ORIGINAL ARTICLE

FUTURE JOURNAL OF PHARMACEUTICALS AND HEALTH SCIENCES

Published by Pharma Springs Publication Journal Home Page: https://pharmasprings.com/fjphs

Cross-linked Polymeric Aceclofenac Hydrogels Formulation and Characterization

Alagusundaram M[1], Nem Kumar Jain[2], Brajesh Singh*[1], Goli Venkateshwarlu[3]

[1]Department of Pharmaceutics, School of Pharmacy, ITM University, Gwalior – 474001 Madhya Pradesh, India
[2]Department of Pharmacology, School of Pharmacy, ITM University, Gwalior – 474001 Madhya Pradesh, India
[3]Department of Pharmaceutical Bio-technology, ITM University, Gwalior – 474001 Madhya Pradesh, India

Article History:

Received on: 02 May 2023
Revised on: 17 May 2023
Accepted on: 19 May 2023

Keywords:

Aceclofenac,
Cross-linking,
Hydrogels,
In-vitro drug release,
Kinetics

ABSTRACT

Hydrogels are cross-linked polymeric networks that may store water within the gaps between the polymeric chains. Drug delivery, cell carriers and/or trapping, wound treatment, and tissue engineering is just a few of the biomedical applications that have made substantial use of hydrogels. Aceclofenac hydrogels were created employing polymers such as HPMC, sodium alginate, and Eudragit RL100 either through the physical cross-linking approach orionotropic gelation process. Aceclofenac hydrogels were tested for bulk density, tapped density, percentage yield, swelling ratio, and water uptake. In all formulations, the results in bulk density, tapped density, and percentage yield were quite excellent. All created formulations were subjected to in-vitro drug release tests in order to determine the drug release pattern, and the in-vitro release data were treated to several kinetic models. The correlation coefficient values (R=0.999644) show that the drug release kinetics were zero order. Peppa's model determined the mechanism of drug release, which shows super-case II transport as demonstrated by diffusion exponent values (n =0.949948). As a result, Aceclofenac may be a good candidate for hydrogel production.

*Corresponding Author

Name: Brajesh Singh
Phone: 9669038833
Email: brajeshsingh.sop@itmuniversity.ac.in

eISSN: 2583-116X pISSN:

DOI: https://doi.org/10.26452/fjphs.v3i2.448

Production and Hosted by

Pharmasprings.com

INTRODUCTION

Hydrogels are cross-linked polymeric networks that may store water within the gaps between the polymeric chains. Drug delivery, cell carriers and/or trapping, wound treatment, and tissue engineering is just a few of the biomedical applications that have made substantial use of hydrogels [1]. The hydrogel's water-holding ability is mostly due to the presence of hydrophilic groups in the polymer chains, specifically amino, carboxyl, and hydroxyl groups [2]. According to Hoffmann, the amount of water in a hydrogel can range from ten percent to hundreds of times the weight of the xerogel [3]. A xerogel is a solid, porous substance formed by the gradual drying of hydrogels at room temperature, with unrestricted shrinkage dependent on the precursors used [4]. The greater the number of hydrophilic groups, the greater the water retaining capacity; however, as crosslinking density increases, equilibrium swelling decreases due to a decrease in hydrophilic groups. As the crosslinking density increases, so does the hydrophobicity of the polymer network, resulting in a corresponding

reduction in stretch ability [5]. As previously mentioned, hydrogels are cross-linked polymeric networks, which give the hydrogel a three-dimensional polymeric network structure.Hydrogels are distinguished by their shape, swelling properties, and elasticity. Porous structure is indicated by morphology. The process of releasing a medication from a swollen polymeric mass is determined by swelling, whereas elasticity impacts the mechanical strength of the network and determines the stability of these drug carriers [6]. Hydrogels because of their hydrophilic character and potential to be biocompatible have been of great interest in biomaterial scientists. Hydrogels can also be used for cell encapsulation and encapsulation of drugs.Hydrogels increase the solubility of poorly soluble NSAIDs such as Aceclofenac, Etoricoxib [7], and others.

Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID) intended to treat osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. It is almost insoluble in water, but freely soluble in acetone and alcohol. Aceclofenac's mode of action is mostly dependent on the suppression of prostaglandin production [8]. Aceclofenac is a strong inhibitor of the enzyme cyclooxygenase, which is involved in prostaglandin generation. The drug reduces the production of the inflammatory cytokines interleukin (IL)-1 and tumour necrosis factor, as well as prostaglandin E2 (PGE2). Neurophils have also been shown to have molecular effects on cell adhesion. In vitro findings show that Aceclofenac inhibits cyclooxygenase (Cox)-1 and 2 in whole blood experiments, with selectivity for Cox-2 [9]. The current study focuses on the formulation and characterization of Aceclofenac cross-linked polymeric hydrogels generated using an orifice ionotropic gelation process.

MATERIAL AND METHODS

Aceclofenac was procured from Drugs India, Hyderabad, India. Sodium alginate (SA) was obtained from Finar Chemicals, Ahemadabad, India. Hydroxypropyl Methyl Cellulose (HPMC) and Polymethaacrylates (Eudragit) were procured from SD Fine Chemicals, Mumbai, India. Calcium chloride was procured from Qualigen Chemicals, Mumbai, India. All other materials used and received were of analytical grade. The Aceclofenac hydrogels were prepared by the orifice ionotropic gelation method using calcium chloride as a cross-linking agent.

Preparation of Aceclofenac hydrogels

Physical crosslinking (the orifice ionotropic gelation process) was used to create the hydrogels [10, 11].

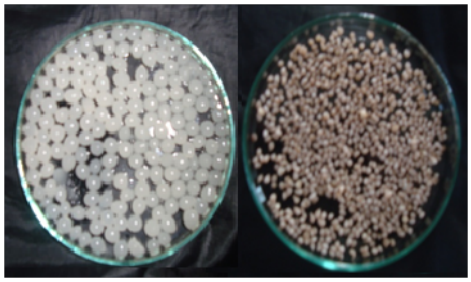

Figure 1: Hydrogel formulation (A2) before and after drying

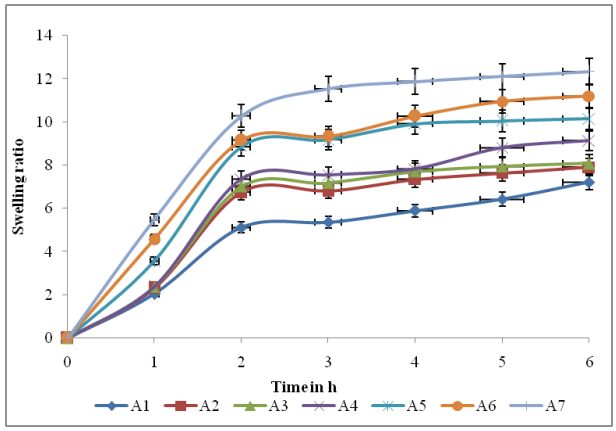

Figure 2: Swelling ratio hydrogel formulations A1-A7

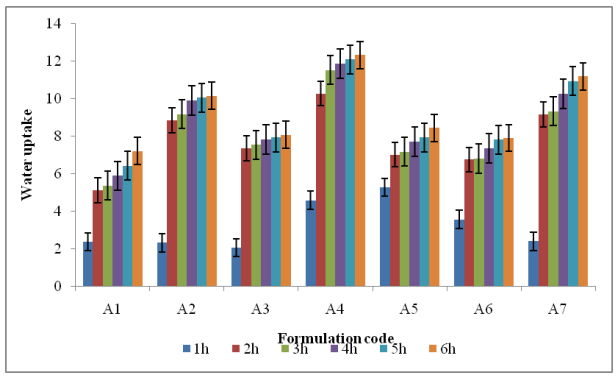

Figure 3: Water uptake of hydrogel formulations A1-A7

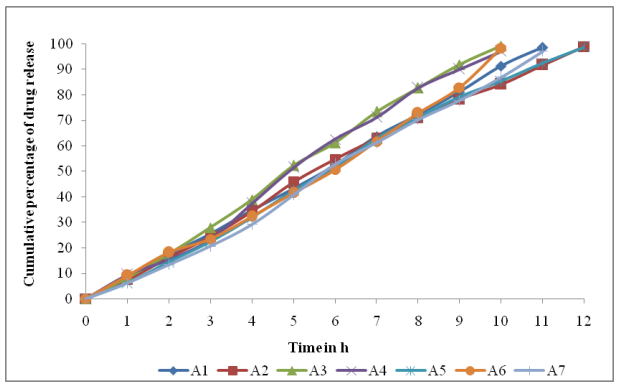

Figure 4: In-vitro release data for formulations A1-A7

Table 1: Composition of Aceclofenac hydrogels

Formulation code	Drug in g	Polymers in ratio		
		Sodium alginate	HPMC	Eudragit RL 100
A1	1	1	1	1
A2	1	1	1.5	0.5
A3	1	1	0.5	1.5
A4	1	1.5	0.5	1
A5	1	0.5	1.5	1
A6	1	0.5	1	1.5
A7	1	1.5	1	0.5

