Original Article

Formulation and in Vitro Evaluation of Moxifloxacin-Lidocaine Base as A Topical Hydrogel Dressing

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Abstract

Hydrogel-based wound dressings hold a unique position in comparison to conventional dressings, owing to their extensive potential as wound and burn healing scaffolds. Moxifloxacin, a synthetic fluoroquinolone, was granted approval by the FDA in 1999 for intravenous administration in the treatment of complex and severe bacterial infections, such as challenging skin and intra-abdominal infections. Lidocaine is a widely recognised local anaesthetic that has been extensively utilised in medical practise for the management of acute wound pain, either as a standalone treatment or in combination with other anaesthetic drugs. A total of eighteen hydrogel formulations were developed by using a mixture of moxifloxacin and lidocaine, utilising different proportions of carbapol 940, poloxamer 407, carboxymethyle sodium, and chitosan polymers. These formulations were assigned unique codes ranging from F1 to F18. The hydrogel formulations (F1-F9) are composed of carbapol 940 as the base polymer, with polymer ratios ranging from 1-2% W/V. On the other hand, formulations (F10-F12) consist of poloxamer 407 as the base polymer, with polymer ratios of 20, 25, and 30% W/V, respectively. Additionally, formulations (F13-F15) are based on sodium carboxymethyl cellulose, with polymer ratios of 3, 6, and 10% W/V, respectively. Lastly, formulations (F16-F18) are chitosan-based, with polymer ratios of 2, 4, and 6% W/V, respectively. The formulated compounds were examined for their sensory, physical, chemical, and mechanical characteristics. The present study aimed to investigate the influence of polymer type and concentration on the in vitro release behaviour. Among the tested polymers, F4 exhibited favourable characteristics in terms of release profile and swelling capacity. Based on these findings, it can be inferred that the incorporation of moxifloxacin and lidocaine base into a hydrogel composed of 1.5% carbopol 940 with 0.5% triethanolamine enables sustained release and adequate swelling, making it suitable for the management of burn or wound conditions. Further investigations, such as histological and in vivo studies, could be conducted in the future to evaluate the selected formulation.

Keywords: Hydrogel-based wound dressings, Moxifloxacin, Lidocaine, Carbapol 940, Poloxamer 407, Carboxymethyle sodium, Chitosan, Management of burn

Introduction

When comparing traditional wound dressings to hydrogel-based dressings, it is seen that the latter exhibits enhanced moisturising capabilities for the wounded surface and improved absorption of purulent exudate. The adhesive properties of these substances to the skin around the wound are lacking, hence enhancing the process of autolytic wound turnover. These materials had a significant position in the field due to their extensive potential as drug delivery systems,[1] as well as their application as scaffolds for wound and burn healing, including the introduction of antibiotics.[2]

Hydrocolloids are a type of occlusive dressings that consist of a combination of gel-forming agents (such as gelatin, carboxymethylcellulose, and pectin) together with supplementary components including elastomers and adhesive layers.[3] The mechanism of hydrocolloids involves the formation of a gel layer upon contact with the wound surface, which serves to hydrate the damaged skin and retain the granulation tissue by the absorption of exudate by the dressing materials.

Lidocaine holds significant importance as a medication listed

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on the World Health Organization's essential drug list. It has demonstrated efficacy, safety, and cost-effectiveness, making it a valuable asset for any healthcare institution.[4] The use of this particular painkiller, either on its own or in conjunction with other anaesthetic agents, has been allowed in medical practise for the purpose of alleviating pain in wounded and injured skin tissues.[5-8] The utilisation of lidocaine, which has been saturated, was found to be efficacious in the control of localised pain throughout the process of wound healing, as demonstrated by the study conducted by Sussman and Bates-Jensen in 2012.

The issue of antibiotic resistance is well recognised as a significant obstacle in the management of wound infections. The danger of wound infection is heightened when the factors in the immediate vicinity, such as the presence of eschar and the state of blood flow, create a more favourable environment for microbial development rather than promoting host defence. This might result in the failure of wound healing, the presence of bacteremia, or perhaps sepsis, which is often associated with significant morbidity and mortality.[9] Moxifloxacin is a chemically synthesised fluoroquinolone compound that has a broad range of antibacterial activity. The mechanism of action involves the inhibition of DNA gyrase, a type II topoisomerase, and topoisomerase IV, an enzyme that is crucial for the separation of bacterial DNA strands, resulting in the impairment of cellular division. [10] The intravenous formulation of Moxifloxacin received approval from the Food and Drug Administration (FDA) in 1999 for the purpose of treating complex and life-threatening microbial infections, including serious skin and skin structure infections (cSSSI) and complicated intra-abdominal infections (cIAI).[11]

The objective of this study is to fabricate and assess the release kinetics of a hydrogel dressing using a unique blend of moxifloxacin and lidocain HCl, utilising various polymer matrices.

Material

Moxifloxacin HCl provided by Pharmachem Pvt.ltd factory, lidocaine base gift from Samara Drug Industries, carbapol 940, chitosan, poloxamer 407, triethanolamine and CMC Na from Hi-media,

Methods

Identification: All identification like determination of lambda max and FTIR studies were done for moxifloxacin and lidocaine base. polymers used also identified by their melting.

Preparation of hydrogel

Eighteen formulas of moxifloxacin HCl plus lidocaine base topical hydrogel were prepared by different methods according to the type of polymer used.

1- Carbapol 940 hydrogel preparation: known amount of carbapol 940 soaked with distilled water for two hours, then added triethanolamine 5% drop by drop until get a homogenous hydrogel.[12]
2- Poloxamer 407 hydrogel preparation: poloxamer added to a citrate phosphate buffer pH 4 with continues stirring for fifteen minutes, then cooled by refrigerator to get a hydrogel finally.
3- Carboxy methyl cellulose sodium hydrogel preparation: citrate phosphate buffer pH added gradually to the carboxy methyl cellulose sodium with stirring until a hydrogel formed.
4- Chitosan hydrogel preparation: chitosan mixed with 5 ml lactic acid to form paste the citrate phosphate buffer pH 4 added slowly to the mixture with continues stirring for enough time to get a hydrogel.[13]

Table 1. composition of hydrogel formulas

Formula no.	Carbapol 940 (gm)	Triethanol-amine (50 %)(ml)	Poloxamer 407 (gm)	CMC Na (gm)	Chitosan (gm)	Lactic acid (ml)	Citrate phosphate buffer 4 add to 100 ml	D.W add to 100 ml
F1	1	0.5						100
F2	1	1						100
F3	1	1.5						100
F4	1.5	0.5						100
F5	1.5	1						100
F6	1.5	1.5						100
F7	2	0.5						100
F8	2	1						100
F9	2	1.5						100
F10			20				100	
F11			25				100	
F12			30				100	
F13				3			100	
F14				6			100	
F15				10			100	
F16					2	5	100	
F17					4	5	100	
F18					6	5	100	

Addition of drug to the formulas

Moxifloxacin HCl equal to 0.01% dissolved in 1 ml distilled water and lidocaine Hcl equal to 2% dissolved in propylene glycol,[14] then add to the dispersion media of citrate phosphate buffer or distilled water according to the of hydrogel method called in-situ method.[15]

Physical properties of the hydrogel

1- Macroscopic examination: examination of consistency and homogeneity visually.[16]
2- pH determination: all formulas subjected to the pH

determination in the first day of preparation and after 30 days this test done by litmus paper which immersed inside the hydrogel for 2 minutes then compare the results.

3- Swelling study: one-gram sample soaking into 5 ml of buffer phosphate 5.5 for a precise time then removed access buffer and weighed again, this process done after one and three hours, the results used in the following formula Swelling ratio=WS-W/W×100 Were Ws represented the weight of the distended hydrogel at time t and W is the primary weight.[17]

4- Drug content uniformity determination: one gram of hydrogel dissolved in 5 ml ethanol then complete to 100 ml with distilled water, from this solution 5ml taken and diluted to 50 ml with distilled water. The absorbance was detected by UV-spectrophotometer to calculate the content.[18]

5- Invitro dissolution behavior: modified syringe with (cellophane semipermeable membrane M.wt 14000 dalton) put in the basket paddle of dissolution apparatus a one gram sample put inside the modified syringe with dissolution media 500 ml of phosphate buffer pH 5.5 at rpm 100 and 37.0 C. 5 ml sample taken at the following intervals (15,30,45,60,120,180 minutes and replaced with 5 ml of phosphate buffer pH 5.5 then reading by UV-spectrophotometer.[19]

Variable affecting release profile

1- Effect of different types of polymers on the release profile of moxifloxacin HCl and lidocaine base.

