

# Effect of Crosslinking on Control Drug Release of Hydroxychloroquine Sulphate Drug-Using Alginate Beads

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**Abstract:** Sodium alginate (SA), brown seaweed algae, and Lignosulphonic acid (LS), a plant product, are biodegradable polymers extensively investigated for drug-controlled release. The Hydroxychloroquine sulphate (HCQ) drug, an antimalarial drug, was extensively used in the initial periods of COVID situations. The HCQ drug release from SALS beads is investigated for its control release in a simulated medium (pH1.2 and pH7.4) using different crosslinking agents such as Calcium chloride, Barium chloride and Aluminum chloride. The HCQ release has better controlled in Barium crosslinked beads. They are found to be relatively intact and stable and release the drug for more than 180 minutes in the simulated medium. Further drug entrapment studies prove very high for Ba crosslinked SALS beads. Whereas Aluminum crosslinked beads showed, inferior crosslinking and drug retention in beads is very low and starts degrading in simulated fluids. Drug release kinetics were analyzed using various kinetic model equations to discuss the order of reaction and drug-polymer mechanism. FT-IR investigations of beads show chemical interactions between crosslinking ion and alginate blends.

**Keywords:** Sodium alginate, Swelling, Drug entrapment, Crosslinking etc.

## 1. INTRODUCTION

Alginate is a carbohydrate polymer obtained as a seaweed product. It is a polymeric biomaterial consisting of 1-4 linked  $\alpha$ -L-guluronic acid (G) and  $\beta$ -D-mannuronic acid (M) arranged alternatively [1-3]. It is a non-toxic, biodegradable, gel-forming agent used extensively in drug delivery applications in the pharmaceutical industry. Control drug release is the technique used to slow the release of drugs in the physiological medium administered orally. SA is blended with LS to improve its strength. Lignosulphonic acid is a plant product obtained from the production of wood pulp using sulphite pulping. It is a biodegradable polymer and very well known as a super plasticiser used extensively in the cement industry [4].

HCQ drug is a very well-known antimalarial drug. HCQ is also widely used as it effectively controls dermatological complications in Systemic Lupus Erythematosus, an auto-immune disease [5-6]. It was one of the life-saving drugs used in 2020 during the COVID-19 pandemic. There was a worldwide demand for this drug to save people suffering, and an HCQ drug was prescribed to treat COVID-19 infections. Unfortunately, several reports showed side effects leading to death in patients suffering heart-related

ailments. If HCQ is taken in optimum doses, it is safe, although its safety margin is limited, and a single higher amount may lead to fatal side effects [5]. Therefore, there is a need for randomised, controlled release studies with this drug to prove its efficiency. The present study focuses on the treatment strategy to a controlled release of HCQ as a model therapeutics using SA/LS blends. Whereas SA/LS blends prepared are water-soluble start degrading in simulated fluids. But crosslinking is a prominent feature used to cure the beads their ability to change the volume of alginates beads by many folds in an appropriate solvent medium. Exhaustive research has been reported about chemically crosslinked polymers' swelling and drug release behaviour experimentally and theoretically [7-8].

On the contrary, the swelling behaviour of physically cross-linked alginate [9] has not been fully explored. However, it is believed to significantly affect many properties, such as the ability to establish bioadhesion interactions [10-11], mechanical strength [12], drug release ability [13-14], permeability [15-16]. One of the essential properties of alginate is its affinity towards multivalent cations such as  $\text{Ca}^{2+}$ ,  $\text{Ba}^{2+}$ , and  $\text{Al}^{3+}$  can bind those ions. This process leads to the formation of ionically (i.e. physically) cross-linked alginate gels and makes them

insoluble in an aqueous medium. The affinity of alginates towards ions generally depends on the chemical composition and specifically on the number and length of the guluronate residues (G-blocks) [17].

