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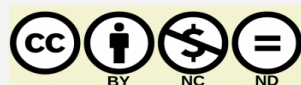
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Preparing of Controlled Release Systems for Atenolol and Studying it is in Vitro Dissolution and Swelling

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Abstract:

In this study, the appropriate polymer solutions were prepared to create chitosan/PVA blends. By altering the ratio of the ingredients, several chitosan/PVA mixtures were produced, as follows: 12% chitosan and 88% PVA, 40% chitosan and 60% PVA, and 15% chitosan and 85% PVA. To generate physically crosslinked hydrogels for the drug delivery of atenolol, several acid cross-linkers, such as fumaric acid and phthalic acid, were applied to the chitosan/PVA blends. The formulations included 15% chitosan and 85% PVA with 0.02% (0.0024, 0.0041, 0.02) mol of fumaric acid, as well as 15% chitosan and 85% PVA with 0.002, 0.003, and 0.0064 mol of phthalic acid.

Using an ultraviolet-visible spectrophotometer, the chemical structures of the modified and unmodified chitosan (Chitosan/PVA) hydrogels were examined. Results regarding the formation of ionic cross-links between the protonated hydroxyl groups of the chitosan and the anionic functional groups of the cross-linking agent were established. The swelling ratio was determined for each hydrogel structure as a function of time in three distinct fluids with pH values of 2, 4, and 7.5, and at three distinct temperatures of 42°C and 44°C. The samples with the greatest swelling ratios were identified as PVA.PA0.002 (chitosan) and PVA.FA0.0024.

Key words : Drug Loading , natural polymers, Atenolol , Chitosan , PVA(poly vinyl alcohol)

1.0 Introduction:

Innovation-based systems known as drug delivery systems (DDS) are utilized to synthesize and store drug molecules in forms suitable for administration, such as tablets or solutions. These systems expedite the delivery of medications to the precise designated location within the body, optimizing therapeutic efficacy and reducing the likelihood of off-target accumulation (B.M. Rayaprolu, 2018). There are several pathways through which drugs can enter the body (A.M. Vargas, 2021). These pathways include, but are not limited to, oral, buccal, and sublingual routes; nasal and ophthalmic pathways; transdermal and subcutaneous routes; as well as transvaginal and intravesical procedures (M.S. Alqahtani, 2021).

When a medication is administered, its components determine its physicochemical characteristics and the effects they have on bodily systems (D. Sahoo, R. Bandaru, 2021). DDS has been successfully employed in recent decades to treat diseases and improve health outcomes due to its enhanced systemic delivery and ability to target the pharmacological activity of the drug (J.O. Morales, 2021). The concept of controlled release emerged as pharmacology and pharmacokinetics progressed, demonstrating the importance of drug release in influencing therapeutic success. The first controlled-release formulation was approved in the 1950s (N.R. Hussein, 2020), and due to its substantial advantages over traditional medications, it has since garnered significant attention. Controlled-release systems deliver medication over a specified period and at a controlled rate. Furthermore, these systems have a lifespan ranging from days to years, as they are not significantly influenced by physiological conditions. In addition to providing continuous or variable release rates, they offer spatial control over drug release. Moreover, controlled drug delivery systems reduce toxicity and enhance drug solubility, target site accumulation, pharmacological activity, pharmacokinetic profiles, patient acceptance, and adherence (A. Thirunavukkarasu, 2022).

Atenolol is the most commonly used beta-blocker. According to available data, initiating beta-blocker therapy for hypertension reduces the risk of cardiovascular disease (CVD) but has little to no effect on mortality. These beta-blockers are less impactful compared to other antihypertensive medications (Wysong CS, 2017). Atenolol (C₁₄H₂₂N₂O₃) is present in amounts of at least 98.0% and not more than 102.0% as measured against the dry weight. It appears as an odorless, white, or almost white powder. The melting points for its ethyl acetate derivative crystallize between 146 and 148 °C. Atenolol dissolves easily in methanol but is moderately soluble in ethanol, water, and isopropanol. The chemical name for atenolol is 2-[p-[2-Hydroxy-3-(isopropylamine) propoxy] phenyl] acetamide, with a molecular weight of 266.34 (Depkes RI, 2020). Its structure is depicted in Figure 1.

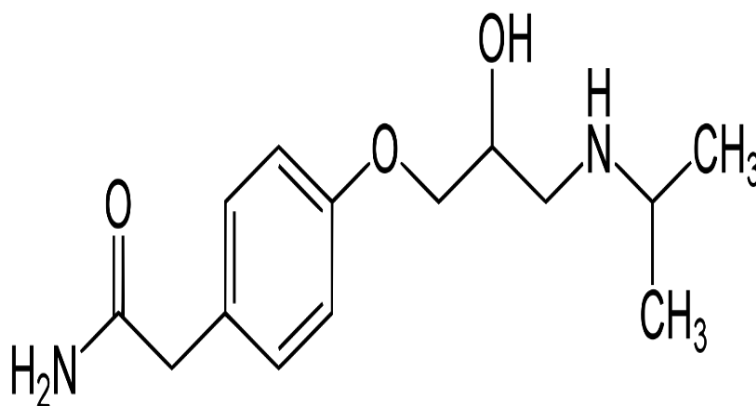


Figure 1 Atenolol's Structure (C₁₄H₂₂N₂O₃)

Orally administered atenolol has a 50% bioavailability rate, with peak blood levels reached two to four hours after ingestion (Chen X, 2017). As previously indicated, atenolol, a hydrophilic β -blocker with poor lipid solubility, exhibits minimal diffusion across the intestinal membrane and the blood-brain barrier. Approximately 10% of the drug binds to plasma proteins. There is minimal

hepatic metabolism of atenolol, and the parent medication is the primary radiolabeled component found in the blood (Zisaki A, 2015).

2.0 Materials and Methods:

2.1 Chemicals:

Solvents were obtained from E. Merck (Darmstadt, Germany), and all compounds were purchased from Sigma-Aldrich Co. (St. Louis, MO). Deionized distilled water was used to prepare all reagents to prevent the presence of metal ions. A complimentary sample of atenolol was supplied by Elder Pharmaceutical Ltd. in Dehradun. All components came from a college laboratory, and the reagents and chemicals used were of analytical grade.