2- Effect of different polymer concentrations on the release profile of moxifloxacin HCl and lidocaine base.

3- Effect of different concentrations of crosslinker agent on the release profile of moxifloxacin HCl and lidocaine base.

Results and Discussion

1- Macroscopic feature (organoleptic): visual examination indicate homogeneity of all formulas, no phase separation with yellow color acquired from moxifloxacin HCl

2- pH determination

Table 2 pH changing during storage

Formula no	pH 1st reading	pH 2nd reading (after 30 day)
F1	6.0	6.2
F2	6.8	6.8
F3	7.0	7.0
F4	6.2	6.2
F5	6.0	6.2
F6	6.8	6.8
F7	5.0	5.0
F8	5.6	5.9
F9	5.6	5.9

Table (2) showed pH stability of the prepared formulas F1-F9 with little increase in some of them, it can be noticed clearly that as we increase the crosslinker concentration with constant polymer concentration (carbapol 940) a slight increase in pH occur due to increase in the triethanolamine concentration which has a basic effect on the formula. In addition to that as polymer concentration increase, the pH will shift to acidic side as shown (F7, F8, F9) this due to acidic effect of (cabapol 940) this could be noticed in comparing F8 and F1, F7 and F4. the pH for all formulas were with in accepted range for topical preparation. The other formulas showed stability in pH because they are prepared in buffer solution pH 4.

3- Swelling ratio

The swelling profile of the hydrogel preparation is important,[20] so this part could be mandatory in evaluation of the preparations, the table (3) illustrate the swelling ability of each one.

Table 3. swelling ratio of formulas

Formula no.	Swelling ratio w/w (after one hour)	Swelling ratio w/w (after three hours)
F1	Zero	58 %
F2	Zero	55 %
F3	10 %	72 %
F4	30 %	119 %
F5	Zero	92 %
F6	30 %	101 %
F7	70 %	147 %
F8	10 %	127 %
F9	Zero	83 %
F10	Soluble	Soluble
F11	Soluble	Soluble
F12	Soluble	Soluble
F13	50 %	Soluble
F14	40 %	150 %
F15	100 %	255 %
F16	Soluble	Soluble
F17	Soluble	Soluble
F18	30 %	Soluble

The formulas F10, F11, F12, F13, F16 and F17 revealed disability to swell in the solution with in the required time, this might be due to ionization of the functional groups of polymer or the hydrophilicity of the hydrogel contents, degree of crosslinking, ionic strength, pH and counter ions type presented in the swelling medium.[21] In general, as the crosslinking percent increase tighter structure formed lead to less swelling capacity,[22] while in case of acidity and swelling the relation appears clear in high and low pH only.[23]

4- Drug content uniformity

All formulas met the accepted requirement between 85% and 99% that is mean the entrapment of both drugs succeeded.

5- Variables affecting in vitro release of drug

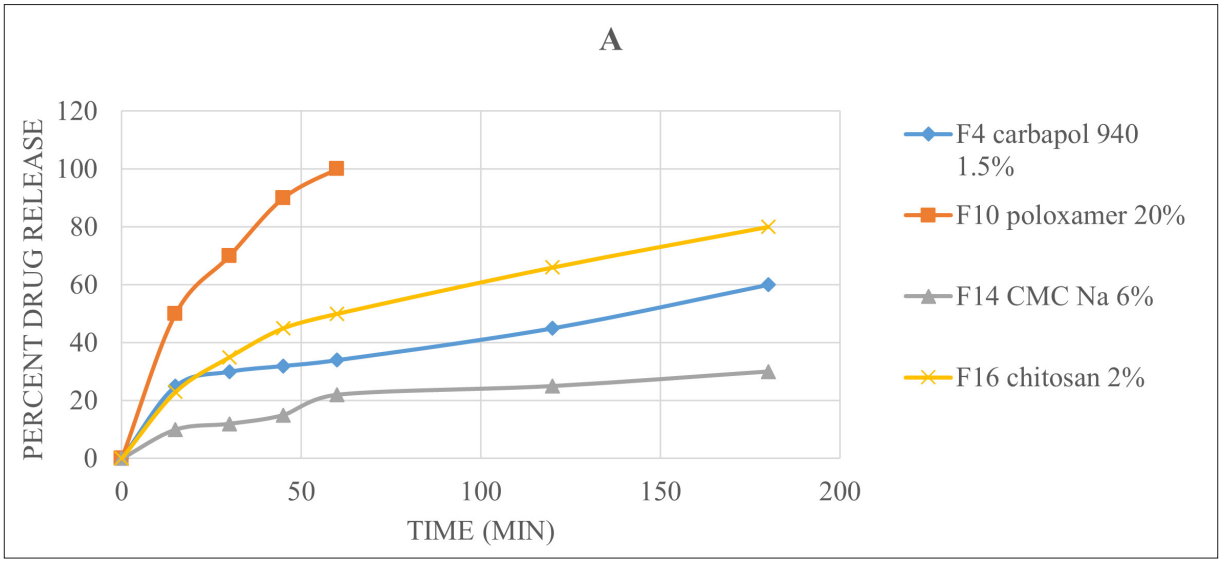
The release profile from all formulas depend on predominantly on them release from matrixes because the cellophane membrane with molecular weight about 14000 dalton that is mean the drug passes freely through the membrane while polymer molecules retarded due to their higher molecular weight.[20]

Effect of Different Types of Polymers on The in Vitro Release

The figures (1) and (2) demonstrate the impact of polymer

on the release profile of both drugs. It is observed that F10 exhibited the highest rate of drug release, followed by F16, F4, and F14. This sequence suggests that the poloxamar polymer is unable to effectively slow down the release of the drug from the formulation. This observation may be attributed to the fact that the polymer is readily soluble in aqueous media. The chitosan formula (F16) exhibited sustained drug release characteristics, whereby the dissolution media penetrated the formula, resulting in wetting and expansion, leading to swelling and the formation of a network of channels or pores. Simultaneously, the active component dissolved and was continuously released through these channels or pores. As the amount of dissolution media trapped within the hydrogel increased, the cumulative drug release percentage reached 80% after three hours of in-vitro release.

The formulation F4, which consisted of carbapol 940, exhibited a significant delay in the release of the drug within the matrix. Only 60% of the drug was released at the conclusion of the trial. This observed behaviour might be attributed to the gelling effect of the polymer, which forms a viscous matrix that hinders the release of the drug.[24] The cellulose polymer CMC Na exhibited the lowest cumulative release percentage when tested with F14. This polymer acted as a viscous medium, effectively trapping the drug within it and delaying its release from the formulation. One contributing factor to this delayed release is the high molecular weight of CMC Na, which is approximately 262.[25] Overall, there is a lack of discernible disparity in the release profiles of moxifloxacin and lidocaine within these formulations.



