2)}$$

Table 2: R^2, n and K_m after data fitting to the korsmeyer peppas model

Formulation	R^2	n	K_m
F1	0.945	0.619	0.082
F2	0.962	0.610	0.088
F3	0.989	0.702	0.100

CONCLUSION

Polymeric drug carriers with different concentrations of Capmul® MCM C8 were prepared successfully using a free radical polymerization method. The formulations were loaded felodipine as a model drug. The effect of added Capmul® MCM C8 on the swelling degree of the polymer was investigated in PBS. There was no significant effect for increasing the concentration of Capmul® MCM C8 on the swelling behavior of the polymer as the three formulations showed statistically similar swelling profiles. All formulations showed a delayed drug release. The formulation with the highest concentration of Capmul® MCM C8 (20 % w/w), exhibited a significant higher drug release compared with the other formulations, which makes a promising system to control and enhance drug release of poorly water soluble drugs.

ACKNOWLEDGEMENT

The author is grateful to the Philadelphia University, Amman, Jordan for the financial support granted to cover the publication fee of this paper.

ABBREVIATION

HEMA: 2-hydroxyethyl methacrylate; BCS: Biopharmaceutics Classification System; SDS: Sodium Dodecyl Sulphate; PBS: Phosphate Buffered Saline.

FUNDING

This work was supported by Philadelphia University, Amman, Jordan.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

No conflicts of interest to disclose.

REFERENCES

1. Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. Int J Pharm Invest 2012;2:12-7.
2. Bremmell K, Prestidge C. Enhancing oral bioavailability of poorly soluble drugs with mesoporous silica based systems: opportunities and challenges. Drug Dev Ind Pharm 2019;45:349-58.
3. Cid A, Simonazzi A, Palma S, Bermudez J. Solid dispersion technology as a strategy to improve the bioavailability of poorly soluble drugs. Ther Delivery 2019;10:363-82.
4. Zhou Y, Du J, Wang L, Wang Y. Nanocrystals technology for improving bioavailability of poorly soluble drugs: a mini-review. J Nanosci Nanotechnol 2017;17:18-28.