In this study, the swelling behaviour of SALS loaded with HCQ drug was characterised experimentally at various crosslinking agents such as bivalent  $\text{Ca}^{2+}$  and  $\text{Ba}^{2+}$  and trivalent  $\text{Al}^{3+}$  ions for different intervals. HCQ drug entrapment efficiency is investigated to the amount of drug trapped within blend composite beads. Also, the stability and behaviour of the various crosslinked beads in simulated fluids of gastric and blood pH mediums are explored. Further FT-IR characterisation of beads was used to investigate the crosslinking density of  $\text{Ca}^{2+}$ ,  $\text{Ba}^{2+}$ , and  $\text{Al}^{3+}$  ions with SALS leading to stability of beads for solvent uptake and correlating with drug release.

## 2. MATERIALS AND METHODS

### 2.1. Materials

The alginic acid sodium salt (SA), whose viscosity ranges from 20000-40000 cps, is used in this experiment. It is a seaweed product obtained from brown algae commercially called sodium alginate (SA), and sodium salt of Lignosulphonic acid (LS) [Mw ~52000], a plant by-product, is obtained from Sigma Aldrich, Germany.

These biodegradable polymers are used as received without any further purification. Calcium chloride, Barium chloride and Aluminium chloride were obtained from SD fine chemicals. Different buffer solutions, pH 1.2 as simulated gastric fluids (SGF) and pH 7.4 as simulated phosphate buffer (SPB), and are prepared to mimic the physiological medium. HCQ sulphate drug was received as a gift sample. All the experiments are performed using deionised water.

### 2.2. Preparation of drug-loaded SALS-HCQ beads

The polymeric drug-loaded beads are prepared using the solution casting and evaporation method. The brief procedure is discussed as follows. Sodium alginate (4 %w/v) was dissolved in double-distilled water. The SA and LS polymers are mixed in 80/20 proportion; then, the mixture is sonicated using an Ultrasonic bath

sonicator for 30 min.

The mixture is stirred to obtain a homogeneous mixture without any bubbles in a 50ml beaker at room temperature. 5% HCQ drug solution (1mg/1ml) was added to this mixture and mixed thoroughly using a magnetic stirrer for 30mins.

### 2.3. Preparation of SALS-HCQ crosslinked beads

Typically, the alginate hydrogels in an aqueous solution could be produced in the solution of divalent and trivalent cations such as  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$  and  $\text{Al}^{3+}$  etc., as the ionic crosslinking agent. Because of the optimal conditions used in the gel formation, the pendant carboxylic acid group of G block chelate di or trivalent ions forms a hydrogel. In this hydrogel, substances such as drugs, proteins, and cells can be successfully entrapped whilst maintaining their biological structure, conformation, and interaction.

The homogeneous alginate mixture prepared was added dropwise into 50 ml crosslinking solutions using a 5 ml syringe (1 mL/min, flowrate). The spherical drug-loaded beads obtained were kept in the crosslinking solution for time intervals of 10 and 20 mins. After crosslinking, the beads are transferred into Petri dishes (Fig 1) and dried in the hot furnace at a temperature of 60°C for 5-6 hrs, as shown in Fig. 2.

### 2.4. METHODS

#### 2.4.1. Drug encapsulation efficiency (DEE)

It has been observed that some HCQ drug is leftover in supernatant solution during crosslinking, and the total amount of drug presence in the SALS blend is reduced. To investigate the amount of HCQ drug presence using DEE.

The DEE of beads was estimated by dividing trapped HCQ in crosslinked SALS beads by the total amount of HCQ while loading or the theoretical value of HCQ quantity before crosslinking. The crosslinking solution was estimated for residual HCQ drug-using UV/Visible spectrophotometer at 342 nm. The DEE was calculated using the equation given below:

Drug encapsulation efficiency (DEE) =

$$\frac{\text{theoretical HCQ drug loaded} - \text{residual HCQ drug in the crosslinking solution}}{\text{theoretical HCQ drug loaded}}$$