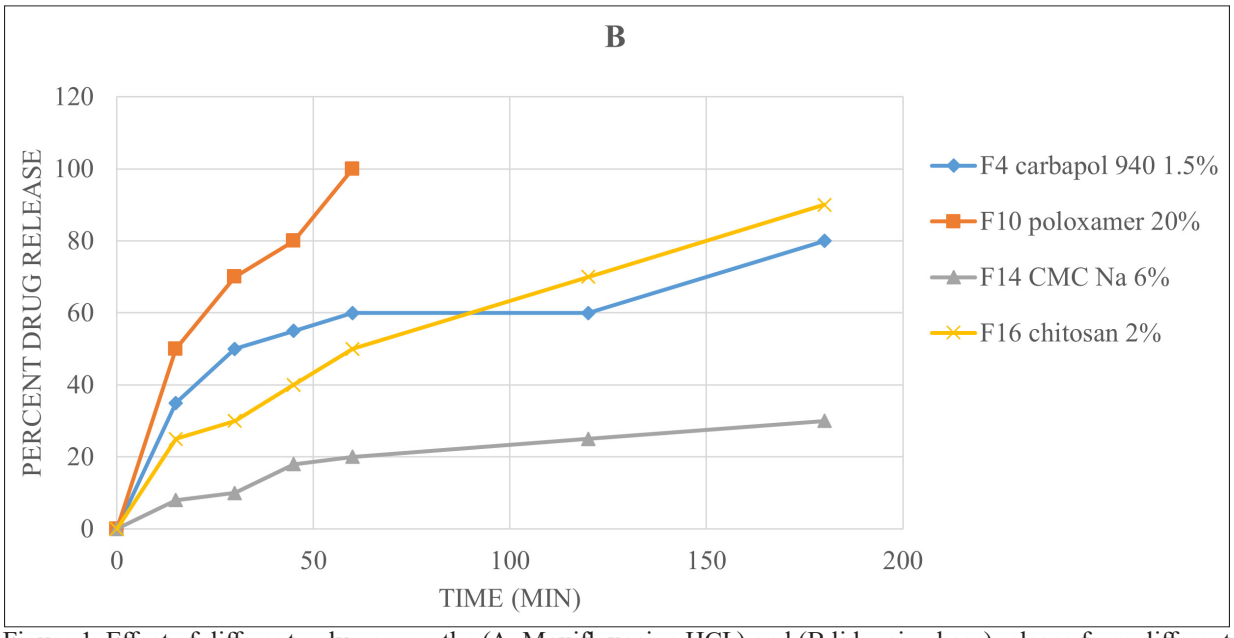


Figure 1: Effect of different polymers on the (A. Moxifloxacine HCL) and (B.lidocaine base) release from different formulas in phosphate buffer pH 5.5 at 37°C temp.

Effect of polymer concentration on the in vitro release

Three poloxamer 407 containing formulas; F10, F11 and F12 with different concentrations revealed that the rise in polymer concentration lead to reduction the release ratio.

Pluronic hydrogels are sticky isotropic liquefied crystals involving of micelles. It is offered that the drug discharged by transmission through the extra micellar water passages of the hydrogels medium and greater amounts of pluronic create smaller size of water networks[26] as in figure (2).

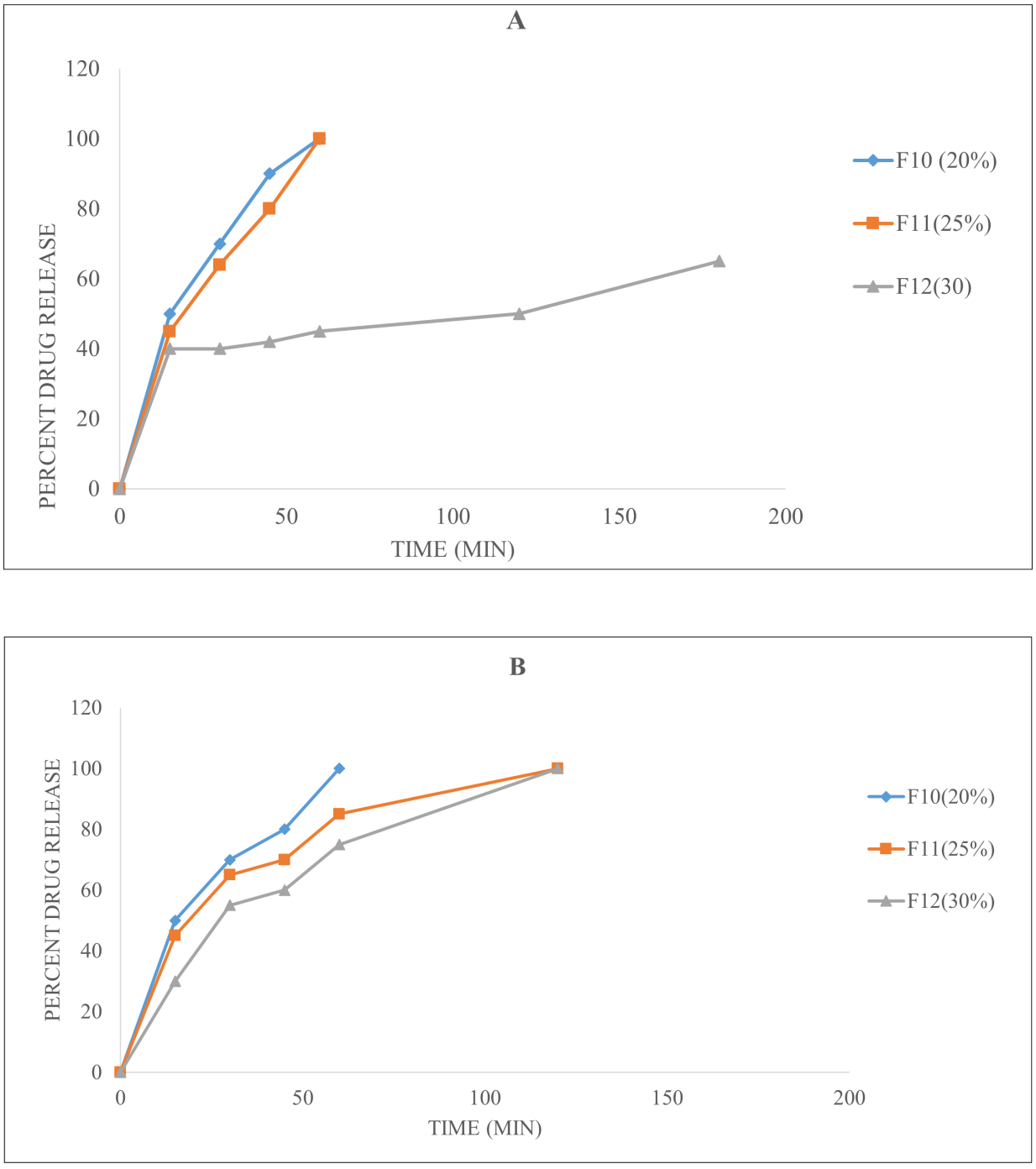


Figure 2: Effect of different poloxamer ratio on the release profile of moxifloxacine in (A) and lidocaine in (B) from F10,F11 and F12

Chitosan containing formulas; F16, F17 and F18 as the concentration increases the release rate decreases for both moxifloxacin and lidocaine as in figure (3).

This phenomenon is associated with higher polymer entanglement and lesser actual molecular transmission capacity as chitosan amount rises.[27]

