# Physicochemical investigations of nanoemulsified, curcumin-loaded, crosslinked κ-carrageenan hydrogels

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## Abstract

Curcumin is a potent drug with several therapeutic benefits; however, its hydrophobicity and rapid metabolism restrict its biomedical application. Nanoemulsions improve the loading and site-specific curcumin delivery, while hydrogels act as a robust delivery vehicle. We synthesized curcumin nanoemulsion-based, crosslinked κ-carrageenan hydrogels using solvent displacement and ionotropic gelation techniques to provide the mutual advantages of nanoemulsions and hydrogels. The crosslinking effect of KCl, $CaCl_2$, and their combination was used to gauge the hydrogels' water retention, chemical composition, surface topography, and rheological features. The microstructure analysis showed that oil droplets were confined in the polymer network, and FTIR revealed no interaction between κ-carrageenan and curcumin, indicating that curcumin was incorporated within the matrix. The *in vitro* drug release study interpreted that hydrogels crosslinked with KCl show a better release behavior over others. This study compares the crosslinking efficiencies of KCl, $CaCl_2$, and their combination in improving the curcumin release behavior from the hydrogels.

**Keywords**: hydrogels, curcumin, κ-carrageenan, crosslinking, drug release

## 1. Introduction

Nanoemulsions are propitious for drug delivery. These are extremely small dispersions (20–200 nm) of two immiscible liquids, which are stabilized by emulsifying agents such as surfactants and polymers. Nanoemulsions offer low skin irritation, high loading capacities, high penetration, and controlled drug release; however, several aspects, such as low viscosity and limited stability at high temperatures and pH, obstruct their implementation [1].

Introducing a polymer matrix like hydrogels could help overcome the hindrances mentioned above. Hydrogels are three-dimensional polymer networks with high mechanical strength through crosslinking and can retain large amounts of water in response to external stimuli due to hydrophilic functional groups [2]. The polymers used in the hydrogel preparation could be from natural or synthetic sources and are selected according to the application.

Carrageenan is a hydrophilic polysaccharide obtained from rhodophytes. Based upon the sulfate content, carrageenan is classified into six forms—namely κ, ι, λ, μ, ν, and θ carrageenan—out of which only three (κ, λ, ι) are commercially significant. Furthermore, these forms are biocompatible and biodegradable, and in recent times, κ-carrageenan based hydrogels have gained attention because of their high swelling and stabilizing properties, persistent viscoelasticity, and robustness—characteristics of potential drug carriers [3].

Curcumin is a hydrophobic phytopolylphenol molecule derived from *Curcuma longa* (turmeric) that aids in wound healing and suppresses carcinogenesis and tumor cell proliferation due to its biological features. However, its physicochemical instability, low pharmacokinetics, hydrophobicity, and sensitivity toward external stimuli limit its practical application [4], [5]. Curcumin can be loaded into a robust hydrophilic carrier to harness its unique properties to enhance its biochemical activity, preserve its antioxidant property, increase its pharmacokinetics, and decrease its interaction with external stimuli.

K-carrageenan can build hydrogels in the presence of cations because its ability to form a gel increases [6]. Katarina et al. have crosslinked κ-carrageenan and alginate with ionic crosslinkers potassium chloride and calcium chloride to build curcumin-loaded hydrogels and test their drug delivery and wound healing characteristics [7], [8]. Such ionic crosslinkers have been previously investigated for their effect on the gelation of κ-carrageenan [9], [10]. This study compares the crosslinking efficiencies of potassium chloride, calcium chloride, and their

combination to build robust hydrogels and deliver hydrophobic molecules by formulating nanoemulsified curcumin-loaded κ-carrageenan hydrogels. We also characterized the hydrogels to assess their morphology, chemical interaction, strength, water-holding capacity, and degradation.

## 2. Materials and methods

### 2.1. Materials

Acetone, potassium chloride (KCl), calcium chloride ($CaCl_2$), and polysorbate 80 were procured from Merk, Mumbai, India; curcumin from Himedia, Mumbai, India; castor oil from Saanvi Enterprises, Udupi, India; κ-carrageenan from SNAP Products, Vellore, India; and potassium bromide (KBr-IR specific) from Finar, Ahmedabad, India. Deionized water was used throughout the procedure.

### 2.2. Preparation of nanoemulsions

We prepared nanoemulsions by the solvent-displacement technique [11]. Briefly, 50 mL nanoemulsion of an aqueous and oil phase was prepared in a 9:1 ratio. A 45 mL aqueous phase was prepared by mixing 5 mL polysorbate 80 in 40 mL deionized water under magnetic stirring at 800 rpm for 10 min. A 5 mL oil phase was prepared by adding 1 mL castor oil to 4 mL acetone. The aqueous and oil phases were mixed and agitated for 25 min at 800 rpm. Acetone was evaporated by placing the mixture in a hot oven at 60 ℃ for 10 min.

### 2.3. Preparation of nanoemulsion-based hydrogel and drug incorporation

A curcumin solution of 10 mg curcumin in 10 mL polysorbate 80 was prepared, and 1000 µL was added to the nanoemulsion under magnetic stirring at 800 rpm. Next, 1.5 g κ-carrageenan was added to the nanoemulsion and heated at 80 ℃ while stirring vigorously at 1600 rpm. KCl and $CaCl_2$ crosslinker solutions of varying concentrations (*Table 1*) were prepared and crosslinked with the nanoemulsion using a 6-well cell culture plate (Himedia, India). The obtained hydrogels were incubated in a hot air oven (Servewell Instruments Pvt Ltd, India) for one hour at 60 ℃ and left for cooling at room temperature. Similarly, a combinational study (*Table 2*) was performed using various percentages of KCl and $CaCl_2$. Simultaneously, a control was prepared without crosslinking.

*Table 1. Parameters in preparation of nanoemulsion-based κ-carrageenan hydrogels loaded with curcumin*

| K-carrageenan | KCl or $CaCl_2$ crosslinker | Curcumin |
|---|---|---|
| 1.5 g in 50 mL nanoemulsion (3%) | 1 g in 100 mL (1%) | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 2 g in 100 mL (2%) | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 3 g in 100 mL (3%) | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 4 g in 100 mL (4%) | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 5 g in 100 mL (5%) | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 6 g in 100 mL (6%) | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 7 g in 100 mL (7%) | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 8 g in 100 mL (8%) | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 9 g in 100 mL (9%) | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 10 g in 100 mL (10%) | 1000 µL |

*Table 2. Permutation of varying percentages of KCl and $CaCl_2$ crosslinkers in the preparation of nanoemulsion-based κ-carrageenan hydrogels loaded with curcumin*

| K-carrageenan | KCl (K) + $CaCl_2$ (C) crosslinker | Curcumin |
|---|---|---|
| 1.5 g in 50 mL nanoemulsion (3%) | 2% K + 8% C | 1000 µL |

| | | |
|---|---|---|
| 1.5 g in 50 mL nanoemulsion (3%) | 4% K + 6% C | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 6% K + 4% C | 1000 µL |
| 1.5 g in 50 mL nanoemulsion (3%) | 8% K + 2% C | 1000 µL |

### 2.4. Swelling index

The swelling index (*Equation 1*) is determined by the difference in the hydrogel's weight immersed in deionized water ($W_a$) and the weight before immersion ($W_b$). The immersed sample is dried for varying predetermined intervals before use, ensuring no weight loss occurs [12].

$$Swelling\ index\ (\%) = \frac{W_a - W_b}{W_b} \times 100 \quad (1)$$

### 2.5. Equilibrium water content

The equilibrium water content quantitatively depicts the absorption of water in hydrogels as given by *Equation 2* below [13]:

$$Equilibrium\ water\ content = \frac{W_a - W_b}{W_a} \times 100 \quad (2)$$

### 2.6. Degradation analysis

The hydrogels were observed for degradation using a shaker incubator (Labline Instruments, India) at 37 ℃. The initial weight of the swollen hydrogels was measured, after which they were placed in a beaker with PBS buffer of pH 7.4 and kept in the shaker incubator. The weight of the hydrogels was recorded after dabbing them on a filter paper to remove extra water every 24 h for the next three weeks [14].