2.2 Apparatus:

- Digital analytical balance from Germany
- Trippin International Crop Oven, Italy
- pH measuring device from Hanna, Romania
- UV-1650 PC Ultraviolet-visible spectrophotometer from Shimadzu, Japan for analyzing atenolol
- Hot plate from Bibby Scientific, UK

Preparation of Calibration Curve:

A standard curve ranging from 0.001 to 0.09 g/L was created for atenolol. Distilled water was used as the solvent in the preparation of stock solutions. Using distilled water as a blank, the absorbance of the resulting solutions was measured at a wavelength of 224.0 nm. The regression analysis demonstrated a linear relationship between atenolol concentration and absorbance, with the standard curve displayed within the range of 0.001–0.09 g/L. The absorbance was again measured at a wavelength of 224.0 nm, and the calibration curve was plotted in distilled water with a pH of 7.

Preparation of Hydrogels:

As indicated in Table 1, the polyvinyl alcohol/chitosan (Chitosan/PVA) hydrogels were created using three distinct mass ratios and the solution casting method on Petri dishes. To prepare the solution, 24.0 g of PVA was dissolved in 276.0 g of distilled water, and the mixture was heated to 90 °C in a water bath. The solution was stored at room temperature for a full day before use. Two weight percent chitosan was obtained by dissolving 4.0 g of chitosan powder in 196.0 g of 1.0 wt% acetic acid solution at room temperature. The solutions were meticulously combined and stirred at various ratios for one hour using a mechanical mixer (Liang, S, 2009). After thoroughly mixing the two solutions, the mixture was polymerized in an oven set to 60 °C for 24 hours.

Table 1 Three distinct mass ratios were utilized in the synthesis of the chitosan/PVA hydrogel.

Sample	Chitosan %	Weight (gm)	PVA %	Weight (gm)
R ₁	30	8	88	18
R ₂	63	24	60	14
R ₃	80	40	85	10

Interaction Between Hydrogels (Chitosan/PVA):

As indicated in Tables 2 and 3, various concentrations of cross-linking agents were added to the dried solution at different mass ratios of chitosan and PVA during the cross-linking stage. After an hour of thorough mixing, the solution was cured for four hours at 140 °C, and the dry weights were recorded.

Table 2 The dry solution is mixed with varying concentrations of fumaric acid, a cross-linking agent.

Fumaric acid (mol)	0.0024	0.0041	0.02
(Chitosan /PVA)%	30/88	30/88	30/88
(Chitosan /PVA)%	63/60	63/60	63/60
(Chitosan /PVA)%	80/85	80/85	80/85

Table 3 The dry solution is mixed with varying concentrations of phthalic acid, a cross-linking agent.

Phthalic acid (mol)	0.002	0.003	0.0064
(Chitosan /PVA)%	30/88	30/88	30/88
(Chitosan /PVA)%	63/60	63/60	63/60
(Chitosan /PVA)%	80/85	80/85	80/85

Swelling Measurement:

The swelling ratio was measured using dried hydrogel fragments. A sample of the hydrogel (0.1 g) was submerged in 100 mL of solutions with varying pH levels (pH = 2, pH = 4, pH = 7.5) and allowed to soak for nine days at different temperatures (42 °C and 44 °C). Every twenty-four hours, the samples were removed from the water for the swelling ratio measurements (A.S. Phanikumar, 2004). After being blotted with filter paper to remove surface water, the swelling ratio was computed using the following formula:

$$[\text{Swelling Ratio}] = \frac{\text{Weight of Swollen Hydrogel} - \text{Weight of Dried Hydrogel}}{\text{Weight of Dried Hydrogel}}$$

$$Rs = (W_s - W_d) 100 / W_d$$

Where W_s = weights of swollen gel, W_d = weight of dried gels.

Drug Atenolol Release:

The amount of atenolol released from the hydrogel network was measured using a loaded hydrogel sample. A sample of the material (0.1 g) was dried and then submerged in 100 mL of

solutions with varying pH levels (2, 4, and 7.5) and temperatures (42 °C and 44 °C). The release of atenolol was measured every 24 hours for nine days using a spectrophotometer at a wavelength of 224.0 nm (P.M. Glassman, 2020).

3.0 Results and Discussion:

Due to its poor bioavailability and favorable compatibility in the intended formulation, atenolol was selected for the investigation. The purity of the drug was confirmed by its melting point and the results of its identification using an ultraviolet-visible spectrophotometer. A pure drug's ultraviolet-visible spectrum should show no incompatibility with the excipients present.

3.1 Swelling Behavior of Hydrogel (Chitosan/PVA):

Since chitosan hydrogels are ionized, their swelling properties are influenced by the medium and the chemical structure. Generally, an increase in the concentration of functional ionizable groups in the formulation and a decrease in the extent of cross-linking during the synthesis process lead to increased swelling of the chitosan/PVA hydrogel at equilibrium. According to the Donnan hypothesis, a gel's capacity to swell is largely dictated by the osmotic pressure gradient between its interior and exterior. The concentration difference of ions between the hydrogel's interior and the surrounding solution represents this osmotic pressure gradient. Due to the high density of fixed-charge groups within the hydrogel, the concentration of counterions is always greater inside. Consequently, the hydrogel behaves like a concentrated solution of ions, resulting in its tendency to absorb more solution in an effort to balance its internal concentration. This osmotic pressure gradient shifts during the swelling process (Gunasekaran, S, 2006).

3.2 Effect of Cross-Linking Agent on Swelling:

At 42 °C, the behavior of the swelling ratio in chitosan/PVA hydrogels was investigated as a function of time and pH. The presence of cross-links significantly reduced the water-absorbing capacity of the polymer network. The amount of cross-linking agent used in the chitosan/PVA hydrogels determines the extent of cross-linking that occurs. In this study, the chitosan/PVA blend matrix was cross-linked using varying concentrations of fumaric acid and phthalic acid. The swelling ratio in the medium was affected by the pH level. For instance, as the concentration of the cross-linking agents (fumaric acid and phthalic acid) increased, the swelling ratio decreased across different pH media (2, 4, and 7.5) [16]. The swelling ratio of the initially dry hydrogel over time at given pH values is displayed in Figures 2.1 through 3.9. The swelling ratio was computed using the formula:

$$[R_s = \frac{(W_s - W_d)}{W_d} \times 100]$$

where (W_s) is the weight of the swollen gel, and (W_d) is the weight of the dried gel (Krishna Rao, 2006).

It was observed that as the molar ratio of the cross-linking agent (0.0024-0.02 mol) increased, the time needed to achieve the swelling ratio of the hydrogels decreased. The swelling ratio of the chitosan/PVA hydrogels and the time required to establish equilibrium between swelling and contraction were unaffected by the concentration of PVA. This is because PVA's molecular structure lacks ionizable groups at any pH level in the buffer. Furthermore, PVA likely acts only as a minor physical entanglement within the chitosan/PVA hydrogel matrix, having no significant contractive effect on the evolving network. Regardless of the PVA concentration, the maximum mass difference

between the swollen state (at pH 4) and the contracted state (at pH 7.5) of the hydrogel was approximately fivefold (Krishna Rao, 2006).