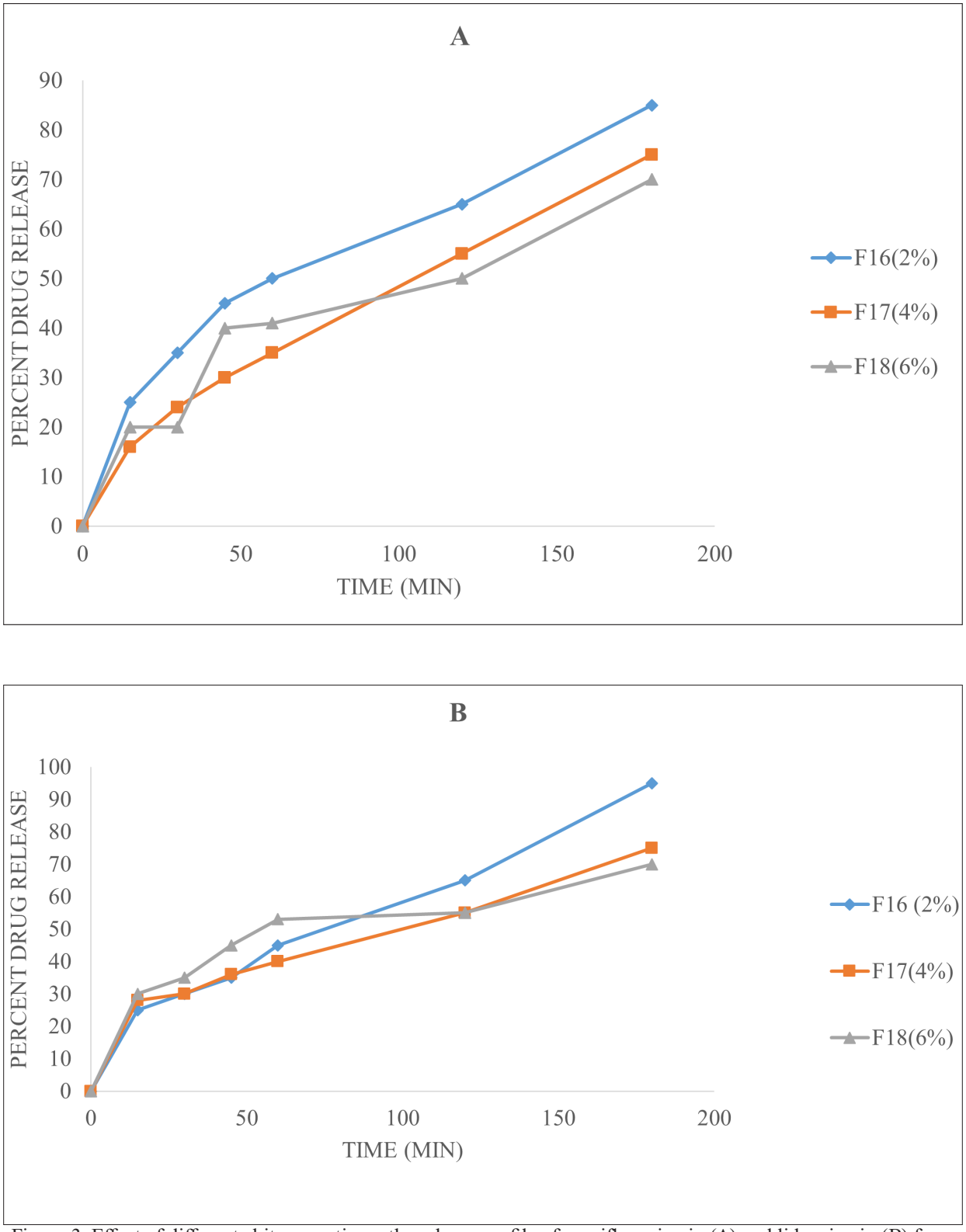


Figure 3: Effect of different chitosan ratio on the release profile of moxifloxacine in (A) and lidocaine in (B) from F16, F17 and F18

CMC Na hydrogel formulas F13, F14 and F15 also show decrease in the release rate as the polymer concentration increases as in the figure (4).

As the concentration of the polymer rises the viscosity of the hydrogel increases, viscous vehicle retarded the release of drugs due to difficult permeation from a sticky cellulose matrix's.

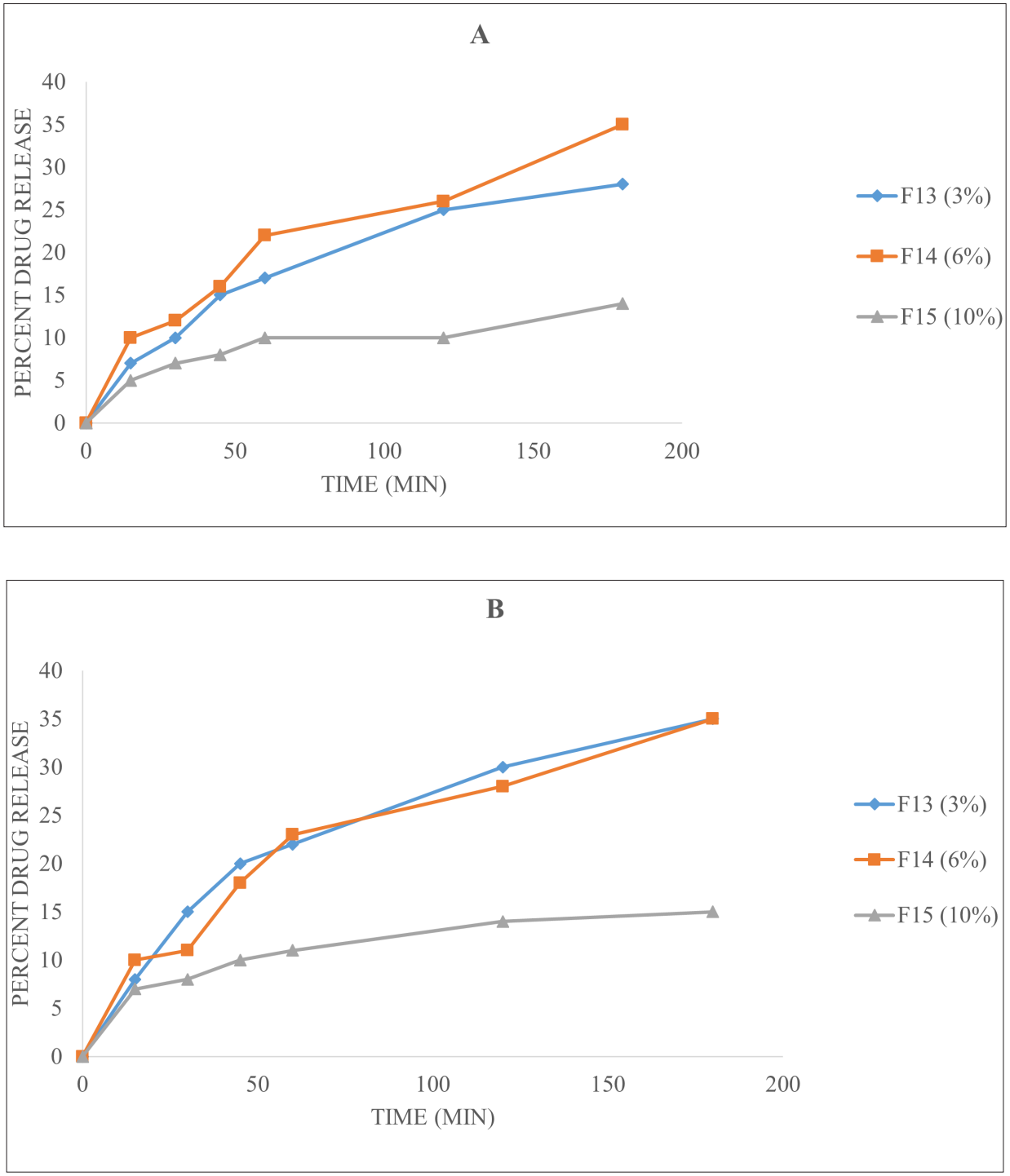


Figure 4: Effect of different CMC Na ratio on the release profile of Moxifloxacine in (A) and Lidocaine in (B) from F13, F14 and F15

Figure (5) illustrate lower release rate in higher polymer amount in relation to the crosslinker as in F7 this is due to the gelling effect of polymer portions that are not busy with crosslinker so it will form a barrier against further wetting and hence diffusion of the solvent to the core of the polymer matrix.