**Ca-SALS**

**Ba-SALS**

**Al-SALS**

**Fig. 1.** SALS-HCQ hydrogels formation in crosslinking solution



**Ca-SALS**

**Ba-SALS**

**Al-SALS**

**Fig. 2.** Crosslinked HCQ drug-loaded SALS beads (dry)

#### 2.4.2. Drug release studies in simulated fluids (SGF & SPB)

The SALS-HCQ drug crosslinked beads were investigated to evaluate release profiles in the SGF (pH 1.2) and SPB (pH 7.4) mediums using UV visible spectroscopy. Initially, the beads are immersed in 50 ml of buffer solution. After every 1 hr, an aliquot of the solution is measured for absorbance of HCQ drug release and poured back into the same solution. The drug release profiles of beads are evaluated for three hours in SGF and SPB mediums. Using a Shimadzu 2600 UV-Visible spectrophotometer, the obtained spectra for aliquots were recorded at  $\lambda_{\max}$  342 nm for SGF and SPB, respectively.

#### 2.4.3. Fourier Transform Infra-Red (FT-IR) spectroscopy studies of SALS-HCQ beads

The SALS and HCQ loaded alginate crosslinked beads, as shown in Fig. 3, are investigated for their extent of crosslinking with different ions for chemical interaction using FT-IR spectrophotometer, Shimadzu IR Spirit-L, Model no. 206-31000-58. The beads are powdered along

with KBR, and pellets are made containing 2-4% by weight of the sample. The specimens were examined in the 400- 4000  $\text{cm}^{-1}$  absorption range. The interferogram is generated using a frequency of 45 scans at a resolution rate of 4 $\text{cm}^{-1}$  utilising LAB SOLUTION software.

### 3. RESULTS AND DISCUSSIONS

#### 3.1. Control release studies of HCQ drug from SALS beads using different crosslinking agents.

The HCQ drug loading in the SALS blend was carried out by the solvent evaporation method. Different electrolytes, so-called crosslinking agents, crosslink the water-soluble beads. The beads are crosslinked for 10 and 20 mins. The DEE was estimated using the method shown above.

The DEE of Ca-SALS-HCQ beads was  $30 \pm 5\%$  and  $50 \pm 5\%$  in Ba-SALS-HCQ beads, whereas it was  $20 \pm 5$  in Al-SALS-HCQ beads. It is observed that  $\text{Al}^{3+}$  beads start disintegrating, as shown in Fig 4.

**Ca-SALS-HCQ****Ba-SALS-HCQ****Al-SALS-HCQ****Fig. 3.** KBR pellets of SALS-HCQ Crosslinked beads showing different colours.

The drug release behaviour of drug-loaded beads in different buffer mediums such as SGF and SPB for 3hrs is monitored using a UV-Visible spectrophotometer to mimic the drug intake in the physiological medium. The results are surprising as we see different release behaviour concerning crosslinking ions such as  $\text{Ca}^{2+}$ ,  $\text{Ba}^{2+}$ , and  $\text{Al}^{3+}$ .

**Fig. 4.** HCQ drug release in pH 1.2 from SALS crosslinked Ca, Al and Ba beads.

It was observed that beads swelled very minimal in SGF and affected the release of HCQ, as evidenced in Fig 5. At the same time, an initial outburst of the drug is high and releases up to 30-50% drug till 3 hrs, as seen in Fig 4. The behaviours of beads in the SGF are due to repulsion between the  $\text{H}^+$  ion of the acidic medium and  $\text{H}^+$  of the carboxylate group in M acid present in alginates. This results in lower water uptake in these beads controlling the drug release. The drug release in SPB was increased due to hydrolysis in the neutral medium (Fig 6) as this pH medium favours swelling of beads, as observed in Fig 7, thereby releasing more drug from beads. The complex behaviour of crosslinked beads throughout the release in 3hrs is discussed. Fig 7 indicates Ca-SALS-HCQ beads showing the high release of drug, and the solution turns turbid due dissolution of beads that affects the drug release [18]. Whereas very

minimal drug is observed in Ba-SALS-HCQ beads, they are remarkably intact [19] and show stable behaviour even after 3 hrs due to robust binding capacity, as shown in Fig 7. At the same time, Al-SALS-HCQ beads start disintegrating or dispersed in simulated fluids, as observed in Fig 7 and release the entire drug within a short period.