Table 2: Micrometric properties of formulations A1 – A7

Formulation code	Angle of repose (θ) ± SD	Bulk density (g/cc) ± SD	Tapped density (g/cc) ± SD	Carr's index (%) ± SD	Hausner's ratio± SD
A1	28.15 ± 0.015	0.797 ± 0.010	0.904 ± 0.026	11.83 ± 0.115	1.134 ± 0.015
A2	24.98 ± 0.026	0.655 ± 0.005	0.894 ± 0.005	15.26 ± 0.010	1.364 ± 0.011
A3	28.72 ± 0.011	0.624 ± 0.011	0.861 ± 0.011	29.86 ± 0.057	1.379± 0.005
A4	30.04 ± 0.022	0.728 ± 0.015	0.827 ± 0.010	11.97 ± 0.115	1.135 ± 0.011
A5	27.15 ± 0.015	0.732 ± 0.015	0.896 ± 0.010	18.30± 0.111	1.224 ± 0.005
A6	29.49 ± 0.005	0.687 ± 0.015	0.840 ± 0.011	18.21 ± 0.010	1.222 ± 0.005
A7	27.73 ± 0.011	0.711 ± 0.005	0.843 ± 0.005	15.65 ± 0.010	1.185± 0.011

Table 3: Diffusion characteristics of Aceclofenac hydrogel formulations

Formulation code	Correlation coefficient values (R2)		Diffusion exponent value(n)
	Zero Order	Higuchi's Model	
A1	0.999644	0.960202	0.956438
A2	0.99772	0.999644	0.949948
A3	0.998753	0.99772	0.908609
A4	0.996319	0.998753	0.901576
A5	0.997818	0.996319	0.883084
A6	0.995155	0.997818	0.97071
A7	0.998037	0.995155	0.852798

Table 4: Diffusion exponent (n) and drug release mechanism

Diffusion exponent value (n)	Drug release mechanism
< 0.45	Fickian release
0.45 to 0.89	Non-fickian release
0.89	Case II transport
> 0.89	Super case II transport

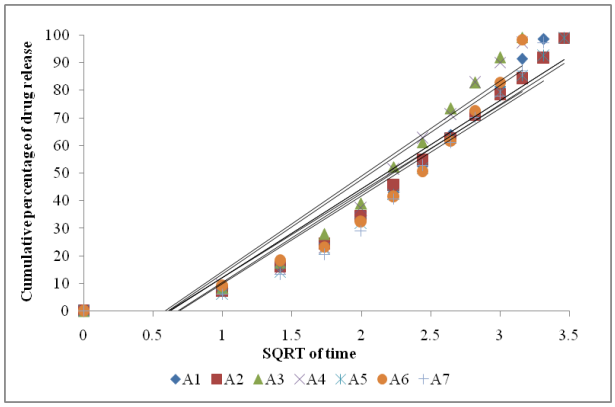

Figure 5: Higuchi's plot for formulations A1-A7

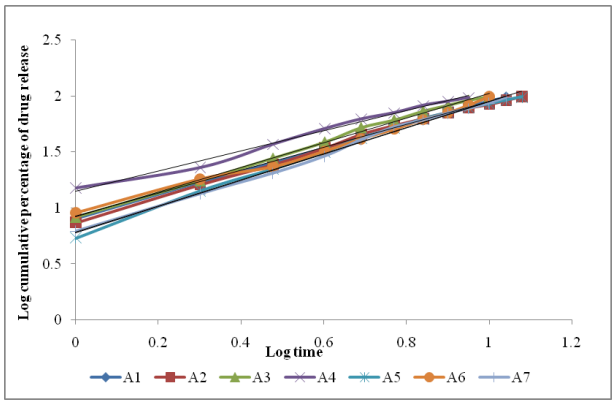

Figure 6: Peppa's plot for formulations A1-A7

An appropriately weighed amount of sodium alginate, HPMC, Eudragit RL100, and the drug Aceclofenac were dissolved in the required quantity of distilled hydroalcoholic solution and homogenised at 500 rpm for 30 minutes. To remove air bubbles, this solution was sonicated for 30 minutes. These were placed into a 2% Cacl2 (as a cross-linking agent) solution with a 21-G syringe and cured for 30 minutes. These hydrogels were rinsed in distilled water and allowed to dry at room temperature. The compositions of the drug Aceclofenac and different polymers are given in Table 1.