In contrast F l and F4 showed insignificant difference between them regarding to drug release and at the same time these two formulas exhibit significant difference ($p<0.05$) in comparison with the release pattern of F7 in which they expel the drug at higher rate. This due to the lower polymer ratio in relation to the cross linker that means more functional polymer groups are filled and hence the network is more noticeable so the solvent can diffuse inside and outside the matrix more freely leading to increase the rate of release.[28,29]

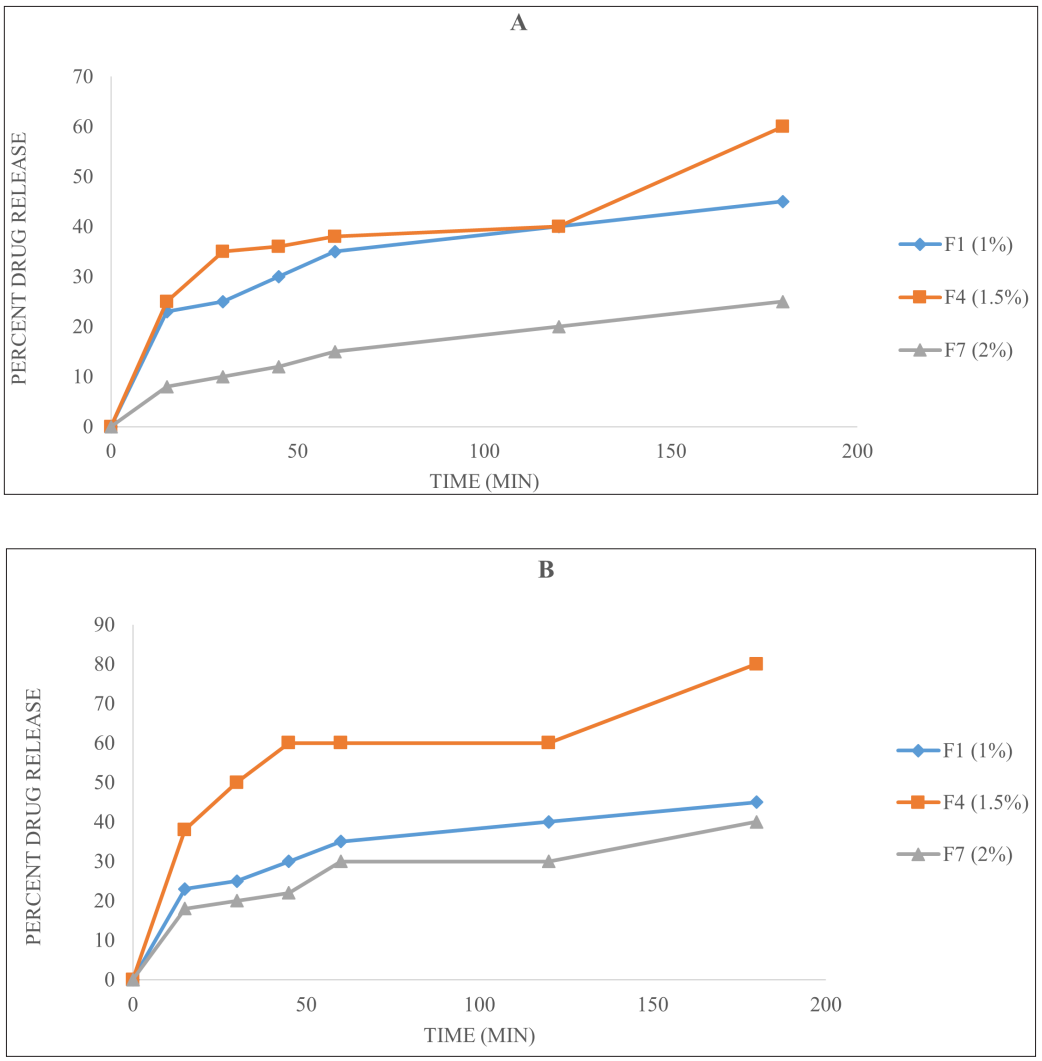
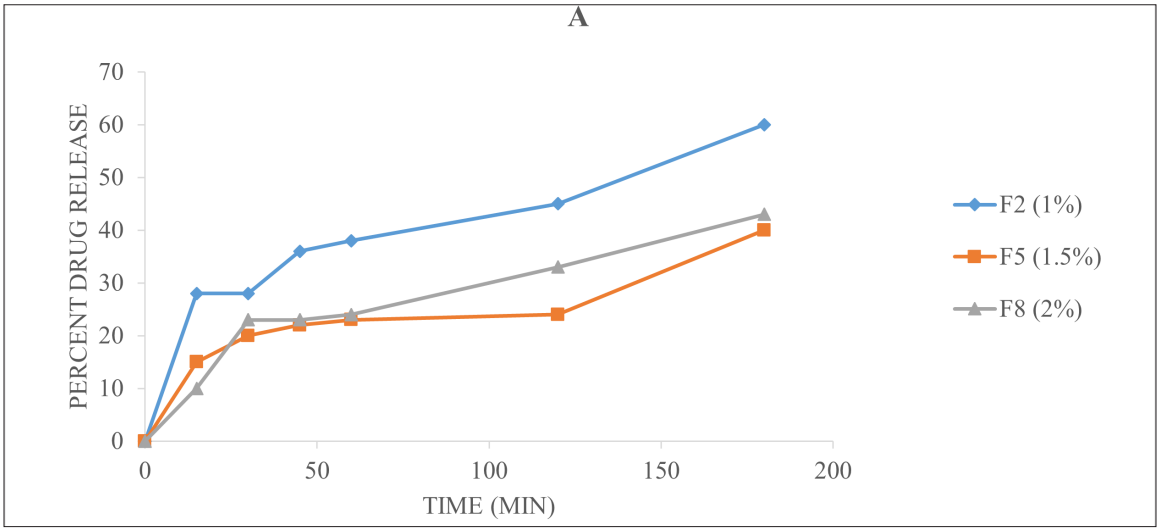


Figure 5: Effect of different carbapol 940 concentrations with same crosslinker ratio (0.5%) on the release profile of Moxifloxacine in (A) and Lidocaine in (B) from F1, F4 and F7

In the figure (6) the release profile of F2 is faster than other F5 and F8. The increase in crosslinker ratio lead to decrease in the release pattern due to the tighter network.



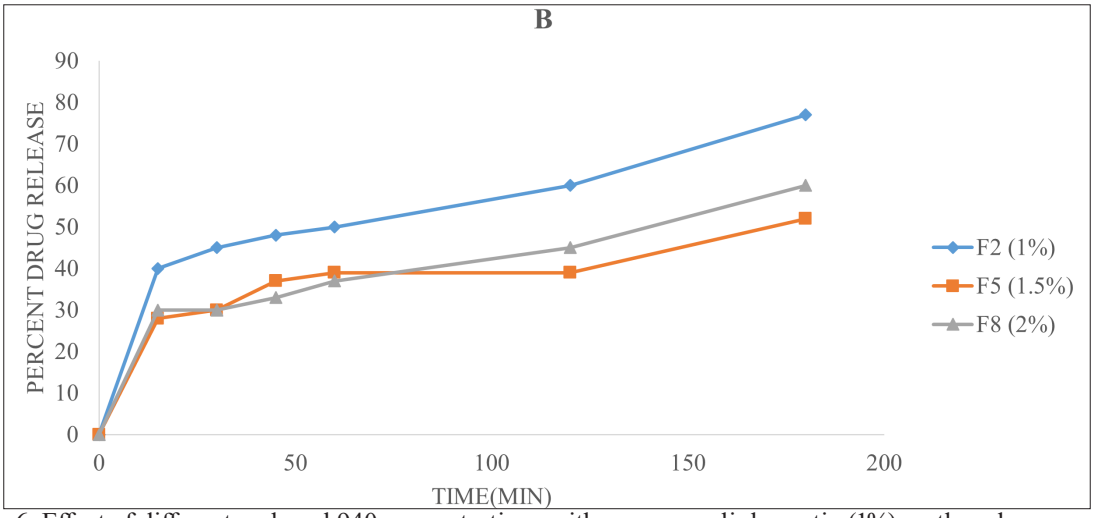


Figure 6: Effect of different carbapol 940 concentrations with same crosslinker ratio (1%) on the release profile of Moxifloxacine in (A) and Lidocaine in (B) from F2, F5 and F8

In the figure (7) the F6 with an optimal crosslinking ratio lead to higher extent of release profile than F3 and F9.