### 2.7. Microstructure and morphological analyses

EVO MA18 with Oxford EDS electron microscope was utilized to examine the surface topography. The samples were cut into approximately 5 × 5 mm pieces and dried in a vacuum

(Labline, Mumbai). Before analysis, the dried hydrogel pieces were sputtered with gold particles (Quorum, India) [15].

### 2.8. X-Ray Diffraction analysis

X-Ray Diffraction (XRD) analysis was performed using Rigaku Miniflex 600 to determine the sample crystallinity. The hydrogel samples were dried, chopped into smaller pieces, and placed in a sample holder [16].

### 2.9. Chemical interaction analysis

The presence of different functional groups and bond linkages were studied using Shimadzu Fourier-Transform Infrared spectroscopy (FTIR) 8300. The hydrogels were diced into fine pieces and dried in a hot air oven (Servewell Instruments, India) at 60 ℃ for a week. The sample pellets were prepared using KBr in the ratio of 1:100 for the analysis [17].

### 2.10. Physicomechanical analysis

A universal testing machine (Shimadzu EZ-SX) was used to examine the hydrogels' physical and mechanical properties. Hydrogel samples of dimensions 30 × 15 mm were put under compression stress at a rate of 1 mm/min and under a load of 500 N [18]. Three samples were tested in each group. The obtained load versus displacement data were converted into nominal stress and nominal strains. The stress-strain data were further used to evaluate Young's modulus, compression strength, and energy. The Young's modulus and energy values are evaluated from curve fitting initial linear zone and evaluation of area within the graph (till first the peak), respectively. The compression strength represents the peak value of nominal stress in the stress-strain graph.

### 2.11. Encapsulation efficiency

The hydrogels' curcumin encapsulation efficiency was determined by immersing them in 50 mL of PBS buffer of pH 7.4. After 24 h, 4 mL aliquots were taken, and the encapsulated curcumin concentration was determined using UV-Vis spectrometry (Shimadzu UV-1800). The encapsulation efficiency was calculated using *Equation 3* [8]:

$$Encapsulation\ efficiency\ \% = \frac{Spectrometrically\ determined\ curcumin\ amount}{Curcumin\ amount\ added} \times 100 \quad (3)$$

### 2.12. Drug release behavior and kinetics

The curcumin release behavior was studied using Shimadzu UV-1800 by immersing the hydrogels in a beaker containing 30 mL of PBS buffer of pH 7.4. The beaker was kept in a shaking incubator (Labline Instruments, India) at room temperature, followed by taking 3 mL aliquots at predetermined intervals for 24 h. The sink conditions were maintained by adding 3 mL of PBS to the beaker [19]. The curcumin release kinetics obtained from the hydrogels were scrutinized by fitting the data across various mathematical models.

## 3. Results and discussion

The hydrogels were observed to exhibit higher crosslinking using KCl than $CaCl_2$. Potassium ions have a higher affinity towards the sulfate groups of κ-carrageenan, resulting in superior compactivity and rigidity compared to $CaCl_2$. Also, crosslinking using $CaCl_2$ formed a more heterogenous structure than KCl—a characteristic consistent with previously reported results [9]. When combined, the presence of both potassium and calcium ions makes the gel highly polymerized due to the alternative binding of potassium and calcium ions to the free sulfate groups—the presence of calcium ions reinforces the κ-carrageenan network; however, the actual gel formation process is induced by potassium ions [9].

In the presence of monovalent cations, which interact with the sulfate groups in the $4^{th}$ carbon position [10], κ-carrageenan undergoes a coil-to-helical transition, resulting in a double helix [20]. Recombining these helical domains produces a polymeric hydrogel on cooling [21]. Also, the gelation of κ-carrageenan is proportional to the cation concentration, with quick stability being achieved at higher concentrations [9]. This explains our rationale for choosing 3% κ-carrageenan to fabricate the hydrogels, as the gelation was weak at concentrations below 3%, whereas rapid gelation within the beaker was observed at concentrations above 3%.

### 3.1. Physical and morphological properties

#### 3.1.1. Microstructure and morphological analyses

Scanning Electron Microscopy (SEM) analysis was performed to study the surface topography and visualize the diffusivity of the hydrogels. The topographic images were captured at 5kx magnification and 10kV accelerating voltage. The SEM image (*Figure 1*) of κ-carrageenan

hydrogels depicts the hydrogels having a smoother surface compared to those of nanoemulsified hydrogels [22], which interestingly showed uniform and corrugated surfaces [11]. *Figure 2* shows the SEM images of κ-carrageenan crosslinked with KCl, $CaCl_2$, and their combination.

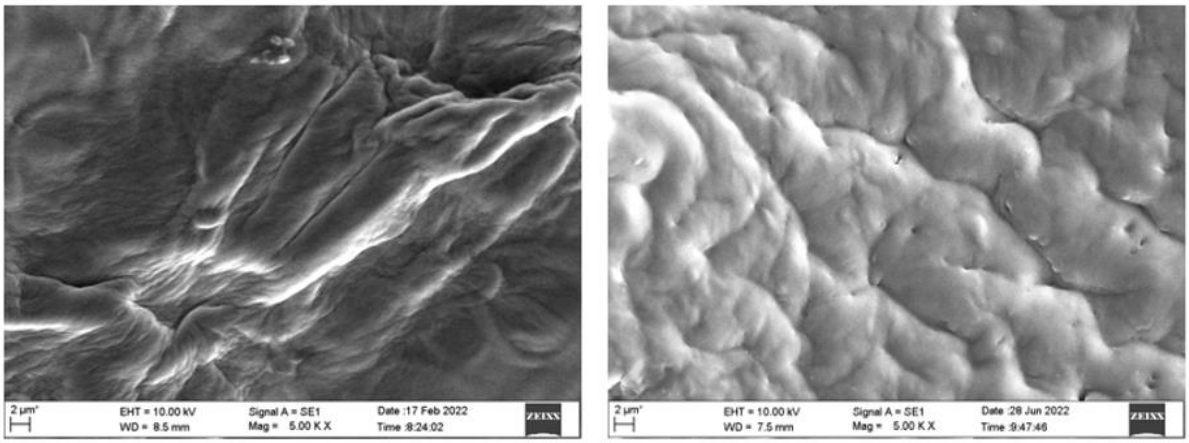



*Figure 1. SEM images of (A) κ-carrageenan hydrogels (B) nanoemulsified κ-carrageenan hydrogels*