Evaluation of micromeritic properties

Angle of repose

Angle of repose has been used as an indirect method of quantifying powder flow ability because of its relationship with interparticle cohesion. A static heap of powder will begin to slide when the angle of inclination is large enough to overcome frictional forces. This sliding will stop when the angle of inclination is below that required to overcome adhesion or cohesion, i.e. sliding occurs until the gravitational forces balance the inter-particle forces. This balance of forces causes the powder poured from a container onto a horizontal surface to form a conical mount or heap [12]. The sides of the heap formed in this way make an angle with the horizontal, which is called the angle of repose, represented by θ.

$$\theta = \tan^{-1}(h/r)$$

Where θ = Angle of repose

h = height of heap

r =horizontal surface radius of heap.

Bulk density

An accurately weighed quantity of hydrogel beads was poured into a graduated cylinder. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called the bulk volume, and the bulk density is calculated by the following formula [13]:

$$Bulk\ density = (Weight\ of\ hydrogels)/ Bulk\ volume\ of\ hydrogels$$

Tapped density

Tapped density refers to the bulk density of the powder after a specified compaction process, usually involving vibration of the container. After measuring the bulk volume, the same measuring cylinder was set into the tap density apparatus. The tapped density is calculated by the following formula:

$$Tapped\ density = (Weight\ of\ hydrogels)/ Volume\ of\ hydrogels\ after\ tapping$$

Carr's Index

Carr's index is one of the most important parameters to characterize the nature of the flow ability of powders and granules [14]. The formula that follows can be employed to calculate it.

$$Carr's\ index = ((Tapped\ density - Bulk\ densit)/ Tapped\ density) \times 100$$

Hausner's ratio

Hausner's ratio is a key factor in determining powder and granule flow properties. This can be calculated using the formula below.

$$Hausner's\ ratio = (Tapped\ density\ )/(Bulk\ density)$$

Swelling ratio

The swelling of hydrogel was carried out in triplicate by the gravimetric method. Known weights of hydrogels were taken and immersed in excess distilled water for different time intervals at 37 °C, and then the hydrogels were removed, wiped with tissue paper to remove excess solvent, and weighed immediately [15]. The difference in weight has increased the amount of water taken up by hydrogels after definite time intervals.The formula below can be employed to calculate this.

$$Swelling\ ratio = (Wt - Wo)/Wo$$

Where,

w_t represents weight of hydrogels at time t

w_o represents initial weight of hydrogels

Water uptake studies

Hydrogels with known weights were soaked in excess distilled water at various time intervals at 37 °C, then removed, wiped with tissue paper to remove excess solvent, and weighed immediately [16]. The weight differential has enhanced the amount of water taken up by hydrogels after certain intervals of time.The water uptake studies are calculated by the following formula:

$$Water\ uptake = W_S/W_D$$

Where, W_S= weight of swollen hydrogels, W_D=weight of dried hydrogels.

In-vitro drug release studies

In-vitro drug release from the hydrogels of Aceclofenac was performed using dissolution test apparatus (paddle method). The USP dissolution apparatus was thermostated at temperature of 37±1°C and stirred at rate of 50 rpm. Each 100 mg equivalent hydrogels of every formulation were taken and immersed in 900 ml of pH 7.4 phosphate buffer for 12 h. The aliquots of 1 ml were withdrawn at time interval of every hour, filtered and replaced with equal volume of dissolution medium. The sink condition was maintained throughout the study [17, 18]. The samples were analyzed spectrophotometrically at 263 nm and cumulative amount of drug release at various time intervals was calculated.

RESULTS AND DISCUSSION

The oral bioavailability of Aceclofenac has been reported to be significant. It is well absorbed by the stomach when administered orally. Hydrogel drug delivery ensures the specific release of Aceclofenac, which affects the time delay between administration and the onset of action. Hydrogels of Aceclofenac were formulated by the physical cross linking method (orifice ionotropic gelation method) by using polymers like HPMC, sodium alginate, and Eudragit RL100. The hydrogel formulation of Aceclofenac is shown in Figure 1 before and after drying.