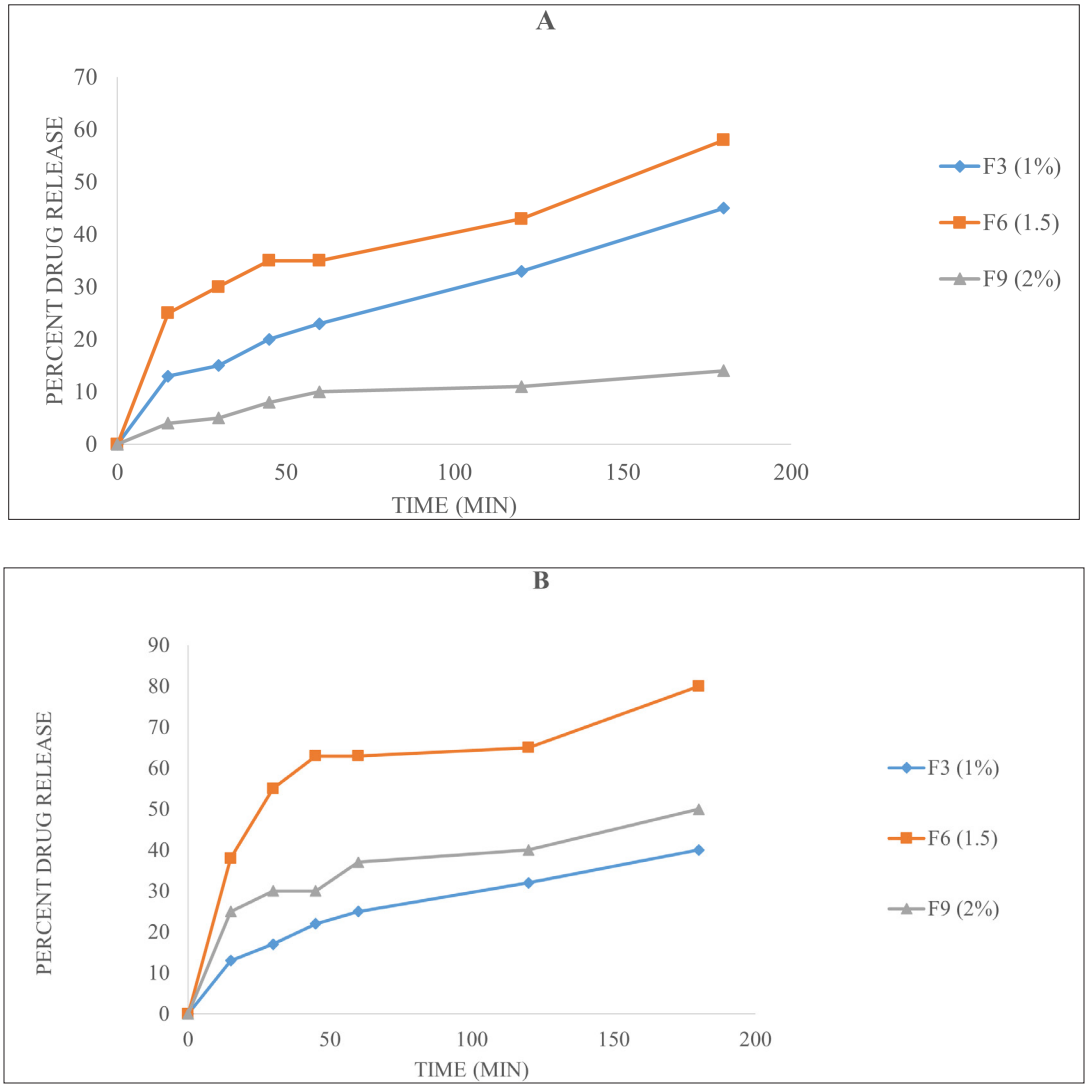


Figure 7: Effect of different carbapol 940 concentrations with same crosslinker ratio (1.5%) on the release profile of Moxifloxacine in (A) and Lidocaine in (B) from F3, F6 and F9

Effect of Different Cross Linker Concentrations on the in vitro release

Figure (8) illustrated the effect of increasing crosslinking agent on the release profile, indicated there is an optimum crosslinking ratio founded in F2 leaded to faster release rate than Fl and F3 the lower and higher crosslinking ratio respectively.[30]

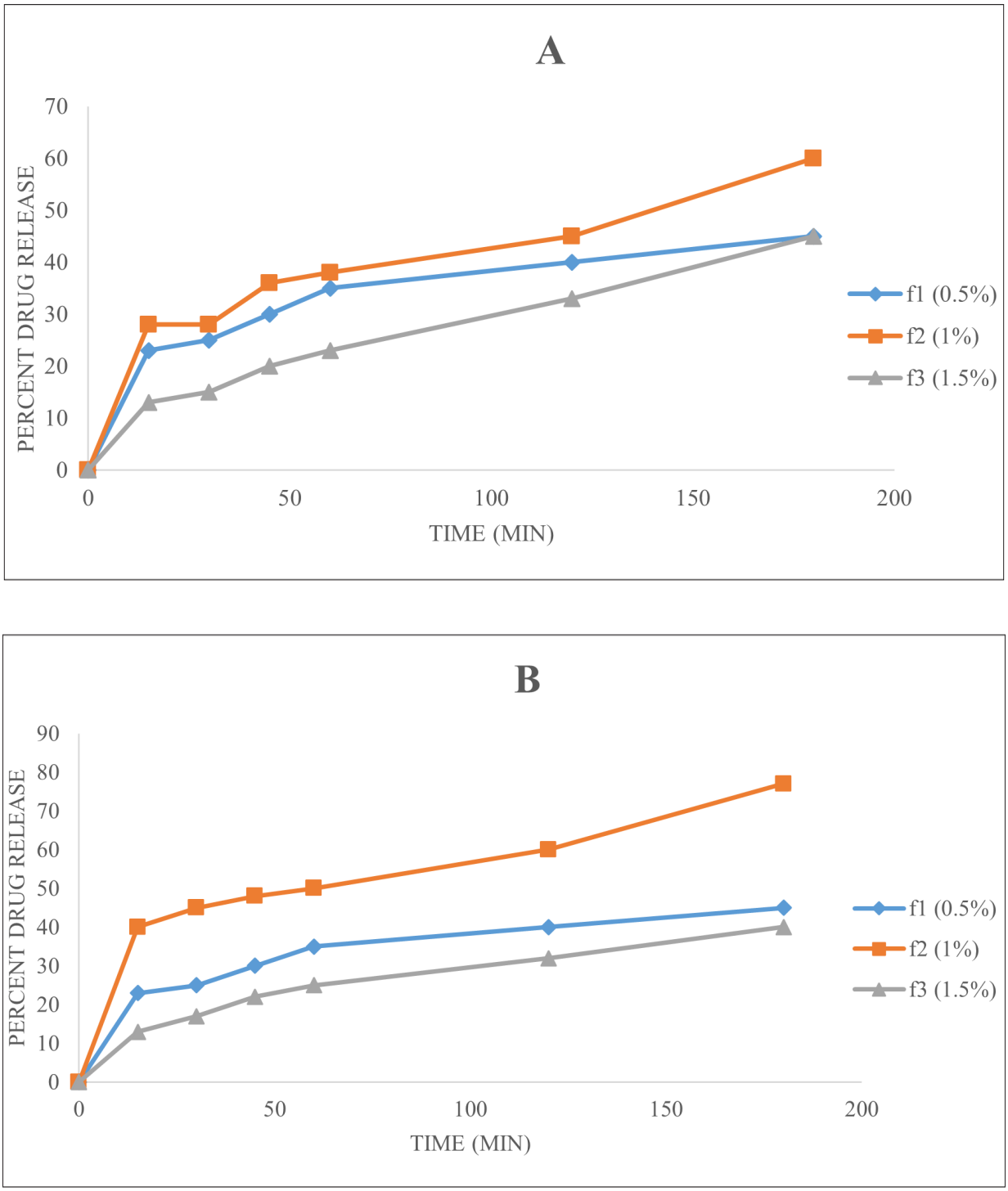


Figure 8: Effect of different cross linker concentrations with the same carbapol 940 concentration (0.5%) on the A. moxifloxacine Hcl and B. lidocaine release from different formulas

F5 and F4 release profiles affected by the polymer more than crosslinking network effect but the F6 have an optimal crosslinking ratio this could be seen in the figure (9).