 **$\text{Ca}^{2+}$**  **$\text{Ba}^{2+}$**  **$\text{Al}^{3+}$** **Fig. 5.** Stability of beads in SGF (pH 1.2) after 1 hr**Fig. 6.** HCQ drug release in pH 7.4 from SALS crosslinked Ca, Al and Ba beads**Ca-SALS-HCQ****Ba-SALS-HCQ****Al-SALS-HCQ****Fig. 7.** Stability of beads PBS (pH 7.4) after 1 hr

In contrast, Ba, more prominent in size, could occupy more space between the carboxylic groups present and resist complete hydrolysis or swelling, making beads more compact and intact, as seen in Fig 1 and Fig 7. It is reported that



bivalent ions Ca, and Ba are bonded with carboxylate ions in a two-dimensional manner similar to the egg shape model [20]. Al-SALS-HCQ beads being trivalent, forms a three-dimensional structure,  $\text{Al}^{3+}$  ion, smaller in size than  $\text{Ca}^{2+}$  and  $\text{Ba}^{2+}$  ions, can diffuse within the alginate matrix without crosslinking, ultimately resulting in poor crosslinking. Moreover, in Fig 4 and 7, Al crosslinked beads show reddish-brown colour and degradation behaviour in simulated fluids from the initial stages. At the same time, Ca-SALS crosslinked beads show some stability in SGF, whereas showing some effect of degradation behaviour in the SPB medium.

### 3.2. Kinetics of HCQ drug release from SALS beads

The drug release values are discussed to study the

drug release kinetics in different pH solutions of SGF and SIF from SALS blends crosslinked for  $\text{Ca}^{2+}$ ,  $\text{Ba}^{2+}$  and  $\text{Al}^{3+}$  ions. Various kinetic models were used in order to discuss the mechanism of drug release. *In-vitro* HCQ drug release kinetics in two different pH mediums were discussed by plotting cumulative drug release (CDR) versus time. The Zero order, First order, and Higuchi equation [23] used are listed in Table 1. The correlation coefficient, and rate constants values obtained by the best fitting method are furnished in Table 2. From Table 1, the HCQ drug release data values, as seen in Fig 8 and Fig 9 obtained by best fit method attributes for First-order and Higuchi model for 20 min  $\text{Ba}^{2+}$  and  $\text{Ca}^{2+}$  crosslinked beads in both media. The release in the First order and Higuchi model are in the range of 2-5% /hr, and the coefficient of correlation was 0.98-0.99%.

**Table 1.** Kinetic model equations used to evaluate drug diffusion and polymer relaxation mechanism.

Model	Formula used	Parameters
Zero-order model	$M/M_{\infty} = k_0 t$ (1)	$M/M_{\infty}$ is a fraction of drug released, $k_0$ , $k_1$ , and $k_2$ are zero, and first, second-order constants of a reaction. $n$ -diffusion exponent
First order model	$\text{Log}(M/M_{\infty}) = k_1 t^n$ (2)	
Higuchi model	$M/M_{\infty} = k_2 t^{0.5}$ (3)	
Korsemeyer-Peppas model	$M/M_{\infty} = kt^n$ (4)	