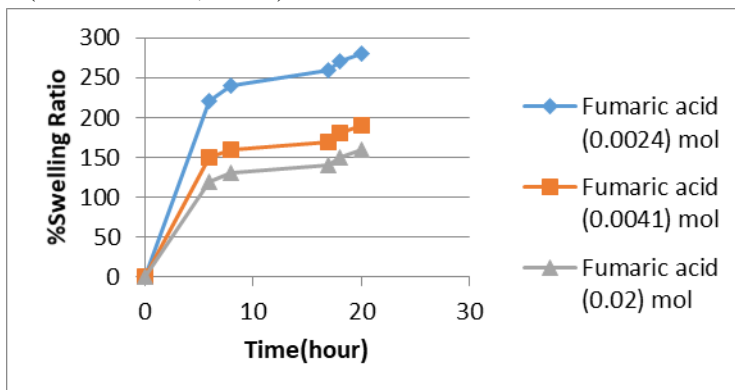


Figure (2.1) Swelling Cross-Linking Ratio (Chitosan=30%) with (PVA) by (FA) vs. time at pH=2

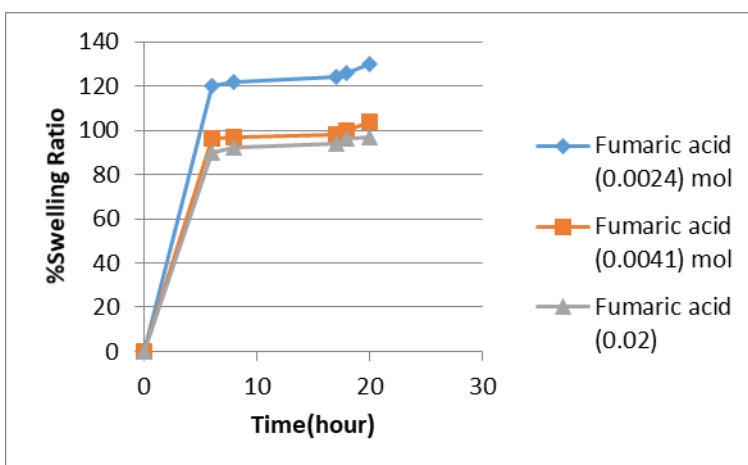


Figure (2.2) Swelling Cross-Linking Ratio (Chitosan =30%) with (PVA) by (FA).vs. time at pH=4

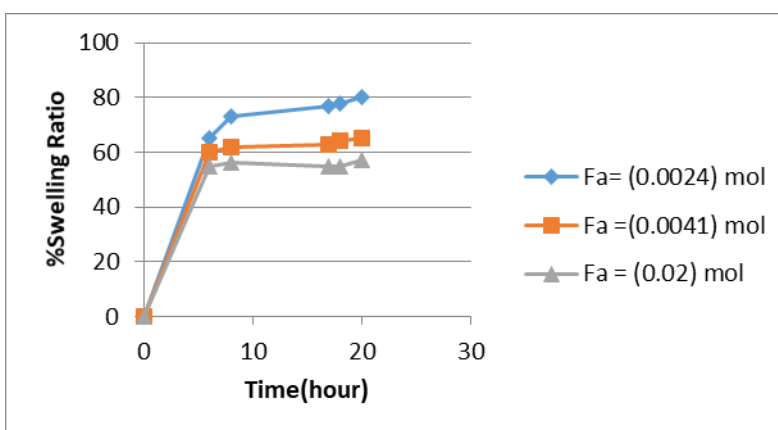


Figure (2.3) Swelling Cross-Linking Ratio (Chitosan =30%) with (PVA) by (FA) vs. time at pH=7.5

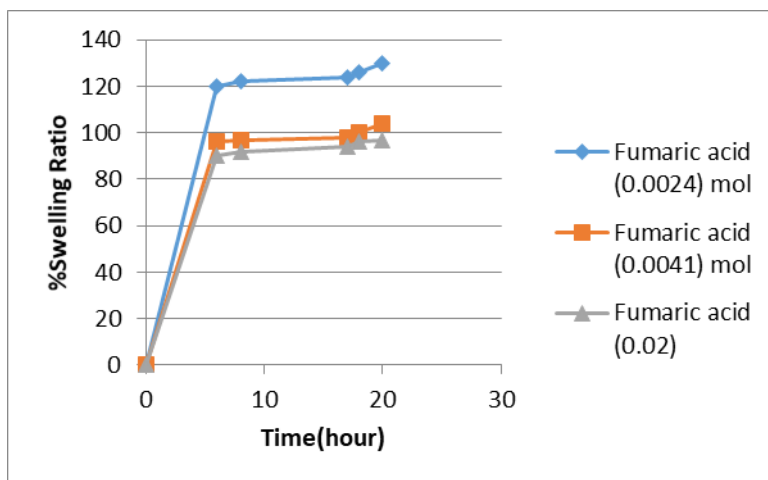


Figure (2.4) Swelling Cross-Linking Ratio (Chitosan=63%) with (PVA) by (FA) vs. time at pH=2

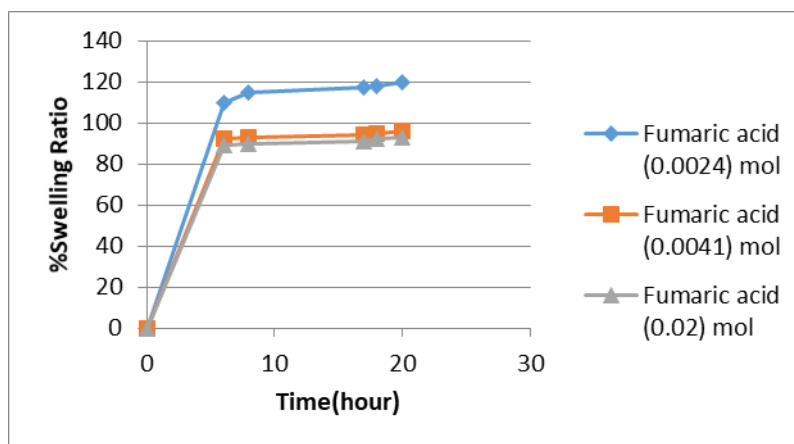


Figure (2.5) Swelling Cross-Linking Ratio (Chitosan=63%) with (PVA) by (FA) vs. time at pH=4