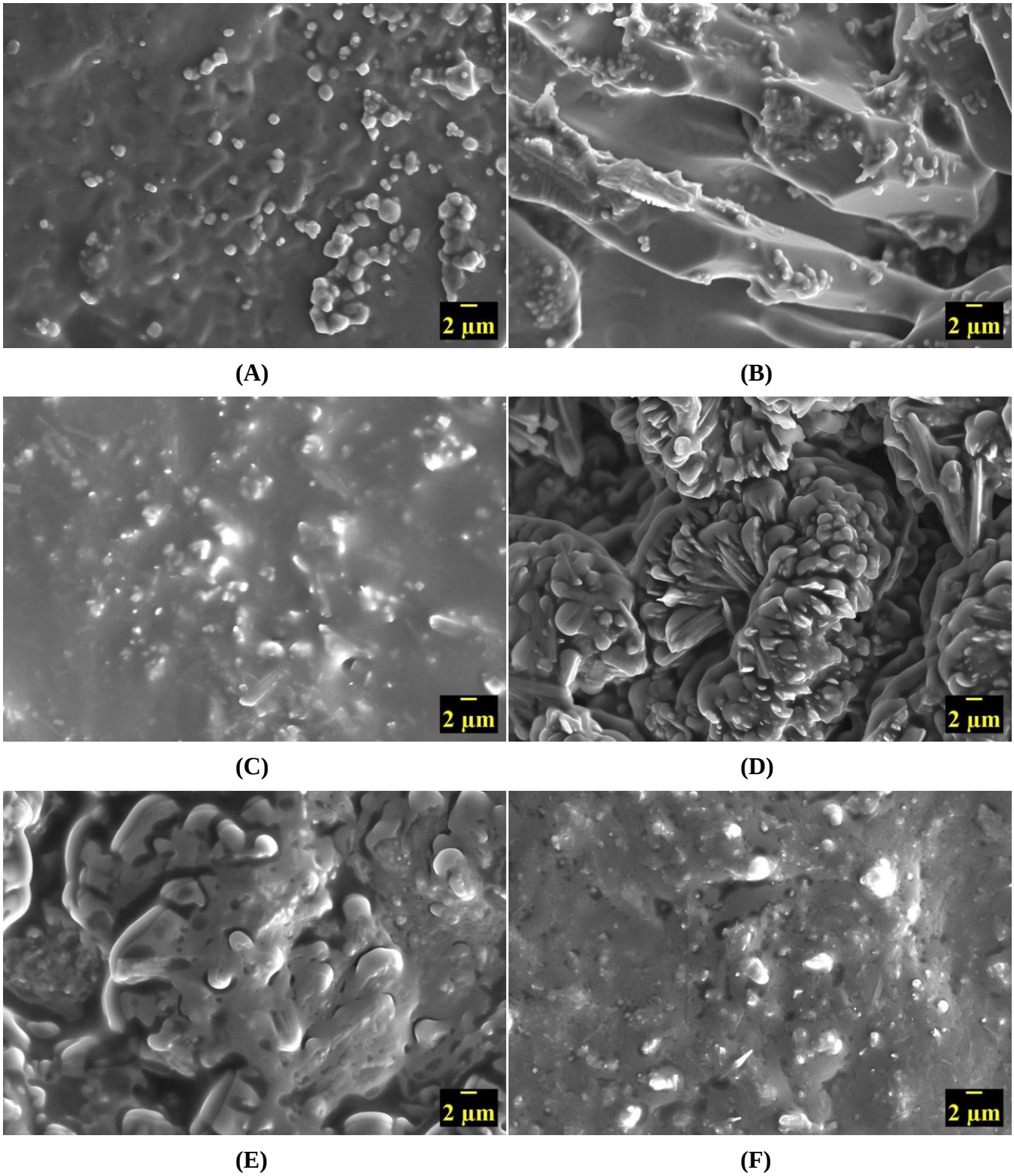



*Figure 2. SEM images of crosslinked κ-carrageenan hydrogels of (A) 6% KCl with curcumin (B) 6% KCl (C) 5% $CaCl_2$ with curcumin (D) 5% $CaCl_2$ (E) 6% KCl + 4% $CaCl_2$ with curcumin (F) 6% KCl + 4% $CaCl_2$*

### 3.1.2. X-Ray Diffraction analysis

*Figure 3* shows the XRD spectrum of κ-carrageenan and the crosslinked hydrogels. Curcumin molecules showed sharp peaks at diffracted angles of 2θ (7.83°, 8.78°, 9.86°, 11.99°, 13.76°, 15.79°, 17.13°, and 21.01°)—indicating its crystalline structure [23].

The spectrum for κ-carrageenan shows a semi-crystalline nature between 10–250° [22]. The significant peaks at 26.62°, 30.8°, and 33.76° indicate κ-carrageenan is semi-crystalline due to the presence of both crystalline and amorphous regions [24].

Sharp peaks at 29.08° and 59.26° confirm that KCl has a cubic structure with the symmetry of an Fm-3m space group. The spectrum for hydrogels crosslinked with KCl depicts sharp peaks that illustrate the crystalline nature of KCl; the broad peaks indicate the semi-crystalline nature of κ-carrageenan [25]; and intense peaks at 29.12°, 41.34°, and 50.98° confirms the crystallinity of $CaCl_2$ [26]. Hydrogels crosslinked with both KCl and $CaCl_2$ showed peaks at 41.32° and 50.88°—indicating hydrogel crystallinity higher than those crosslinked using $CaCl_2$ but lower than KCl [27].