In order to find out the micromeritic properties of all the prepared Aceclofenac hydrogel formulations, the angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were determined. The results obtained are shown in Table 2. To know the reaction, interaction, and compatibility between the drug and polymer, influence of the solvent during the formation of Aceclofenac hydrogel, the prepared formulation was calculated for percentage yield. The percentage in the range of 92.5 to 98.7 and the highest percentage yield were obtained from the formulation A2 because of its higher percentage of HPMC (1.5%), sodium alginate (1%) and less percentage of Eudragit RL100 (0.5 %).

During administration, the hydrogels absorb the gastrointestinal fluid and swell due to mucoadhesive polymers and sodium alginate; thereby, drug permeation takes place through the pores of the hydrogels after swelling. The swelling ratios were calculated until equilibrium swelling occurred, or up to 6 h. The results obtained are shown in Figure 2.

Water uptake studies can determine the dried hydrogel formulations' capacity to absorb water and return to their original position by swelling without losing their structure. The water uptake studies were performed for up to 6 h for each formulation. The results obtained are shown in Figure 3.

In order to find out the drug release from the hydrogels, all the formulations were carried out for in-vitro drug release studies by using the USP dissolution apparatus (paddle method) for up to 12 h. All the formulations showed a controlled rate of drug release. Among all the formulations, formulation A2 shows sustained and controlled release of the drug up to 99 % at the end of the 12^{th} hour. Further, the obtained data were subjected to various kinetic model treatments to determine the mechanism as well as the order of drug release. Data from in-vitro release were fit into different equations and kinetic models to explain the release kinetics of Aceclofenac from the hydrogels. The kinetic models used were a zero-order equation, Higuchi's model, and Peppa'smodel. The obtained results in these formulations were plotted in various model treatments as follows: i.e., cumulative percentage of drug release vs. time (zero order) (Figure 4), cumulative percentage of drug release vs. square root of time (Higuchi's) (Figure 5), and log cumulative percentage of drug release vs. log time (Peppa's) (Figure 6).

To find out the mechanism of drug release from hydrogels, the in-vitro dissolution data of each formulation with different kinetic drug release equations Namely, zero order: $Q=K_0t$; Higuchi's square rate at time: $Q=K_Ht^{1/2}$ and Peppas: $F=K_mt^n$, where Q is the amount of drug release at time t, F is the fraction of drug release at time t, $K_{0\ is\ the}$ zero order kinetic drug release constant, K_H is Higuchi's square root of time kinetic drug release constant, K_m is constant incorporatinggeometric and structural characteristics of the hydrogels, and n is the diffusion exponent indicative of the release mechanism [19, 20].

The correlation co-efficient values (R^2) indicate the kinetics of drug release were zero order (Table 3). The mechanism of drug release was determined by Peppa's model, which indicates non-Fickian [21, 22] release and super case II transport as evidenced by diffusion exponent values (n) (Table 4).

CONCLUSION

The physical cross-linking orifice ionotropic gelation approach was used to successfully create Aceclofenac hydrogels from three distinct polymers and their combinations. HPMC, sodium alginate, and Eudragit RL100 are the polymers used. In all formulations, the results in bulk density, tapped density, and percentage yield were quite excellent. The data from the in-vitro drug release tests were fitted into multiple kinetic models, revealing a zero order release pattern followed by non-Fickian and super case II transport processes. As a result, it believes that Aceclofenac may be a promising choice for hydrogel formulation.

Conflict

Nil.

Funding

Nil.

REFERENCES

[1] V K A Devi, R Shyam, A Palaniappan, A K Jaiswal, T H Oh, and A J Nathanael. Self-Healing Hydrogels: Preparation, Mechanism and Advancement in Biomedical Applications. *Polymers (Basel)*, 13(21):3782–3782, 2021.

[2] Enas M Ahmed. Hydrogel: Preparation, characterization, and applications: A review. *Journal of Advanced Research*, 6(2):105–121, 2015.

[3] S Chong, B J Riley, J A Peterson, M J Olszta, and Z J Nelson. Gaseous iodine sorbents: A comparison between Ag-loaded aerogel and xerogel scaffolds. *ACS Appl. Mater. Interfaces*, 12:26127–26136, 2020.