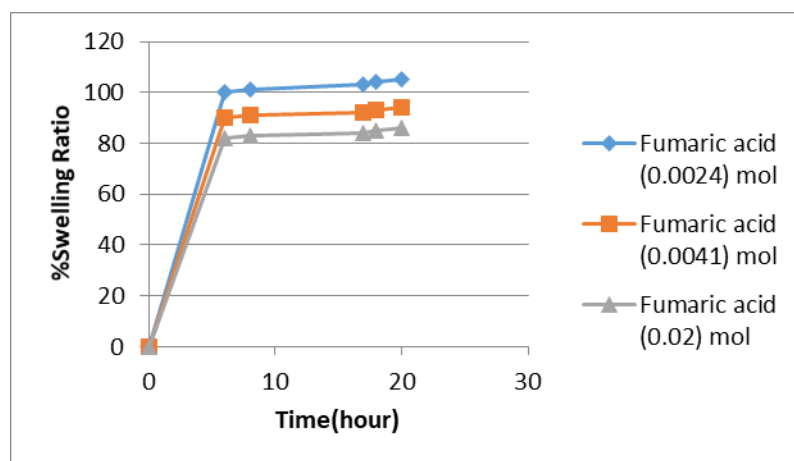


Figure (2.6) Swelling Cross-Linking Ratio (Chitosan=63%) with (PVA) by (FA) vs. time at pH=7.5

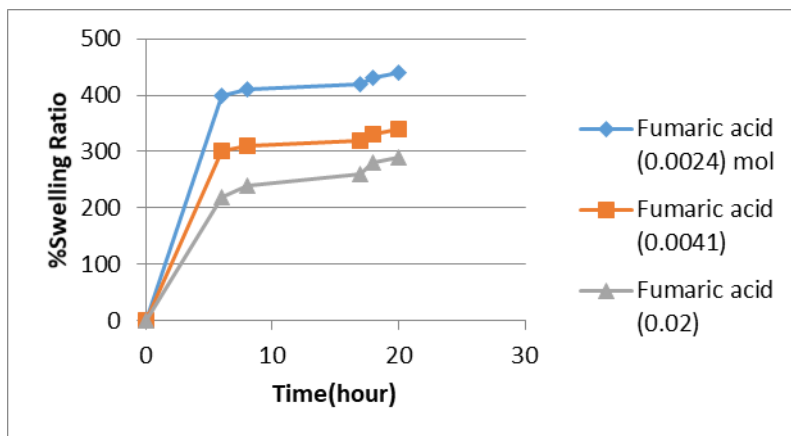


Figure (2.7) Swelling Cross-Linking Ratio (Chitosan=80%) with (PVA) by (FA) vs. time at pH=2

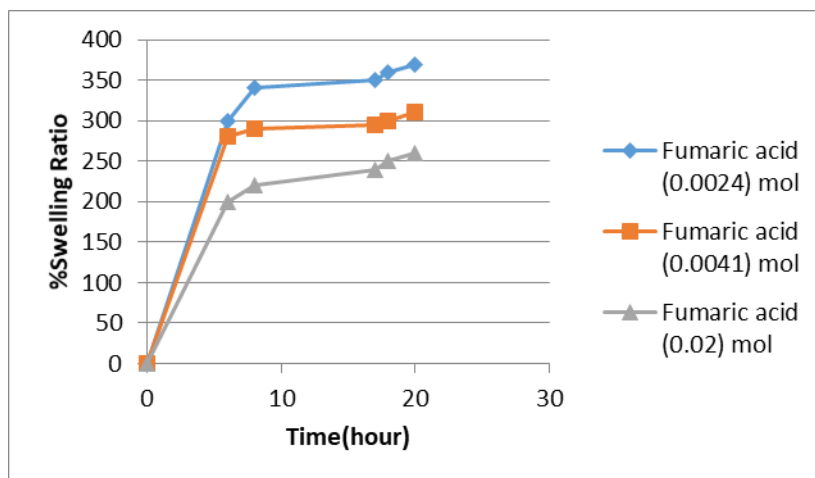


Figure (2.8) Swelling Cross-Linking Ratio (Chitosan=80%) with (PVA) by (FA) vs. time at pH=4

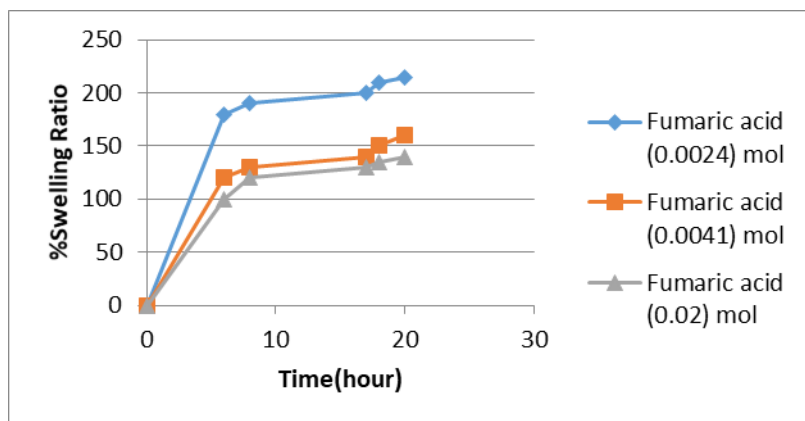


Figure (2.9) Swelling Cross-Linking Ratio (Chitosan=80%) with (PVA) by (FA) vs. time at pH=7.5

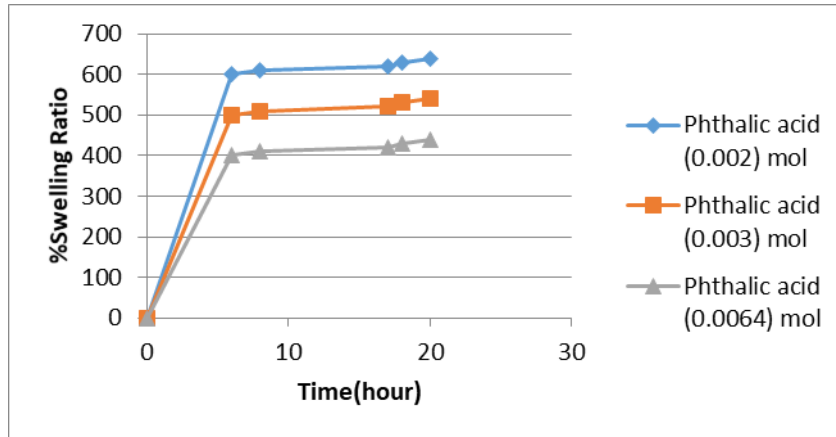


Figure (3.1) Swelling Cross-Linking Ratio (Chitosan =30%) with (PVA) by (PA) vs. time at pH=2