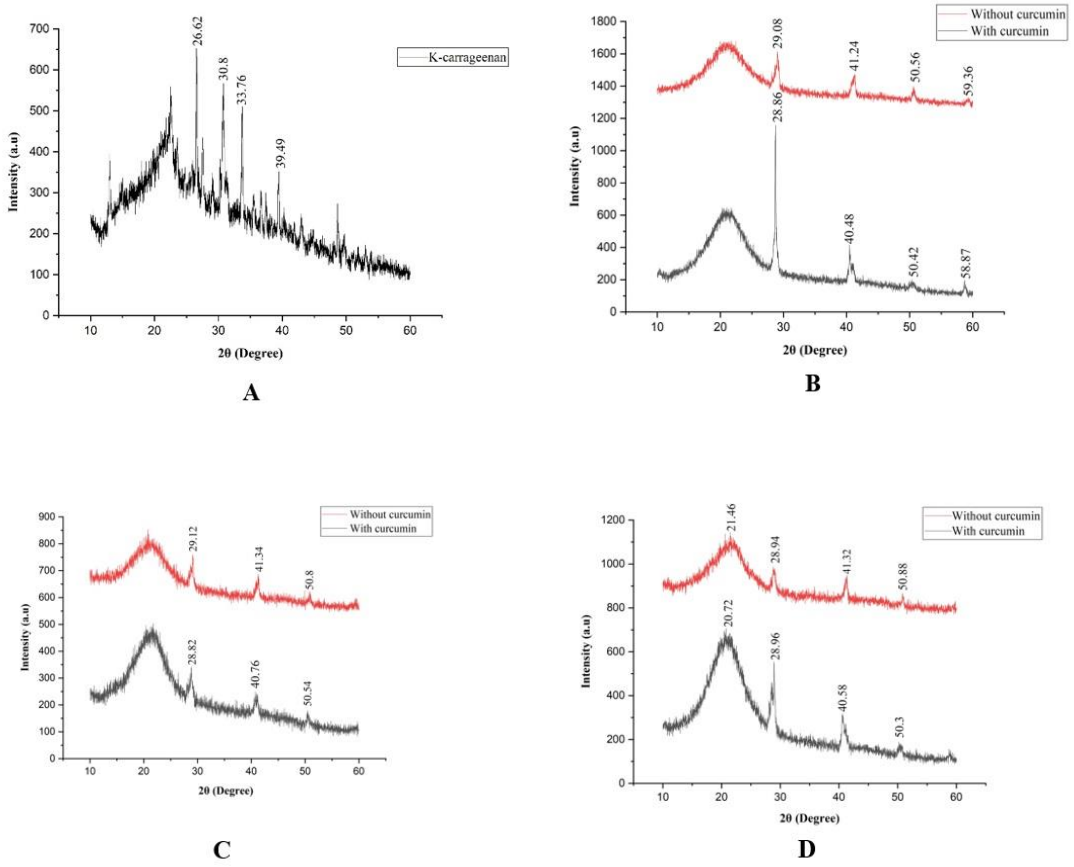



*Figure 3. XRD images of (A) K-carrageenan (B) KCl crosslinked κ-carrageenan hydrogels (C) $CaCl_2$ crosslinked κ-carrageenan hydrogels (D) KCl and $CaCl_2$ crosslinked κ-carrageenan hydrogels*

### 3.1.3. Chemical interaction analysis

FTIR is used to study the molecular interactions between different functional groups. *Figure 4* shows the FTIR spectrum of the various crosslinked hydrogels.

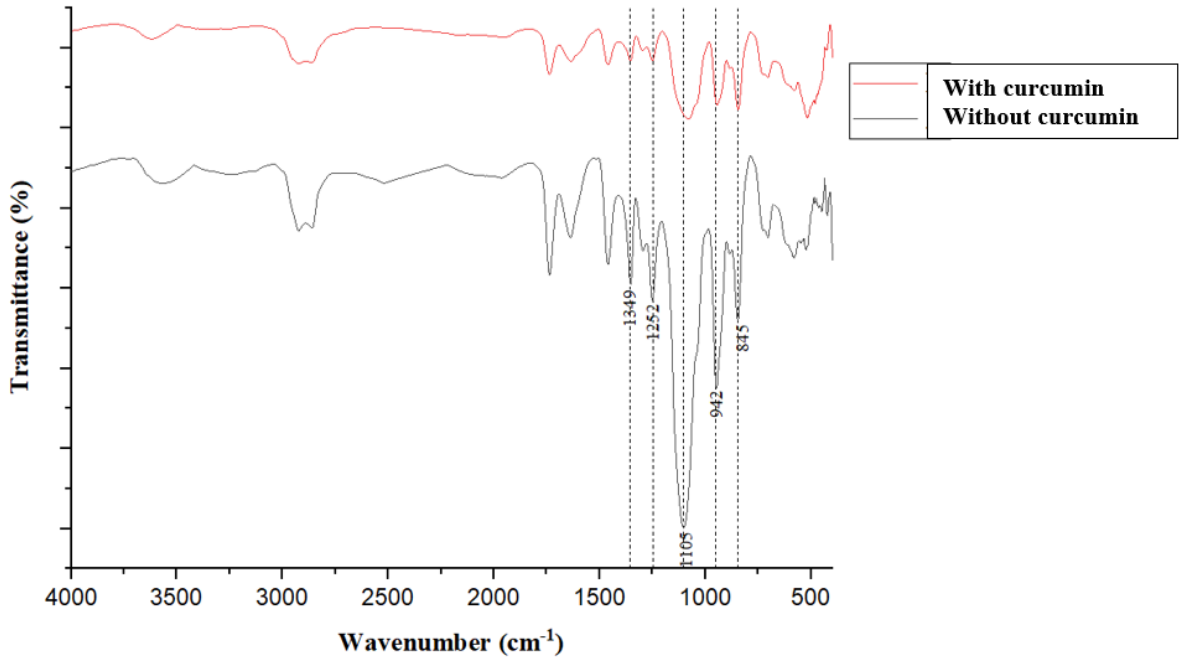
K-carrageenan shows characteristic peaks at 1260 $cm^{-1}$ and 1048 $cm^{-1}$ that indicate S=O stretching for sulfate, 921 $cm^{-1}$ for anhydrous glycosidic linkage, and 845 $cm^{-1}$ for galactose-4-sulfate [28].

Polysorbate 80 shows C-H stretching at 2919 $cm^{-1}$ and 2878 $cm^{-1}$. The peak at 1733 $cm^{-1}$ corresponds to C=O stretching, and the peak at 1109 $cm^{-1}$ is due to C-O-C stretching. O-H stretching observed a broad peak (3700-3100 $cm^{-1}$) [29].

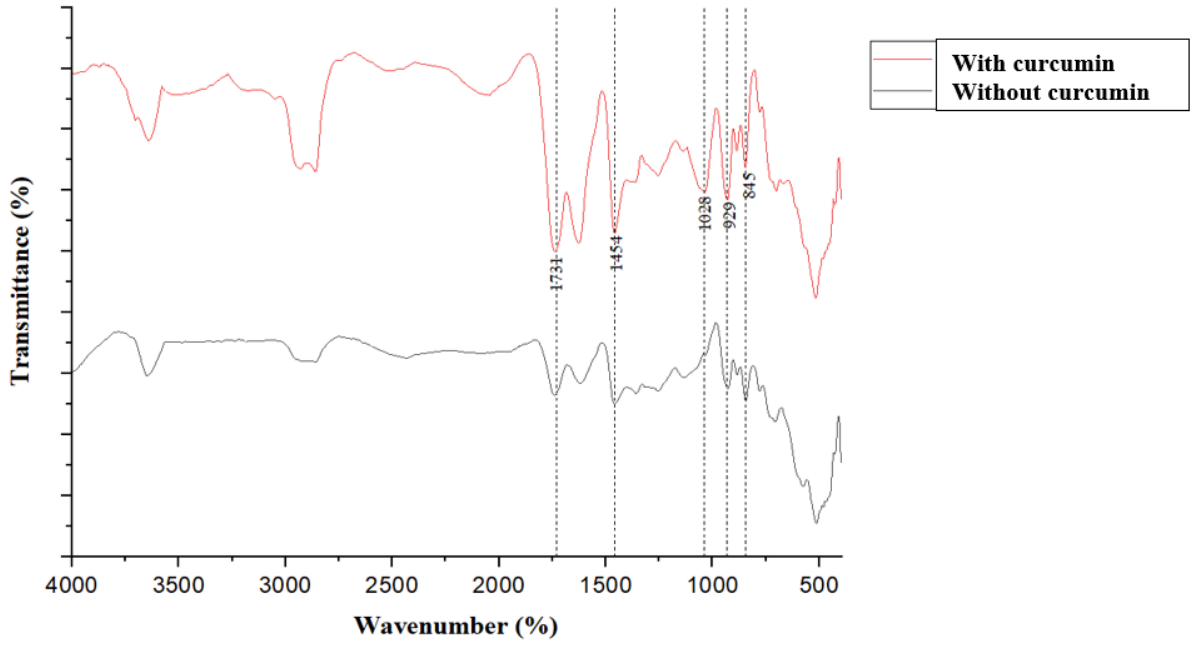
Curcumin shows its peak around 3000 $cm^{-1}$—inferring the presence of phenolic O-H stretching. The peak at 1628 $cm^{-1}$ indicates C=C aromatic stretching; 1510 $cm^{-1}$ for C=O and C=C

stretching; 1427 $cm^{-1}$ for olefinic O-H bending; 1280 $cm^{-1}$ for C-O aromatic stretching; 1024 $cm^{-1}$ for C-O-C stretching [30]–[32].