**Fig. 8.** Plots for Kinetic models of HCQ drug release in SGF (pH 1.2)

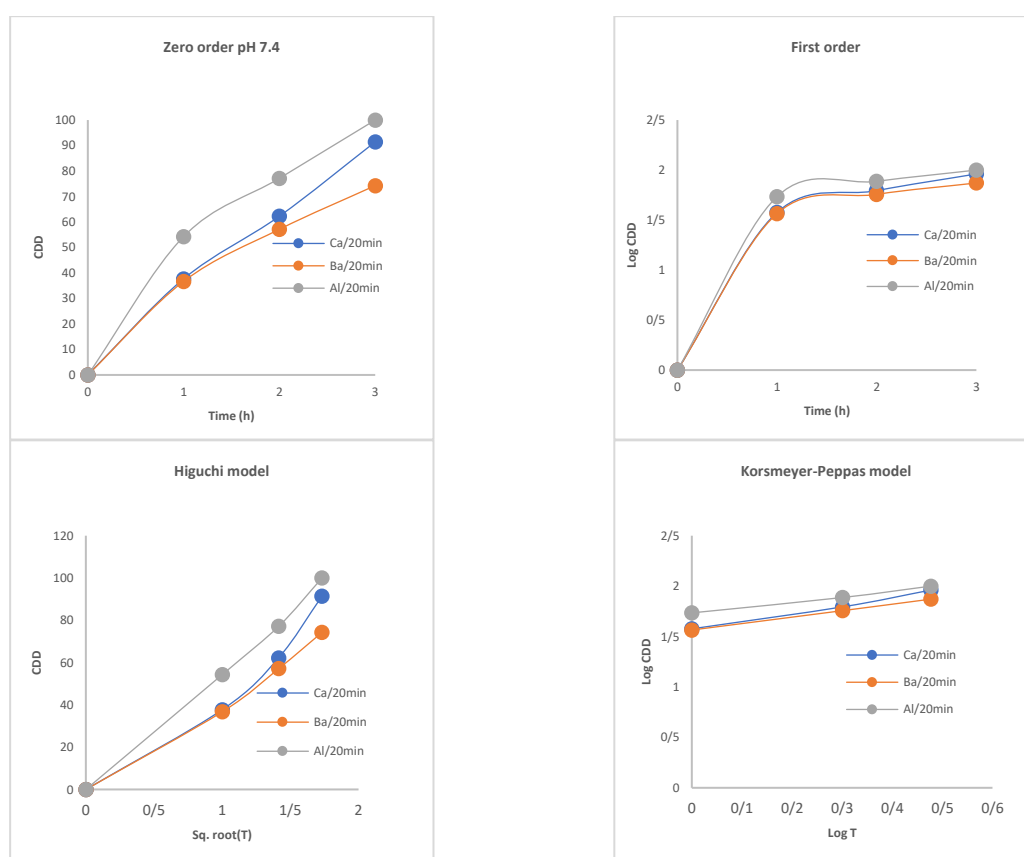


Fig. 9. Plots for Kinetic models of HCQ drug release in SIF (pH 7.4)

The self-assembled alginate framework, associated with diffusion and swelling, erosion-based drug release behaviours resulted in the First-order and Higuchi model release characteristics in SGF and SIF. Whereas the values obtained for  $Al^{3+}$  ion crosslinked beads are ignored because of the degradation shown by beads. Also, the experimental data (Fig 8 and Fig 9) was used to estimate  $n$  and  $k$  values for the drug release mechanism using Korsmeyer-Peppas model [21] in both pH mediums, and these values are listed in Table 2. It was reported that  $n'$  values with exponent = 0.45, the drug diffuses from the polymer matrix which is said to be Fickian diffusion, whereas  $n < 0.45$  is Fickian or quasi Fickian [21]. Anomalous behaviours are defined as  $n'$  values between 0.45 and 1. Based on experimental data using the best fit, the values of

$n$  and  $k$  were found to be dependent on the degree of crosslinking as well as the pH of the medium. The values of  $n'$  observed for  $Ba^{2+}$  ion crosslinked beads in Table 2 are in the range of 0.54 to 0.64, showing characteristics of anomalous transport. These results indicate that HCQ drug release from SALS (80/20) beads is swelling driven or polymer relaxation controlled.