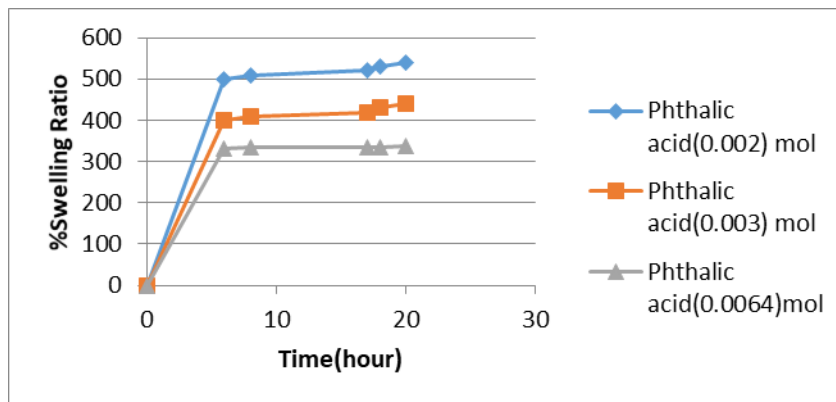


Figure (3.2) Swelling Cross-Linking Ratio (Chitosan =30%) with (PVA) by (PA) vs. time at pH=4

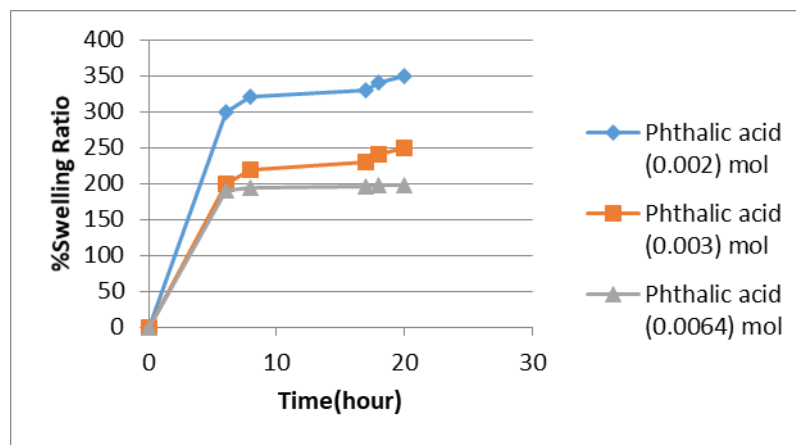


Figure (3.3) Swelling Cross-Linking Ratio (Chitosan =30%) with (PVA) by (PA) vs. time at pH=7.5

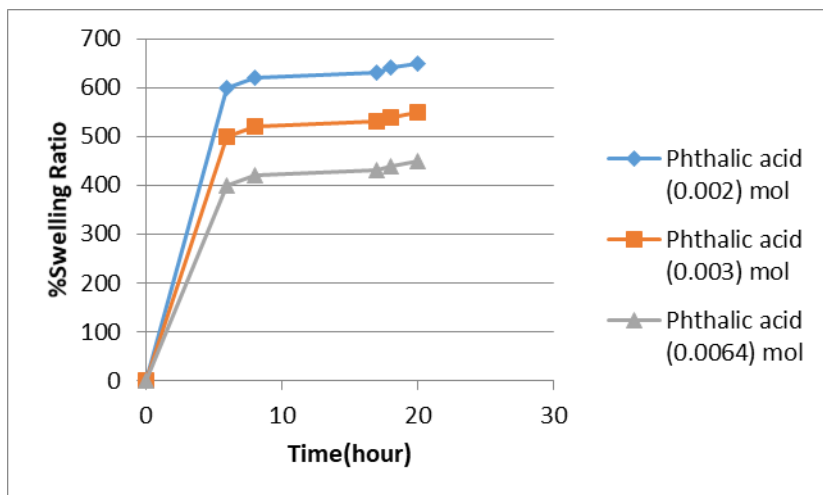


Figure (3.4) Swelling Cross-Linking Ratio (Chitosan = 63%) with (PVA) by (PA) vs. time at pH=2

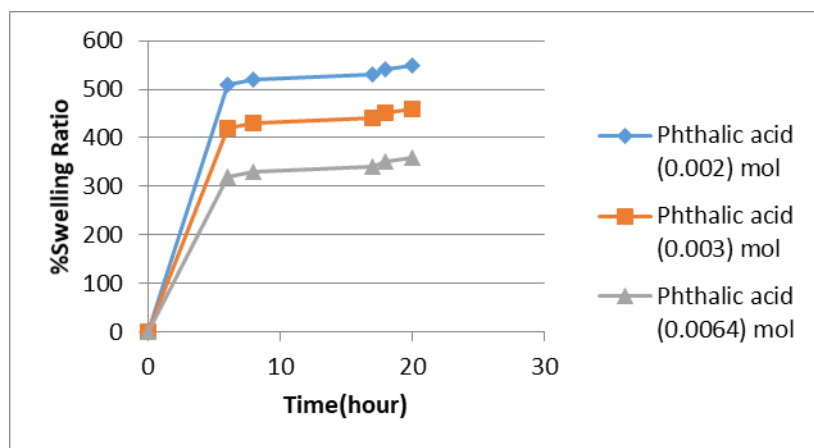


Figure (3.5) Swelling Cross-Linking Ratio (Chitosan =63%) with (PVA) by (PA) vs. time at pH=4

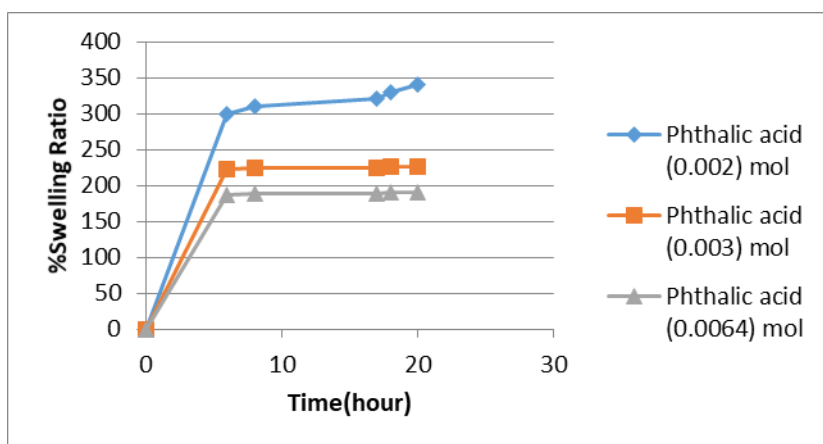


Figure (3.6) Swelling Cross-Linking Ratio (Chitosan =63%) with (PVA) by (PA) vs. time at pH=7.5