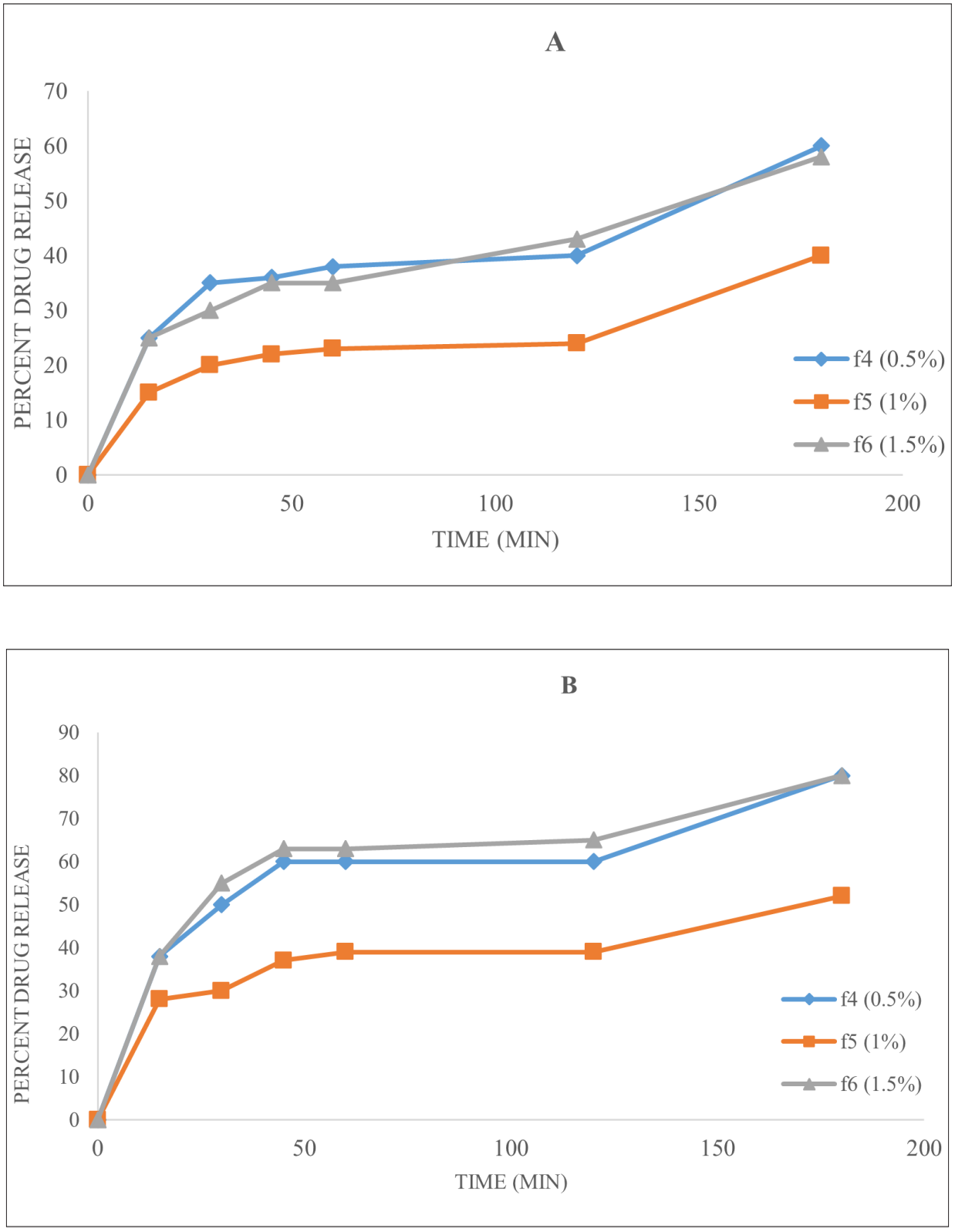


Figure 9: Effect of different cross linker concentrations with the same carbapol 940 concentration (1%) on the A. moxifloxacine Hcl and B. lidocaine release from different formulas

The figure (10) showed F8 with faster release profile because of an optimal crosslinking ratio with significant difference from F9 and F7.

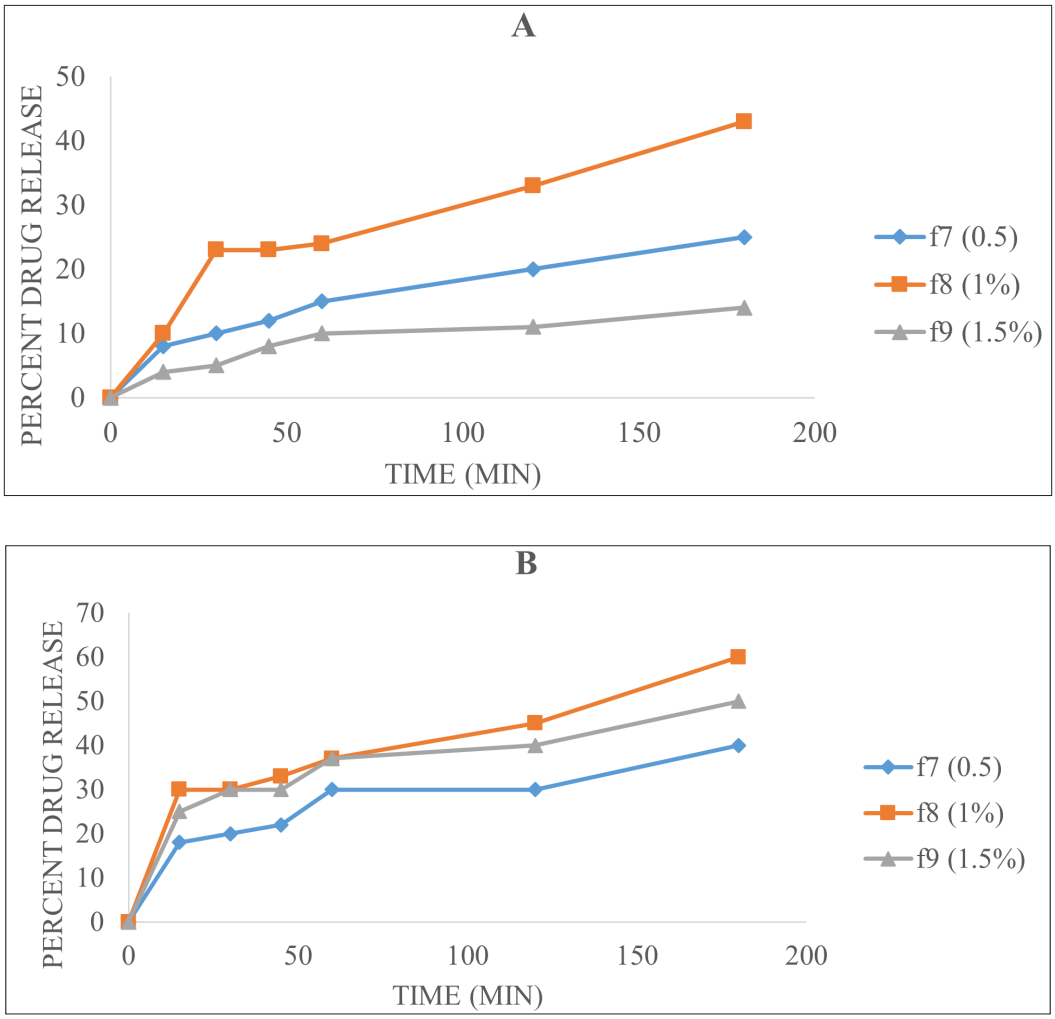


Figure 10: Effect of different cross linker concentrations with the same carbapol 940 concentration (1.5%) on the A. moxifloxacine Hcl and B. lidocaine release from different formulas

Future Study

More studies should be done for the selected hydrogel formula like wound fluid absorption, permeability to O_2, H2O vapors and microbes, blood compatibility, protein adsorption and ex-vivo muco-adhesion.