### 3.3. FT-IR studies of various crosslinking of HCQ loaded blends

The previous section observed that the HCQ drug release was very much controlled in Ba-SALS crosslinked beads in simulated fluids. The chemical interaction of various ions with SALS is discussed in this section. The extent of crosslinking is investigated using FT-IR for chemical interaction and degree of interaction.

Table 2. Kinetic studies of HCQ control drug release from SALS Blends

		Zero order		First order		Higuchi model		Korsmeyer -Peppas model		
		$K_0$	$R^2$	$K_1$	$R^2$	$K_2$	$R^2$	$K$	$n$	$R^2$
SGF	Ca	0.50	0.823	1.38	0.99	0.35	0.99	0.38	0.39	0.998
	Ba	0.16	0.968	0.22	0.98	0.5	0.99	0.25	0.54	0.998
SIF	Ca	0.56	0.823	0.55	0.985	0.47	0.98	0.36	0.83	0.99
	Ba	0.56	0.876	1.52	0.98	0.41	0.99	0.36	0.64	0.99

Our previous study [18] that the interaction between drug and SALS blend shows HCQ drug peaks, indicating its presence in the HCQ-SALS matrix [23]. The flatness range of HCQ loaded SALS beads between 990 and 1183  $\text{cm}^{-1}$  confirms the drug's presence.

In Fig 10, the spectrum of Ba-SALS crosslinked beads shows strong absorption peaks, suggesting the extent of crosslinking compared to Ca-SALS and Al-SALS crosslinked beads. This supports the fact that Ba ions crosslinked SALS is more favourable for controlling the drug release.

#### 4. CONCLUSION

The SALS blend composite loaded with HCQ was prepared by the solution casting method. The blends are crosslinked for different crosslinking agents of Ca, Ba and Al for water uptake in simulated mediums. It was noticed that Ba crosslinked beads possess very high DEE, are very stable compared to Ca-SALS beads and release HCQ for a longer duration. Al-SALS-HCQ beads being trivalent ions, could not provide stability due to their interaction with monomers present in SA. The FTIR study confirms the extent of crosslinking between carboxylic acid

present in SA and crosslinking ions. It ensures that the size of the  $\text{Ba}^{2+}$  ion is the most suitable crosslinking agent. The various Kinetic models confirms the order of reaction for Ba-SALS beads with experimental observations and also approve the alginates behaviour for HCQ drug release is anomalous which is swelling driven. The HCQ was an antimalarial drug and prescribed during COVID situations. Based on the results of this study, it seems that SALS beads are the suitable drug carriers for CDD applications with Barium chloride as a crosslinking agent to carry HCQ drugs, causing minimal side effects.

#### REFERENCES

- [1] Hadas Hecht., Simcha Srebnik., "Structural Characterization of Sodium Alginate and Calcium Alginate". *Biomacromolecules*, 2016, 17, 6, 2160–2167.
- [2] Draget, K.I., Gaserod, O., Aune, I., Andersen, P.O., Storbakken, B., Stokke, B.T., "Effects of molecular weight and elastic segment flexibility on syneresis in Ca-alginate gels". *Food Hydrocolloids.*, 2001, 15(4–6), 485–490.
- [3] Narayanan, D., Pillai, G.J., Shantikumar, V. Nair., Deepthy Menon., "Effect of