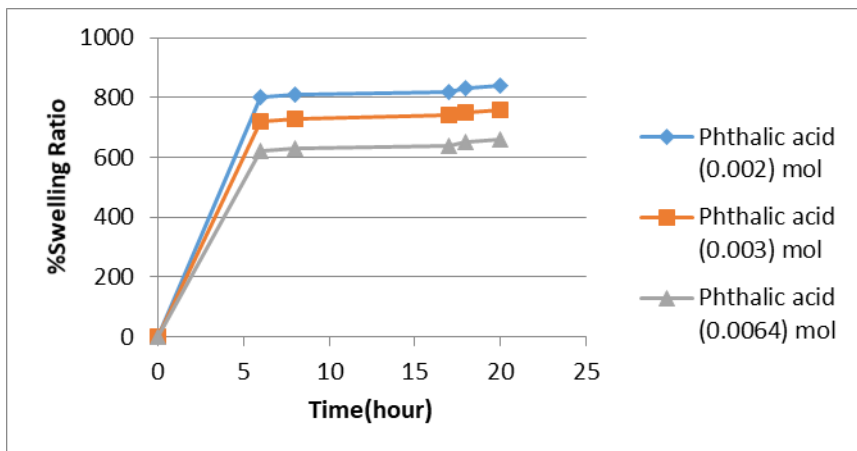


Figure (3.7) Swelling Cross-Linking Ratio (Chitosan =80%) with (PVA) by (PA) vs. time at pH=2

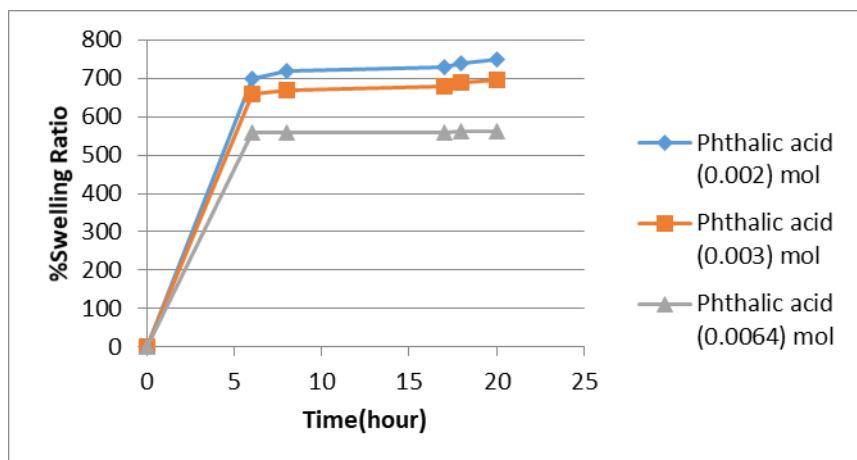


Figure (3.8) Swelling Cross-Linking Ratio (Chitosan =80%) with (PVA) by (PA) vs. time at pH=4

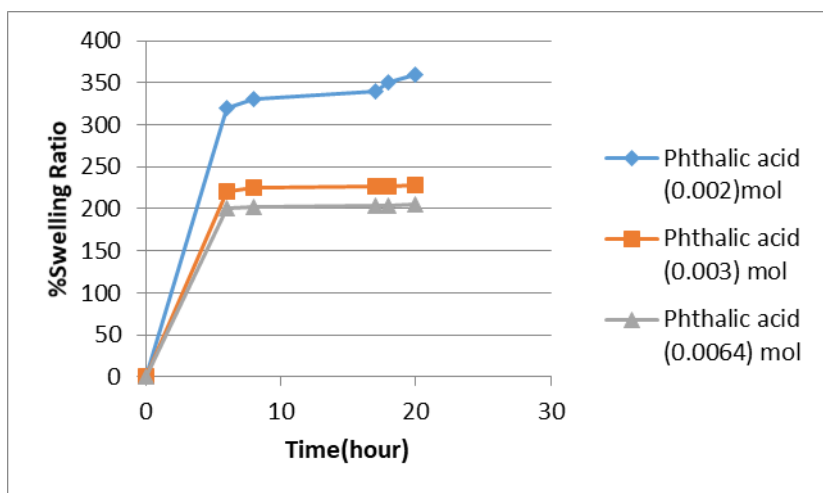


Figure (3.9) Swelling Cross-Linking Ratio (Chitosan=80%) with (PVA) by (PA) vs. time at pH=7.5

3.3 The Effect of the Type of Cross-Linking Agent on the Release of Atenolol:

The effects of different types and amounts of fumaric acid (FA) and phthalic acid (PA) on the release of atenolol at various time points and pH values are depicted in Figures 4.1, 4.2, and 4.3. The order of atenolol release from the hydrogels is as follows:

[\text{PA (0.001 mol)} > \text{FA (0.0025 mol)}]

The network density is the primary determinant of drug release in hydrogel systems. In contrast to the aforementioned characterization, the drug release behavior of chitosan/polyvinyl alcohol membranes cross-linked with FA differs significantly. The reduced drug release is likely attributed to an increase in the density of ionic cross-linking. The ionic cross-linking density is higher in chitosan/PVA-FA membranes, while the maximum drug release is observed in chitosan/PVA-PA membranes, which exhibit significantly varied but not excessively high ionic cross-linking densities (Guan, 1996). An increase in the amount of free water that can be present in the hydrogel network may facilitate the dissociation of hydrogen bonds between the amino groups of chitosan. When a cross-linker is employed to link the polymer chains, the ability of the chains to relax is hindered.