[4] H P S Abdul Khalil et al. Insights into the Role of Biopolymer-Based Xerogels in. *Biomedical Applications. Gels*, 8:334–334, 2022.

[5] G Hoti et al. Effect of the Cross-Linking Density on the Swelling and Rheological Behavior of Ester-Bridged β-CyclodextrinNanosponges. *Materials (Basel)*, 14(3):478–478, 2021.

[6] J Li et al. Designing hydrogels for controlled drug delivery. *Nat Rev Mater*, 1(12):16071–16071, 2016.

[7] Nem Kumar Jain et al. Selective Cyclooxygenase-2 Inhibitor Etoricoxib Attenuated Hypoxic Cancer Milieu induced M2-Polarization of Macrophages and Acquisition of Pro-angiogenic and Pro-invasive Attributes. *Research J. Pharm. and Tech*, 12(12):5871–5877, 2019.

[8] M Grau, J L Guasch, Montero, Felipe, Carrasco, and Julia. Pharmacology of the potent new non-steroidal anti-inflammatory agent aceclofenac. *Arzneimittelforschung*, 41(12):1265–1276, 1991.

[9] Jagannathan Hema et al. A comparative study of Aceclofenac versus Etoricoxib in the management of acute low back pain in a tertiary care hospital. *Journal of Drug Assessment*, 9(1):60–65, 2020.

[10] G Auriemma, P Russo, P Delgaudio, C A García-González, M Landín, and R P Aquino. Technologies and Formulation Design of Polysaccharide-Based Hydrogels for Drug Delivery. *Molecules*, 25:3156–3156, 2020.

[11] P Gadziński et al. Ionotropic Gelation and Chemical Crosslinking as Methods for Fabrication of Modified-Release Gellan Gum-Based Drug Delivery Systems. *Pharmaceutics*, 15:108–108, 2023.

[12] B Haarika and P R Veerareddy. Formulation and evaluation of fast disintegrating Rizatriptan benzoate sublingual tablets. *Malaysian Journal of Pharmaceutical Sciences*, 10:45–60, 2012.

[13] P S Naik and N S Kurup. Design and optimization of fast dissolving tablets containing Metoprolol by sublimation method. *International research journal of pharmacy*, 1:346–357, 2010.

[14] Senthil Kumar, D Dachinamoorthi, R Saravanan, and K Ashok. Design and evaluation of fast dissolving tablet of Metoprololtartarate. *International journal of pharmaceutical science*, 2:2162–2167, 2011.

[15] M Alagusundaram, C M Chetty, and D Dhachinamoorthi. Development and evaluation of novel-trans-mucoadhesive films of Famotidine. *J Adv Pharm Technol Res*, 2(1):17–23, 2011.

[16] Elbadawy A Kamoun. N-succinyl chitosan-dialdehyde starch hybrid hydrogels for biomedical applications. *Journal of Advanced Research*, 79(1):69–77, 2016.

[17] Roberto Ruiz-Caro and María Dolores Veiga-Ochoa. Characterization and Dissolution Study of Chitosan hydrogel Systems for Drug Con-

trolled Release. *Molecules*, 14:4370–4386, 2009.

[18] S S Solanki and R Dahima. Formulation and evaluation of Aceclofenac mouth-dissolving tablet. *J Adv Pharm Technol Res*, 2(2):128–131, 2011.

[19] J M Unagolla and A C Jayasuriya. Drug transport mechanisms and in vitro, release kinetics of vancomycin encapsulated chitosan-alginate polyelectrolyte microparticles as a controlled drug delivery system. *Eur J Pharm Sci*, 114:199–209, 2018.

[20] Soad A Yehia et al. Design and In-vitro/In-vivo Evaluation of Novel MucoadhesiveBuccal Discs of an Antifungal Drug: Relationship Between Swelling, Erosion, and Drug Release. *AAPS PharmSciTech*, 9(4):1207–1217, 2008.

[21] M Grassi and G Grassi. Mathematical modeling and controlled drug delivery: matrix systems. *Curr Drug Deliv*, 2:97–116, 2005.

[22] Y Fu and W J Kao. Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. *Expert Opin Drug Deliv*, 7(4):429–473, 2010.

Cite this article: Alagusundaram M, Nem Kumar Jain, Brajesh Singh, Goli Venkateshwarlu. **Cross-linked Polymeric Aceclofenac Hydrogels Formulation and Characterization**. Future J. Pharm. Health. Sci. 2023; 3(2): 186-192.