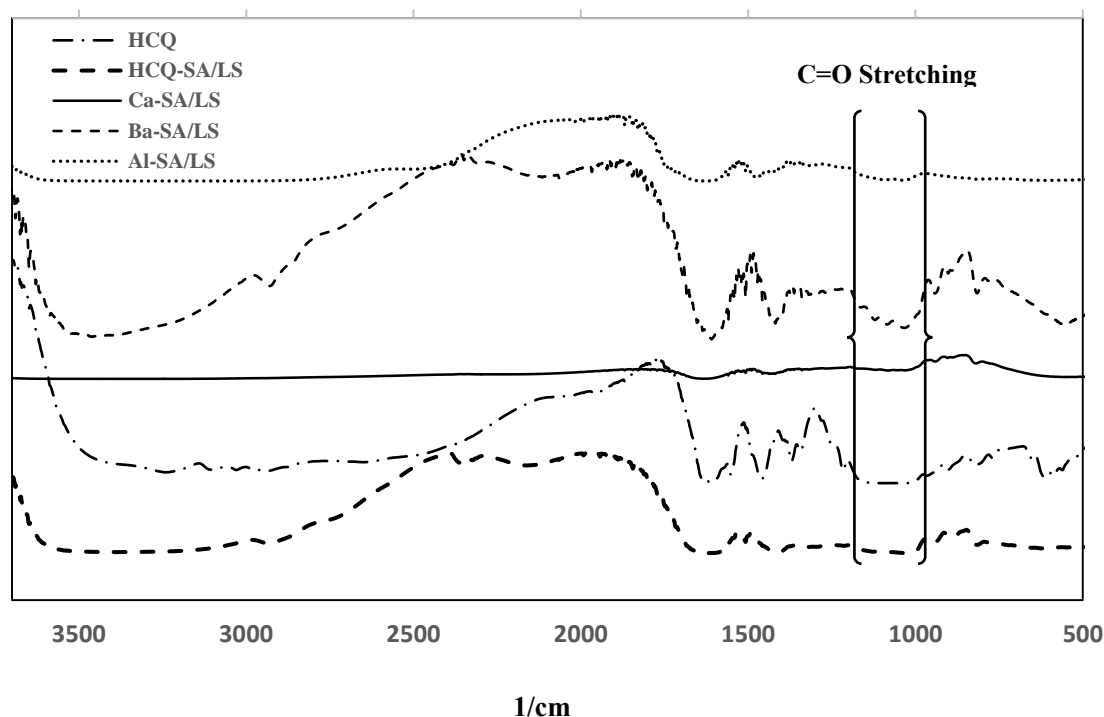


Fig. 10. FTIR spectra of SA/LS Crosslinked beads a) Ba, b) Ca, c) Al

- formulation parameters on pharmacokinetics, pharmacodynamics, and safety of diclofenac nanomedicine”, *Drug Delivery Translational Research*. 2019, 9(5), 867.
- [4] Amrita Thakur., Giridhar Reddy, S., “Spectrophotometric Detection of Mercury Using Lignosulphonic Stabilized Silver Nanoparticles”. *Iranian Journal of Materials Science and Engineering*. 2020, 17(3), 90-95.
- [5] Ben-Zvi, I., Kivity, S., Langevitz, P., Shoenfeld, Y., “Hydroxychloroquine: from malaria to autoimmunity”. *Clinical Reviews in Allergy & Immunology*. 2012, 42, 145-153.
- [6] Walls, A.C., Park, Y.J., Tortorici, M.A., Wall, A., McGuire, A.T., Veasler, D., “Structure, function and antigenicity of the SARS-CoV-2 spike glycoprotein”. *Cell*. 2020, 181, 281-292.
- [7] Flory, P.J., “Molecular distribution in crosslinked systems”, *Principles of polymer chemistry*. Cornell University Press, 1953, 378-384.
- [8] Tanaka, T., Fillmore, D., Sun, S.T, Nishio, I., Swislow, G., Shah, A., Phase transitions in ionic gels., *Physical Review Letters*. 1980. 45(20), 1636–1639.
- [9] Sato, H., Hirashima, Y., Suzuki, A., Goto, M., Tokita, M., “Effects of repeated water exchange on the swelling behavior of poly(sodium acrylate) gels crosslinked by aluminum ions”. *Journal of Polymer Science-Part B: Polymer Physics*. 2005, 43(7), 753–763.
- [10] Baloglu, E., Ozyazici, M., Hizarcioglu, S.Y., Karavana, H.A., “An in vitro investigation for vaginal bioadhesive formulations: Bioadhesive properties and swelling states of polymer mixtures”. *Farmaco*. 2003, 58(5), 391–396.
- [11] Sai Praneeth Thota., Partha Pratim Bag., Praveen Venkata Vadlani., Siva Kumar Belliraj., “Plant Biomass Derived Multidimensional Nanostructured Materials: A Green Alternative for Energy Storage”. *Engineered Science*., 2022, 18, 31-58.
- [12] Feng, X., Pelton, R., “Carboxymethyl cellulose: Polyvinylamine complex hydrogel swelling”. *Macromolecules*., 2007, 40(5), 1624–1630.
- [13] Pillay, V., Fassihi, R., “In vitro release modulation from crosslinked pellets for site-specific drug delivery to the gastrointestinal tract I. Comparison of pH-responsive drug release and associated kinetics”. *Journal Controlled Release*. 1999, 59(2), 229–242.