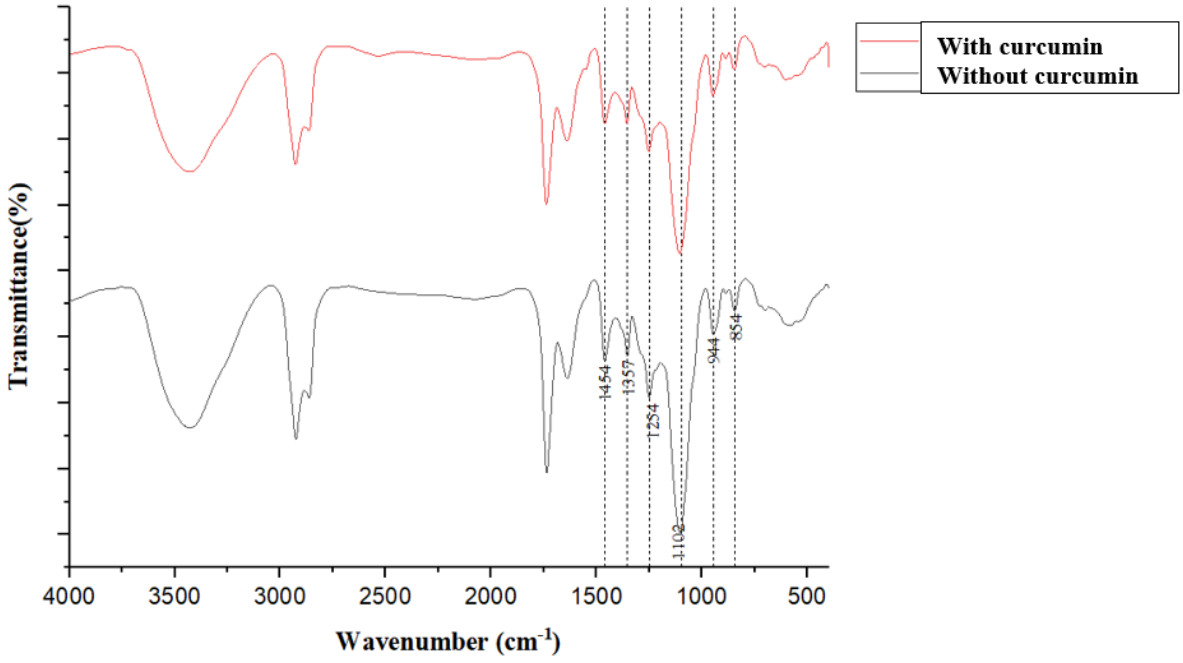
On comparing the various crosslinked hydrogels, we observe that the samples retain the characteristic peaks of κ-carrageenan (1260, 1048, 921, and 845 $cm^{-1}$) and polysorbate 80 (1733, 1463, 1109, and 949 $cm^{-1}$)—indicating their presence in the matrix. The absence of curcumin peaks represents the complete incorporation of the drug into the hydrogel matrix.




**(A)**




**(B)**




**(C)**

*Figure 4. FTIR spectrum of (A) KCl crosslinked κ-carrageenan hydrogels (B) $CaCl_2$ crosslinked κ-carrageenan hydrogels (C) KCl and $CaCl_2$ crosslinked κ-carrageenan hydrogels*

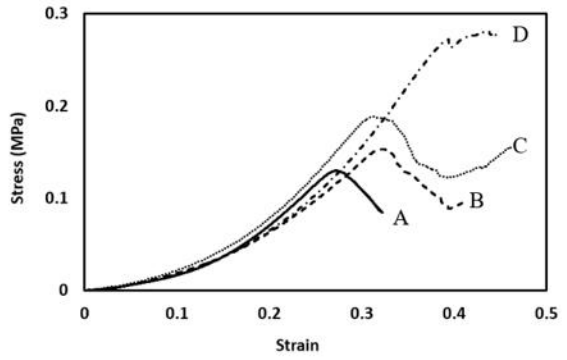
## 3.2. Mechanical properties

### 3.2.1. Physicomechanical analysis

*Figure 5* shows the mechanical response of the various crosslinked κ-carrageenan hydrogels in terms of nominal stress-strain curves. The stress-strain curves are used to extract Young's modulus (MPa), compressive strength (MPa), and energy (J). These mechanical parameters are representative of the quantitative assessment of the crosslinking effect.

It is observed that the control has the least strength and Young's modulus, whereas the crosslinker combination has the most strength. Both potassium and calcium ions form rigid and compact hydrogels compared to lone potassium and calcium ions, resulting in more robust mechanical properties [33]–[35].

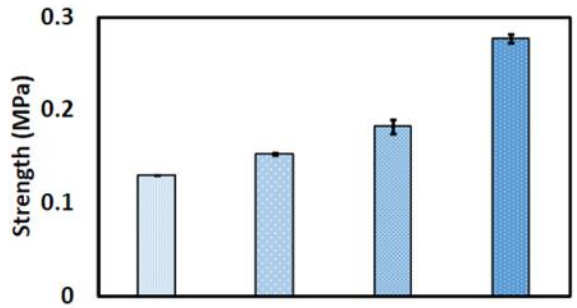
A mechanically robust hydrogel acts as an effective wound dressing material. Silva et al. [36] prepared hydrogels by crosslinking κ-carrageenan with methacrylate and KCl. The group reported slightly higher strength than ours, although the hydrogels were dually crosslinked using 4% methacrylate and 5% KCl, whereas, in the present work, a single crosslinker (referring to group C hydrogels) is used. In another work by Fei et al. [37], the hydrogels were prepared by crosslinking κ-carrageenan with sodium alginate and $CaCl_2$. The group reported relatively inferior strength (referring to group B hydrogels) though the hydrogels were dually crosslinked with substances with a high affinity towards each other. The above evidence proves our hydrogels' superior robustness and potential as a wound dressing material. As depicted in *Figure 5*, the crosslinker combination increased the mechanical strength of the hydrogels (group C) by around 1.5 times—great reinforcement of the hydrogel network by the calcium ions!