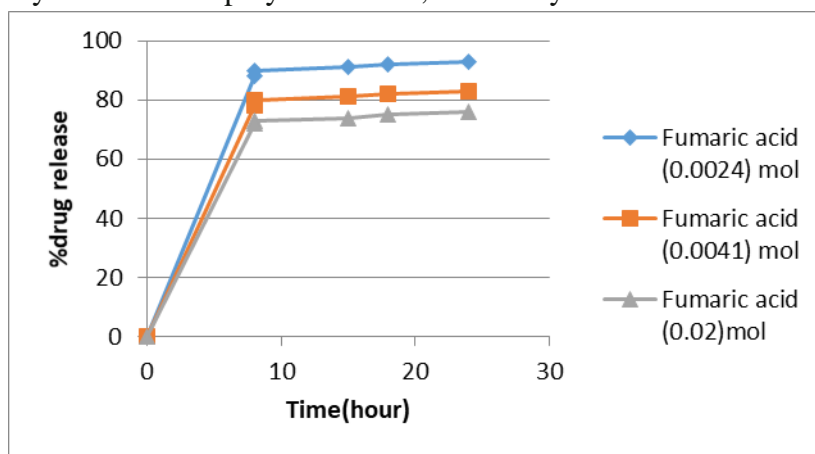


Figure (4.1) Effect of (FA)focus on the discharge of (Atenolol) vs. time at pH=2

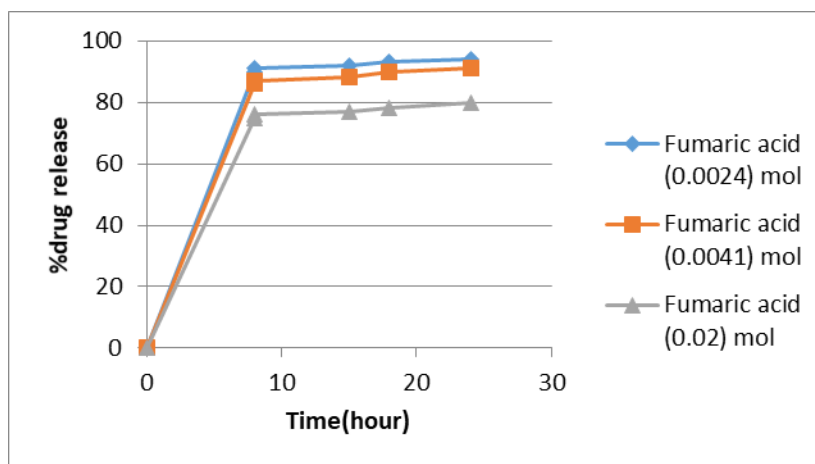


Figure (4.2) Effect of (FA), (PA)focus on the discharge of (Atenolol) vs. time at pH=4

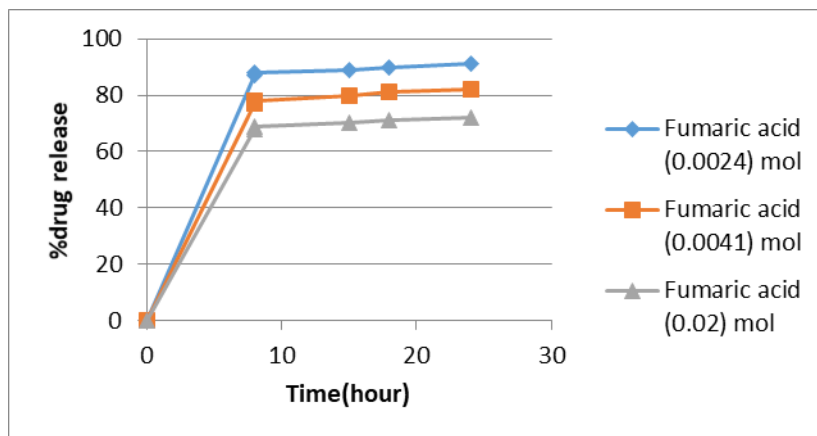


Figure (4.3) Effect of (FA), (PA) focus on the discharge of (Atenolol) vs. time at pH=7.5