- [14] Sharath, S.S., Ramu, J., Shantikumar, V. Nair., Iyer, S., Ullas Mony., Jayakumar Rangasamy., “Human Adipose Tissue Derivatives as a Potent Native Biomaterial for Tissue Regenerative Therapies”. *Tissue Engineering and Regenerative Medicine*. 2020, 17(2), 123-140.
- [15] Morch, Y.A., Donati, I., Strand, B.L., Skjaak-Braek, G., “Effect of  $\text{Ca}^{2+}$ ,  $\text{Ba}^{2+}$ , and  $\text{Sr}^{2+}$  on alginate microbeads”. *Biomacromolecules*, 2006, 7(5), 1471–1480.
- [16] Pillay, V., Fassihi, R., “In vitro release modulation from crosslinked pellets for site-specific drug delivery to the gastrointestinal tract I. Comparison of pH-responsive drug release and associated kinetics.” *Journal Controlled Release*. 1999, 59(2), 229–242.
- [17] Padmakumar, S., Bindhu Paul., Pavithran, K., Vijaykumar, D., Kottarathi., Rajanbabu, A., Sivanarayanan, T., Balakrishn., Kadakia, E., Amiji, M.M., Shantikumar, V. Nair, and Deepthy Menon., “Long-term Drug Delivery using Implantable Electrospun Woven Polymeric Nanotextiles”. *Nanomedicine: Nanotechnology, Biology, and Medicine*, 2019, 15(1), 274-284.
- [18] Giridhar Reddy, S., “Controlled release studies of Hydroxychloroquine sulphate (HCQ) drug-using Biodegradable polymeric Sodium alginate and Lignosulphonic acid Blends”. *Rasayan Journal of Chemistry*, 2021, 4, 2209-2215.
- [19] Giridhar Reddy, S., Amrita Thakur., Akanksha Saxena Pandit., “Study on the Effects of crosslink agents on Sodium Alginate and Lignosulphonic Acid Blends”. *Polymer (Korea)*, 2016, 40(1), 63-69.
- [20] Grant, G.T., Morris, E.R., Rees DA, Smith PJ, Thom D, *FEBS Lett*, 1973, 32, 195.
- [21] Oh, T.O., Kim, J.Y, Ha, J.M, “Preparation



- of highly porous gastroretentive metformin tablets using a sublimation method". *Eur J Pharm Biopharm* 2013, 83, 460-467.
- [22] Ritger, P.L., Peppas, N.A., "A simple equation for description of solute release II. Fickian and anomalous release from swellable devices". *J Control Release*, 1987, 5, 37-42.
- [23] Amanda Naves Ferreira Moraes., Luís Antônio Dantas Silva., Maysa Aparecida de Oliveira., Eder Magno de Oliveira., Thais Leite Nascimento., Eliana Martins Lima., Ieda Maria Sapateiro Torres., Danielle Guimarães., Almeida Diniz., "Compatibility study of hydroxychloroquine sulfate with pharmaceutical excipients using thermal and nonthermal techniques for the development of hard capsules"., *Journal of Thermal Analysis and Calorimetry.*, 2020, 140, 2283.