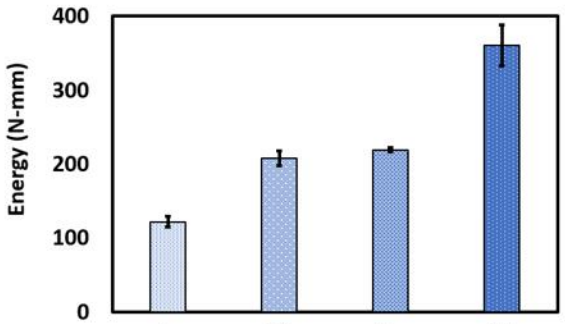

(i)

| Hydrogels | Young's Modulus (MPa) |
|---|---|
| A | 0.4805±0.045 |
| B | 0.4834±0.018 |
| C | 0.5555±0.048 |
| D | 0.7693±0.118 |

(ii)




(iii)




(iv)

*Figure 5. (i) Compressive behavior of the hydrogels (ii–iii) Young's modulus and compressive strength of the hydrogels (iv) Plot of energy absorbed by the hydrogels till the first peak in the load vs. displacement curve (A: κ-carrageenan; B: κ-carrageenan + 5% $CaCl_2$; C: κ-carrageenan + 6% KCl; D: κ-carrageenan + 6% KCl + 4% $CaCl_2$)*

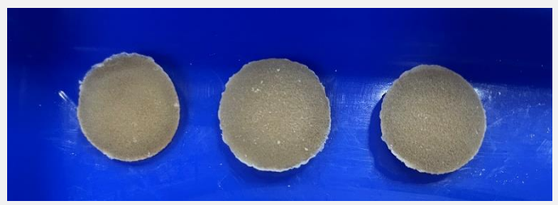
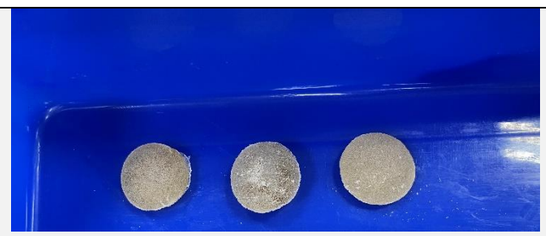
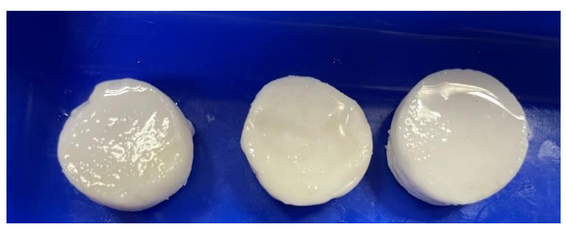
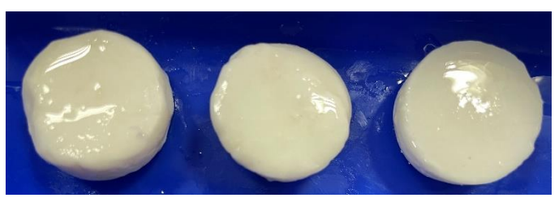
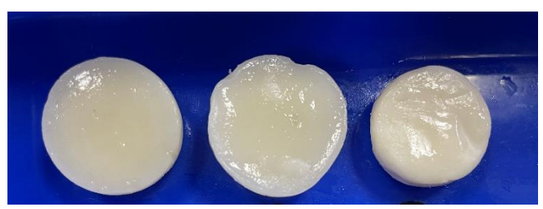
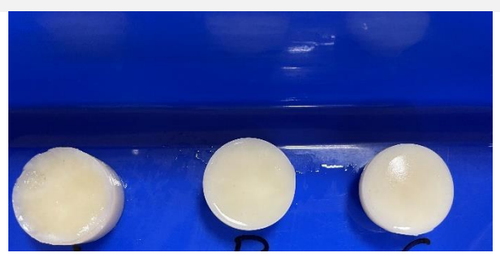
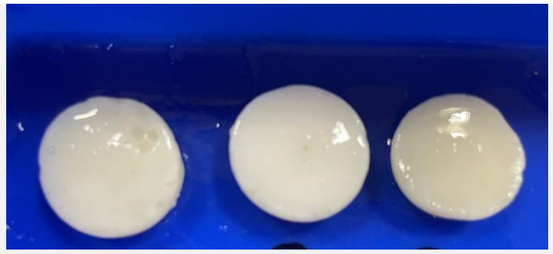
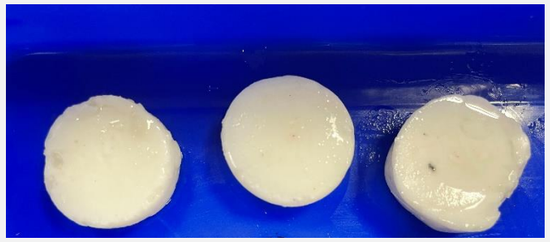
### 3.2.2. Swelling studies

*Table 3* shows the hydrogel swelling studies performed in triplicates. The higher initial swelling rate can be accredited to the ionic potential difference responsible for controlling the process. This continues until the internal and external ions reach a state of equilibrium, leading to a lower ionic potential difference between the matrix and solvent, resulting in a decreased swelling rate [38].

The extent of swelling is dependent on the matrix crosslinking as given by the Flory-Huggins theory. *Figure 6* shows that the control exhibits the maximum swelling (565.81%), followed by $CaCl_2$ (416.23%) and KCl (379.94%). The sample containing the crosslinker combination exhibited the slightest swelling (251.54%) since the hydrogel is solid and brittle, which results in decreased swelling behavior [34], [35]. Existing literature stating that higher cations adversely impact the hydrogel swelling abilities supports our result [35], [39].

Hadi et al. [40] investigated the swelling behavior of their κ-carrageenan/hydroxyethyl cellulose hydrogels in varying pH levels before and after crosslinking with genipin. The majority of the hydrogels attained equilibrium quickly and displayed poor swelling. A similar study by Sperisa et al. [41] investigated the swelling behavior of κ-carrageenan hydrogels crosslinked with varying glutaraldehyde concentrations in solvents of varying pH levels. However, poor results were achieved. We achieved significantly higher swelling, indicating that ionic crosslinkers encourage better hydrogel swelling than polymer crosslinkers. Our result is comparable to [7], which proves that we achieved excellent swelling using the crosslinker combination.