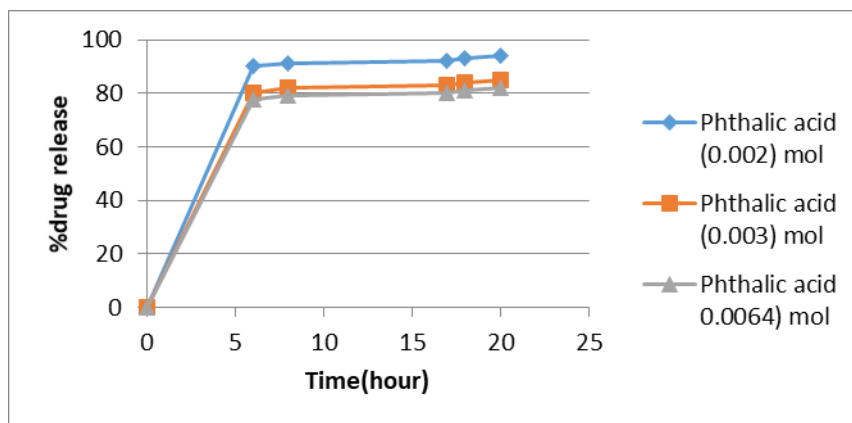


Figure (4.4) Effect of (PA) focus on the discharge of (Atenolol) at pH=2

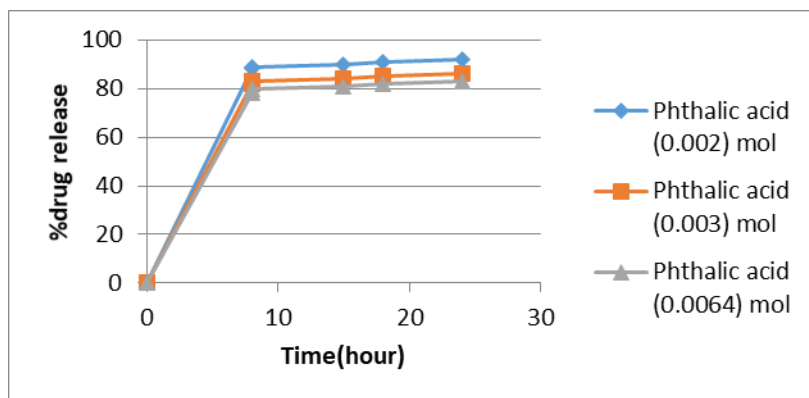


Figure (4.5) Effect of (PA) focus on the discharge of (Atenolol) at pH=4

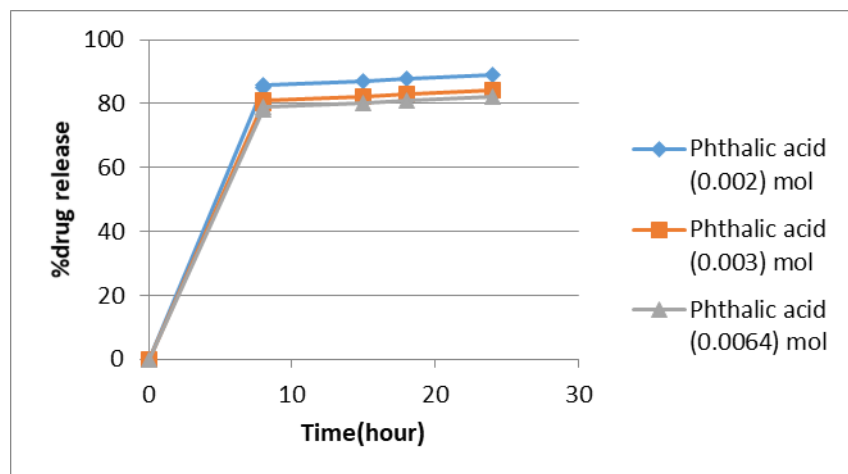


Figure (4.6) Effect of (PA) focus on the discharge of (Atenolol) at pH=7.5

4.0 Conclusion:

The percentage of medication release from gel networks was favorable due to the network properties, demonstrating effective degradation in balanced medium-term gels with well-prepared swelling ratios. The acidic functional groups have a significant influence on the drug release rates from polymeric gel networks.

5.0 Recommendations:

Given that the majority of medications used to treat chronic illnesses are now delivered through these systems, it is recommended to explore the incorporation of additional polymers with the drugs. Further research should be conducted to investigate the performance of these systems both in vivo (within the living body) and in vitro (outside the living body) to optimize their efficiency and effectiveness.

References:

1. B.M. Rayaprolu, J.J. Strawser, G. Anyarambhatla, Excipients in parenteral formulations: selection considerations and effective utilization with small molecules and biologics, *Drug Dev. Ind. Pharm.* 44 (2018) 1565–1571, <https://doi.org/10.1080/03639045.2018.1483392>
2. A.M. Vargason, A.C. Anselmo, S. Mitragotri, The evolution of commercial drug delivery technologies, *Nat. Biomed. Eng.* 5 (2021) 951–967, <https://doi.org/10.1038/s41551-021-00698-w>
3. M.S. Alqahtani, M. Kazi, M.A. Alsenaidy, M.Z. Ahmad, Advances in oral drug delivery, *Front. Pharmacol.* 12 (2021), 618411, <https://doi.org/10.3389/fphar.2021.618411>.
4. D. Sahoo, R. Bandaru, S.K. Samal, R. Naik, P. Kumar, P. Kesharwani, R. Dandela, in: P. Kesharwani, S. Taurin, K.B. T.-T., A. of N.N. GreishGreish (Eds.), Chapter 9 - Oral Drug Delivery of Nanomedicine, Academic Press, 2021, pp. 181–207, <https://doi.org/10.1016/B978-0-12-820466-5.00009-0>.
5. J.O. Morales, P.R. Vuddanda, S. Velaga, Controlled drug delivery via the buccal and sublingual routes, in: *Fundam. Drug Deliv.*, 2021, pp. 433–448, <https://doi.org/10.1002/9781119769644.ch17>.
6. N.R. Hussein, H.K. Omer, A.M.A. Elhissi, W. Ahmed, in: W. Ahmed, D.A. Phoenix, M.J. Jackson, C.P.B.T.-A. in M., S.E. Charalambous (Eds.), Chapter 15 - Advances in Nasal Drug Delivery Systems, Academic Press, 2020, pp. 279–311, <https://doi.org/10.1016/B978-0-12-819712-7.00015-2>

7. A. Thirunavukkarasu, R. Nithya, J. Jeyanthi, Transdermal drug delivery systems for the effective management of type 2 diabetes mellitus: a review, *Diabetes Res. Clin. Pract.* (2022), 109996, <https://doi.org/10.1016/j.diabres.2022.109996>.
8. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. *Cochrane database of systematic reviews*. 2017 doi: 10.47760/ijpsm.2020.v05i11.002
9. Depkes RI. *Farmakope Indonesia VI*. Depkes RI, Jakarta. 2020. doi: 10.47760/ijpsm.2020.v05i11.002
10. Chen X, Slättengren T, de Lange ECM, Smith DE, Hammarlund-Udenaes M. Revisiting atenolol as a low passive permeability marker. *Fluids Barriers CNS*. 2017 Oct 31;14(1):30. <https://creativecommons.org/licenses/by-nc-nd/4.0/>
11. Zisaki A, Miskovic L, Hatzimanikatis V. Antihypertensive drugs metabolism: an update to pharmacokinetic profiles and computational approaches. *Curr Pharm Des*. 2015;21(6):806-22. <https://creativecommons.org/licenses/by-nc-nd/4.0/>
12. Liang, S., Liu, L., Huang, Q. and Yam, K. (2009). Preparation of single or double-network chitosan/Poly(vinyl alcohol) gel films through selectively cross-linking method, *Carbohydr. Polyme.*, 77: 718-724.
13. A.S., Phanikumar, B.R., and Sharma, R.S. 2004. Prediction of swelling characteristics of remolded and compacted expansive soils using free swell index. *Quarterly Journal of Engineering Geology and Hydrogeology*, 37(3): 217–226. doi:10.1144/1470-9236/03-052.
14. P.M. Glassman, C.H. Villa, A. Ukidve, Z. Zhao, P. Smith, S. Mitragotri, et al., Vascular drug delivery using carrier red blood cells: focus on RBC surface loading and pharmacokinetics, *Pharmaceutics* 12 (5) (2020 May 9) 440, <https://doi.org/10.3390/pharmaceutics12050440>. PMID: 32397513; PMCID: PMC7284780.
15. Gunasekaran, S., Wang, T. and Chai, C. (2006). Swelling of pH-sensitive chitosan-Poly(vinyl alcohol) hydrogels, *Appl. polym. Sci.* **102**: 4665-4671.
16. Krishna Rao, K.S.V., Vijaya Kumar Naidu, B., Subha, M.C.S., Sairam, M. and Aminabhavi, T. M. (2006). Novel chitosan-based pH-sensitive interpenetrating network microgels for the Controlled release of cefadroxil, *Carbohydr. Polym.* **66**: 333-344.
17. Guan, Y. L., Shao, L., Liu, J. and Yao, K. D. (1996). pH Effect on correlation between water state and swelling kinetics of the cross-linking chitosan polyether semi-interpenetrating polymer network (IPN) hydrogel, *J. Appl. Polym. Sci.* **62**: 1253-1258