References

1. Savina IN, Zoughaib M, Yergeshov AA. Design and Assessment of Biodegradable Macroporous Cryogels as Advanced Tissue Engineering and Drug Carrying Materials. Gels. 2021; 7(3): 79. doi: https://doi.org/10.3390/gels7030079.
2. Sun CK, Ke CJ, Lin YW, Lin FH, Tsai TH, Sun JS. Transglutaminase Cross-Linked Gelatin-Alginate-Antibacterial Hydrogel as the Drug Delivery-Coatings for Implant-Related Infections. Polymers (Basel). 2021; 13(3): 414. doi: https://doi.org/10.3390/polym13030414.
3. Silva JM, Pereira CV, Mano F, et al. Therapeutic Role of Deep Eutectic Solvents Based on Menthol and Saturated Fatty Acids on Wound Healing. ACS Appl Bio Mater. 2019; 2(10): 4346-55. doi: https://doi.org/10.1021/acsabm.9b00598.
4. Weinberg L, Peake B, Tan C, Nikfarjam M. Pharmacokinetics and pharmacodynamics of lignocaine: A review. World J Anesthesiol. 2015; 4(2): 17-29. doi: http://dx.doi.org/10.5313/wja.v4.i2.17.
5. Cuomo R, D'Aniello C, Grimaldi L, et al. EMLA and Lidocaine Spray: A Comparison for Surgical Debridement in Venous Leg Ulcers. Adv Wound Care (New Rochelle). 2015; 4(6): 358-61. doi: https://doi.org/10.1089/wound.2014.0605.
6. Desai C, Wood FM, Schug SA, Parsons RW, Fridlender C, Sunderland VB. Effectiveness of a topical local anaesthetic spray as analgesia for dressing changes: a double-blinded randomised pilot trial comparing an emulsion with an aqueous lidocaine formulation. Burns. 2014; 40(1): 106-12. doi: https://doi.org/10.1016/j.burns.2013.05.013.
7. Gaufberg SV, Walta MJ, Workman TP. Expanding the use of topical anesthesia in wound management: sequential layered application of topical lidocaine with epinephrine. Am J Emerg Med. 2007; 25(4): 379-84. doi: https://doi.org/10.1016/j.ajem.2006.11.013.

8. Pasero C. Lidocaine patch 5% for acute pain management. J Perianesth Nurs. 2013; 28(3): 169-73. doi: https://doi.org/10.1016/j.jopan.2013.03.005.
9. Steinstraesser L, Tack BF, Waring AJ, et al. Activity of novispirin G10 against Pseudomonas aeruginosa in vitro and in infected burns. Antimicrob Agents Chemother. 2002; 46(6): 1837-44. doi: https://doi.org/10.1128/aac.46.6.1837-1844.2002.
10. Drlica K, Zhao X. DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiol Mol Biol Rev. 1997; 61(3): 377-92. doi: https://doi.org/10.1128/mmbr.61.3.377-392.1997.
11. Willby M, Sikes RD, Malik S, Metchock B, Posey JE. Correlation between GyrA substitutions and ofloxacin, levofloxacin, and moxifloxacin cross-resistance in Mycobacterium tuberculosis. Antimicrob Agents Chemother. 2015; 59(9): 5427-34. doi: https://doi.org/10.1128/aac.00662-15.
12. Raut S, Uplanchiwar V, Bhadoria S, Gahane A, Jain SK, Patil S. Comparative evaluation of zidovudine loaded hydrogels and emulgels. Research J Pharm and Tech. 2012; 5(1): 41-45. Available from: https://rjptonline.org/AbstractView.aspx?PID=2012-5-1-27.
13. Wang YY, Hong CT, Chiu WT, Fang JY. In vitro and in vivo evaluations of topically applied capsaicin and nonivamide from hydrogels. Int J Pharm. 2001; 224(1-2): 89-104. doi: https://doi.org/10.1016/s0378-5173(01)00755-4.
14. Jacobsen F, Fisahn C, Sorkin M, et al. Efficacy of topically delivered moxifloxacin against wound infection by Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 2011; 55(5): 2325-34. doi: https://doi.org/10.1128/aac.01071-10.
15. Lin CC, Metters AT. Hydrogels in controlled release formulations: network design and mathematical modeling. Adv Drug Deliv Rev. 2006; 58(12-13): 1379-408. doi: https://doi.org/10.1016/j.addr.2006.09.004.
16. Mohamed MI. Optimization of chlorphenesin emulgel formulation. Aaps j. 2004; 6(3): e26. doi: https://doi.org/10.1208/aapsj060326.
17. Anumolu SNSP. Poly (ethylene glycol) hydrogels for sustained topical drug delivery to the eyes and skin. Doctoral Dissertation, Rutgers University-Graduate School-New Brunswick; 2010. doi: https://doi.org/doi:10.7282/T3736R31.
18. Panigrahi L, Ghosal SK, Pattnaik S, Maharana L, Barik BB. Effect of Permeation Enhancers on the Release and Permeation Kinetics of Lincomycin Hydrochloride Gel Formulations through Mouse Skin. Indian J Pharm Sci. 2006; 68(2): 205-11. Available from: https://www.ijpsonline.com/articles/effect-of-permeation-enhancers-on-the-release-and-permeation-kinetics-of-lincomycin-hydrochloride-gel-formulations-throu.pdf.
19. Capková Z, Vitková Z, Vysokaiová V. Pre-formulation studies of the H1-antihistamine loratadine for a topical dosage form. Ceska Slov Farm. 2005; 54(3): 109-13. Available from: https://pubmed.ncbi.nlm.nih.gov/15945456.
20. Mishra A, Chaudhary N. Study of povidone iodine loaded hydrogels as wound dressing material. Trends Biomater Artif Organs. 2010; 23(3): 122-28. Available from: https://www.researchgate.net/publication/45626139.
21. Gemeinhart RA, Guo C. Fast Swelling Hydrogel Systems. In: Reflexive Polymers and Hydrogels: Understanding and Designing Fast Responsive Polymeric Systems. CRC Press; 2004:245-57. Available from: https://www.taylorfrancis.com/chapters/mono/10.1201/9780203485354-22.
22. Hiremath JN, Vishalakshi B. Effect of Crosslinking on swelling behaviour of IPN hydrogels of Guar Gum & Polyacrylamide. Der Pharma Chemica. 2012; 4(3): 946-55. Available from: https://www.derpharmachemica.com/pharma-chemica/effect-of-crosslinking-on-swelling-behaviour-of-ipn-hydrogels-of-guar-gum--polyacrylamide.pdf.
23. Kumar PS, Srikanth B, Satyanarayana T, et al. Formulation and evaluation of nebivolol mucoadhesive buccal tablet. Pharmacologyonline. 2011; 3: 869-85. Available from: https://pharmacologyonline.silae.it/files/newsletter/2011/vol3/087.kumar.pdf.
24. Emeje MO, Kunle OO, Ofoefule SI. Effect of the molecular size of carboxymethylcellulose and some polymers on the sustained release of theophylline from a hydrophilic matrix. Acta Pharm. 2006; 56(3): 325-35. Available from: https://pubmed.ncbi.nlm.nih.gov/19831281.
25. El-Bana A, Abdelghany A, Meikhail M. Molecular structure and optical attributes of (Na-CMC/SA) natural polymer blend. Bull Chem Soc Ethiop. 2022; 36(3): 707-16. doi: https://doi.org/10.4314/bcse.v36i3.19.
26. Ho HO, Huang FC, Sokoloski TD, Sheu MT. The influence of cosolvents on the in-vitro percutaneous penetration of diclofenac sodium from a gel system. J Pharm Pharmacol. 1994; 46(8): 636-42. doi: https://doi.org/10.1111/j.2042-7158.1994.tb03873.x.
27. Barichello JM, Morishita M, Takayama K, Nagai T. Absorption of insulin from Pluronic F-127 gels following subcutaneous administration in rats. Int J Pharm. 1999; 184(2): 189-98. doi: https://doi.org/10.1016/S0378-5173(99)00119-2.
28. Lee CK, Kitagawa K, Uchida T, Kim NS, Goto S. Transdermal delivery of theophylline using an ethanol/panasate 800-ethylcellulose gel preparation. Biol Pharm Bull. 1995; 18(1): 176-80. doi: https://doi.org/10.1248/bpb.18.176.
29. Tsai H-S, Wang Y-Z. Properties of hydrophilic chitosan network membranes by introducing binary crosslink agents. Polym Bull (Berl). 2008; 60: 103-13. doi: https://doi.org/10.1007/s00289-007-0846-x.
30. Rujiravanit R, Kruaykitanon S, Jamieson AM, Tokura S. Preparation of crosslinked chitosan/silk fibroin blend films for drug delivery system. Macromolecular Bioscience. 2003; 3(10): 604-11. doi: https://doi.org/10.1002/mabi.200300027.