*Table 3. Various crosslinked hydrogel swelling studies performed in triplicates*

| Time | KCl | $CaCl_2$ | KCl + $CaCl_2$ | Control |
|---|---|---|---|---|
| Dry |  |  |  |  |
| 12 h |  |  |  |  |
| 24 h |  |  |  |  |

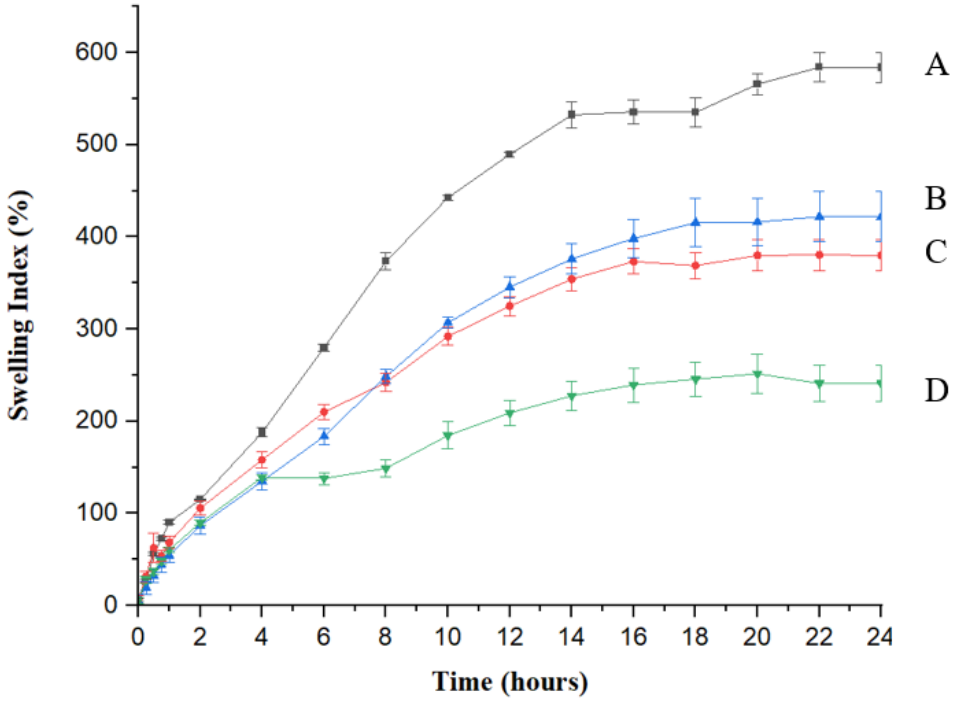



*Figure 6. Swelling indices of various crosslinked κ-carrageenan hydrogels (A) κ-carrageenan (B) κ-carrageenan + 5% $CaCl_2$ (C) κ-carrageenan + 6% KCl (D) κ-carrageenan + 6% KCl + 4% $CaCl_2$*

### 3.2.3. Equilibrium water content

A hydrogel's equilibrium water content is the maximum diffusion at its most swollen state [42]. *Figure 7* represents the equilibrium water content of the κ-carrageenan hydrogels. It can be inferred that the control has the maximum equilibrium water content (84.18%), followed by $CaCl_2$ (79%) and KCl (77.1%). This is because KCl crosslinked hydrogels are brittle and compact, whereas $CaCl_2$ crosslinked hydrogels form elastic and softer gels, indicating higher water absorption capacities. Also, the hydrolysis rate increases with reduced concentration of ions [34], and thus, the crosslinker combination exhibits the least equilibrium water content (69.47%). Our result is comparable to Haima et al. [43], indicating that the prepared hydrogels possess excellent absorption properties.

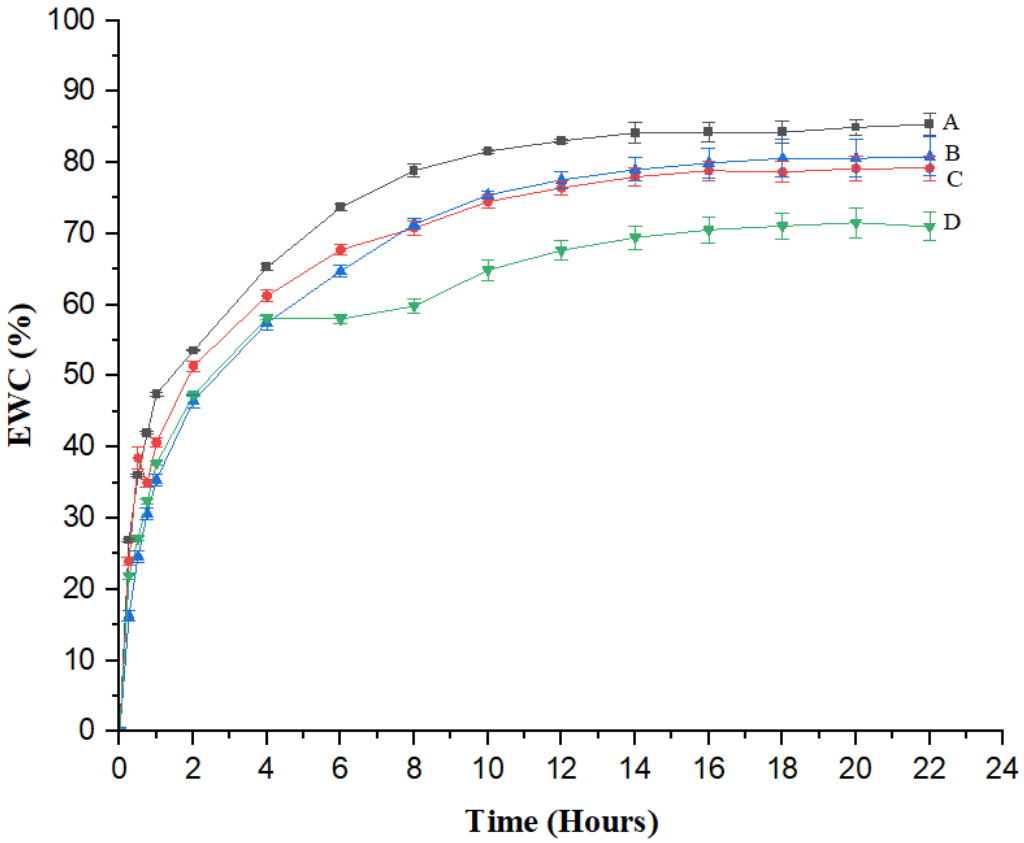



*Figure 7. Equilibrium water content (EWC) of various crosslinked κ-carrageenan hydrogels (A) κ-carrageenan (B) κ-carrageenan + 5% $CaCl_2$ (C) κ-carrageenan + 6% KCl (D) κ-carrageenan + 6% KCl + 4% $CaCl_2$*

### 3.2.4. Degradation analysis

Degradation is the percentage of mass loss from the maximum swollen mass. *Figure 8* shows the degradation pattern of the hydrogels where the control has the highest degradation (109%), followed by $CaCl_2$ (95.53%) and KCl (90.19%). The crosslinker combination shows the least degradation (81.40%) due to high crosslinking that lowers water retention, resulting in controlled degradation [14], [44]. The result indicates that the crosslinker combination produced durable hydrogels, and the degradation trends are similar to those reported by [36], [45], [46].