5. Aloisio C, Antimisiaris S, Longhi M. Liposomes containing cyclodextrins or meglumine to solubilize and improve the bioavailability of poorly soluble drugs. J Mol Liquids 2017;229:106-13.
6. Abuzar S, Hyun S, Kim J, Park H, Kim M, Park J, *et al*. Enhancing the solubility and bioavailability of poorly water-soluble drugs using supercritical antisolvent (SAS) process. Int J Pharm 2018;538:1-13.
7. Potphode V, Deshmukh A, Mahajan V. Self-micro emulsifying drug delivery system: an approach for enhancement of bioavailability of poorly water soluble drugs. Asian J Pharm Technol 2016;6:159-68.
8. Repka M, Bandari S, Kallakunta V, Vo A, McFall H, Pimparade M, *et al*. Melt extrusion with poorly soluble drugs–an integrated review. Int J Pharm 2018;535:68-85.
9. Li S, Madan P, Lin S. Effect of ionization of drug on drug solubilization in SMEDDS prepared using capmul MCM and caprylic acid. Asian J Pharm Sci 2017;12:73-82.
10. Lee Y, Dalton C, Regler B, Harris D. Drug solubility in fatty acids as a formulation design approach for lipid-based formulations: a technical note. Drug Dev Industrial Pharm 2018;44:1551-6.
11. Efiana N, Dizdarevic A, Huck C, Bernkop Schnürch A. Improved intestinal mucus permeation of vancomycin via incorporation into nanocarrier containing papain-palmitate. J Pharm Sci 2019;108:3329-39.
12. Shailendrakumar A, Ghate V, Kinra M, Lewis S. Improved oral pharmacokinetics of pentoxifylline with palm oil and Capmul® MCM containing self-nano-emulsifying drug delivery system. AAPS PharmSciTech 2020;21:1-12.
13. Meola T, Schultz H, Peressin K, Prestidge C. Enhancing the oral bioavailability of simvastatin with silica-lipid hybrid particles: the effect of supersaturation and silica geometry. Eur J Pharm Sci 2020;150:1053-7.
14. Tran N, Yang M. The ophthalmic performance of hydrogel contact lenses loaded with silicone nanoparticles. Polymers 2020;12:1128.
15. Ozay O, Ilgin P, Ozay H, Gungor Z, Yilmaz B, Kıvanç M. The preparation of various shapes and porosities of hydroxyethyl starch/p (HEMA-co-NVP) IPN hydrogels as programmable carrier for drug delivery. J Macromolecular Sci Part A 2020;57:379-87.
16. Gyles D, Castro L, Silva Jr J, Ribeiro Costa R. A review of the designs and prominent biomedical advances of natural and synthetic hydrogel formulations. Euro Polymer J 2017;88:373-92.
17. Karabanova L, Mikhalovsky S, Lloyd A. Gradient semi-interpenetrating polymer networks based on polyurethane and poly (2-hydroxyethyl methacrylate) for biomedical applications. J Materials Chem 2012;22:7919-28.
18. Bayan M, Bayan R. Recent advances in mesalamine colonic delivery systems. Future J Pharm Sci 2020;6:1-7.
19. Pradhan A, Rana P, Sahoo P. Biodegradability and swelling capacity of kaolin based chitosan-g-PHEMA nanocomposite hydrogel. Int J Biol Macromolecules 2015;74:620-6.
20. Ozay O, Ilgin P, Ozay H, Gungor Z, Yilmaz B, Kıvanç M. The preparation of various shapes and porosities of hydroxyethyl starch/p (HEMA-co-NVP) IPN hydrogels as programmable carrier for drug delivery. J Macromolecular Sci Part A 2020;57:379-87.
21. Mangiacotte N, Prosperi Porta G, Liu L, Dodd M, Sheardown H. Mucoadhesive nanoparticles for drug delivery to the anterior eye. Nanomaterials 2020;10:1400.
22. Rashid Z, Ranjha N, Rashid F, Raza H. Pharmacokinetic evaluation of microgels for targeted and sustained delivery of acid labile active pharmaceutical agent in animal model. J Drug Delivery Sci Technol 2020;57:101770.
23. Stegemann S, Leveiller F, Franchi D, De Jong H, Linden H. When poor solubility becomes an issue: from early stage to proof of concept. Eur J Pharm Sci 2007;31:249-61.
24. Palazi E, Karavas E, Barmpalexis P, Kostoglou M, Nanaki S, Christodoulou E, *et al*. Melt extrusion process for adjusting drug release of poorly water soluble drug felodipine using different polymer matrices. Eur J Pharm Sci 2018;114:332-45.
25. Jing B, Wang Z, Yang R, Zheng X, Zhao J, Tang S, *et al*. Enhanced oral bioavailability of felodipine by novel solid self-microemulsifying tablets. Drug Dev Ind Pharm 2016;42:506-12.
26. Shah U, Joshi G, Sawant K. Improvement in antihypertensive and antianginal effects of felodipine by enhanced absorption from PLGA nanoparticles optimized by factorial design. Mater Sci Eng 2014;35:153-63.
27. Wu C, Zhao Z, Zhao Y, Hao Y, Liu Y, Liu C. Preparation of a push–pull osmotic pump of felodipine solubilized by mesoporous silica nanoparticles with a core–shell structure. Int J Pharm 2014;475:298-305.
28. Obaidat R, Tashtoush B, Bayan M, Al Bustami R, Alnaief M. Drying using supercritical fluid technology as a potential method for preparation of chitosan aerogel microparticles. AAPS PharmSciTech 2015;16:1235-44.
29. Patel H, Pandey N, Patel B, Ranch K, Bodiwala K, Vyas B. Enhancement of *in vivo* hypoglycemic effect of gliclazide by developing self-microemulsifying pellet dosage form. Future J Pharm Sci 2020;6:1-14.
30. Tran N, Yang M. Synthesis and characterization of silicone contact lenses based on TRIS-DMA-NVP-HEMA hydrogels. Polymers 2019;11:944.
31. Ferrell W, Kushner D, Hickner M. Investigation of polymer–solvent interactions in poly (styrene sulfonate) thin films. J Polym Sci Part B: Polym Phys 2017;55:1365-72.
32. Mohanrao B, Sundar P, Nagsen S. Oral bioavailability enhancement of a poor water soluble drug by cosurfactant free self-emulsifying drug delivery system (SEDDS). Res J Pharm Technol 2011;4:1557-62.
33. Alhasani K, Kazi M, Ibrahim M, Shahba A, Alanazi F. Self-nanoemulsifying ramipril tablets: a novel delivery system for the enhancement of drug dissolution and stability. Int J Nanomed 2019;14:5435.
34. Uchida T, Toida Y, Sakakibara S, Miyanaga Y, Tanaka H, Nishikata M, *et al*. Preparation and characterization of insulin-loaded acrylic hydrogels containing absorption enhancers. Chem Pharm Bull 2001;49:1261-6.
35. Onoyima C, Okibe F, Sholadoye Q. Kinetics and mechanisms of doxorubicin release from hydroxyapatite-sodium alginate nanocomposite. Nigerian J Pharm Appl Sci Res 2020;9:7-13.
36. Sharma P, Tailang M. Design, optimization, and evaluation of hydrogel of primaquine loaded nanoemulsion for malaria therapy. Future J Pharm Sci 2020;6:1-11.
37. Li J, Mooney D. Designing hydrogels for controlled drug delivery. Nat Rev Mater 2016;1:1-17.
38. Hamedi S, Koosha M. Designing a pH-responsive drug delivery system for the release of black-carrot anthocyanins loaded in halloysite nanotubes for cancer treatment. Appl Clay Sci 2020;197:105770.
39. Rezaei A, Nasirpour A. Evaluation of release kinetics and mechanisms of curcumin and curcumin-β-cyclodextrin inclusion complex incorporated in electrospun almond gum/PVA nanofibers in simulated saliva and simulated gastrointestinal conditions. BioNanoScience 2019;9:438-45.
40. Raj S, Chandrasekhar K, Reddy K. Formulation, *in vitro* and *in vivo* pharmacokinetic evaluation of simvastatin nanostructured lipid carrier loaded transdermal drug delivery system. Future J Pharm Sci 2019;5:1-14.
41. Quintanilla de Stefano J, Abundis Correa V, Herrera Flores S, Alvarez A. pH-sensitive starch-based hydrogels: synthesis and effect of molecular components on drug release behavior. Polymers 2020;12:1974.
42. Gupta P, Purwar R. Electrospun pH responsive poly (acrylic acid-co-acrylamide) hydrogel nanofibrous mats for drug delivery. J Polymer Res 2020;27:1-10.
43. Sharma P, Mittal H, Jindal R, Jindal D, Alhassan S. Sustained delivery of atenolol drug using gum dammar crosslinked polyacrylamide and zirconium based biodegradable hydrogel composites. Colloids Surf A 2019;562:136-45.