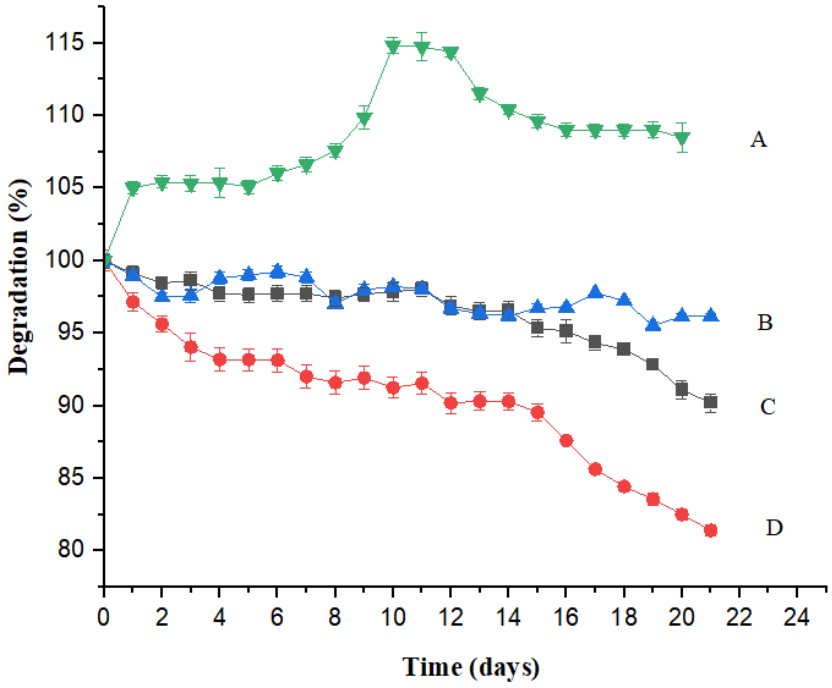



*Figure 8. Degradation of various crosslinked κ-carrageenan hydrogels (A) κ-carrageenan (B) κ-carrageenan + 5% $CaCl_2$ (C) κ-carrageenan + 6% KCl (D) κ-carrageenan + 6% KCl+ 4% $CaCl_2$*

### 3.3. Drug release behavior

#### 3.3.1. Cumulative drug release

*Figure 9* shows the cumulative drug release for the prepared hydrogels. The higher release of curcumin can be correlated to poor crosslinking and wider pore size [38]. From the graph, we infer that the control shows the most release (72.34%), followed by $CaCl_2$ (64.07%) and KCl (41.24%) crosslinked hydrogels. The crosslinker combination displays a controlled release (41.07%) due to the high ionic interaction between potassium and sulfate groups in κ-carrageenan that forms a firmer and rigid hydrogel [34], [39].

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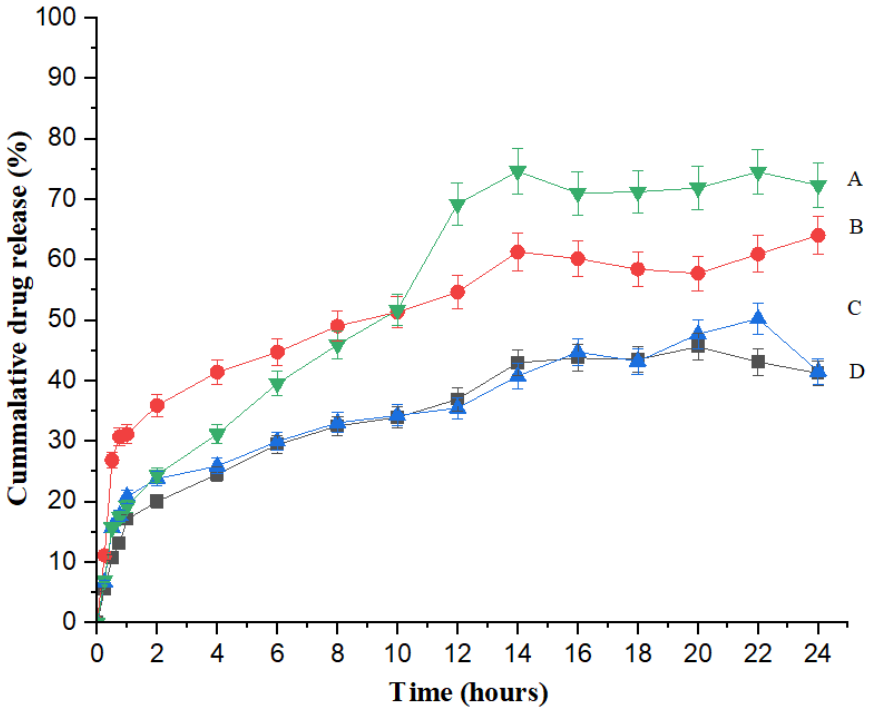


*Figure 9. Cumulative curcumin release for different crosslinked κ-carrageenan hydrogels (A) κ-carrageenan (B) κ-carrageenan + 5% $CaCl_2$ (C) κ-carrageenan + 6% KCl (D) κ-carrageenan + 6% KCl + 4% $CaCl_2$*

### 3.3.2. Drug release kinetics

Various mathematical equations were applied to the drug dissolution data to investigate the mechanism of curcumin release from the crosslinked κ-carrageenan hydrogels (zero-order kinetics, first order, the Higuchi model, and Korsmeyer–Peppa's model). *Table 4* shows the correlation coefficient values (k and $R^2$) [8].

Based on the analysis, curcumin release from the κ-carrageenan hydrogels could be best explained using Higuchi's model, which is controlled by Fick's law of diffusion. The curcumin release kinetics for control, KCl, and crosslinker combination can also be described by zero-order. For $CaCl_2$ crosslinked hydrogels, the kinetics is best described by Korsmeyer-Peppa's model, and since the obtained 'n' value was below 0.43, we can presume that Fick's law of diffusion influences the release mechanism [47]–[49]. Our result is similar to the curcumin release kinetics obtained by Katarina et al. [7], [8].

*Table 4. Values of correlation coefficients, rate constants, and release exponent for respective models*

| **Control** | **k** | **$R^2$** |
|---|---|---|
| Zero order | 5.1522 | 0.9341 |
| First order | 0.0823 | 0.7136 |
| Higuchi | 0.3202 | 0.9876 |
| Korsmeyer- Peppa's | 0.1296 | 0.9041 |
| **KCl** | **k** | **$R^2$** |
| Zero order | 2.8413 | 0.9236 |
| First order | 0.0506 | 0.8074 |
| Higuchi | 0.3202 | 0.9876 |
| Korsmeyer- Peppa's | 0.1296 | 0.9041 |
| **$CaCl_2$** | **k** | **$R^2$** |
| Zero order | 3.4576 | 0.8764 |
| First order | 0.0616 | 0.5012 |
| Higuchi | 0.3202 | 0.9876 |
| Korsmeyer- Peppa's | 0.212 | 0.8924 |
| **KCl + $CaCl_2$** | **k** | **$R^2$** |
| Zero order | 2.7621 | 0.926 |
| First order | 0.0643 | 0.6057 |
| Higuchi | 0.3202 | 0.9876 |
| Korsmeyer- Peppa's | 0.1296 | 0.5271 |

### 3.3.3. Encapsulation efficiency

*Figure 10* shows the curcumin encapsulation efficiency of the crosslinked κ-carrageenan hydrogels. The control has the highest encapsulation efficiency (50.88%), followed by $CaCl_2$ (36.76%) and the crosslinker combination (36.03%). KCl crosslinked hydrogels showed the least efficiency (30.29%) due to high crosslinking, resulting in compact polymeric structure and curcumin's sustained release. Contrarily, the presence of calcium ions leads to higher swelling and, therefore, shows higher encapsulation than KCl crosslinked hydrogel [8]. Our result is consistent with the encapsulation efficiency obtained by Katarina et al. [7], [8], and the low curcumin encapsulation obtained in all three studies is due to curcumin's hydrophobic

nature, which affects its encapsulation adversely. However, it is also responsible for its sustained release [50].

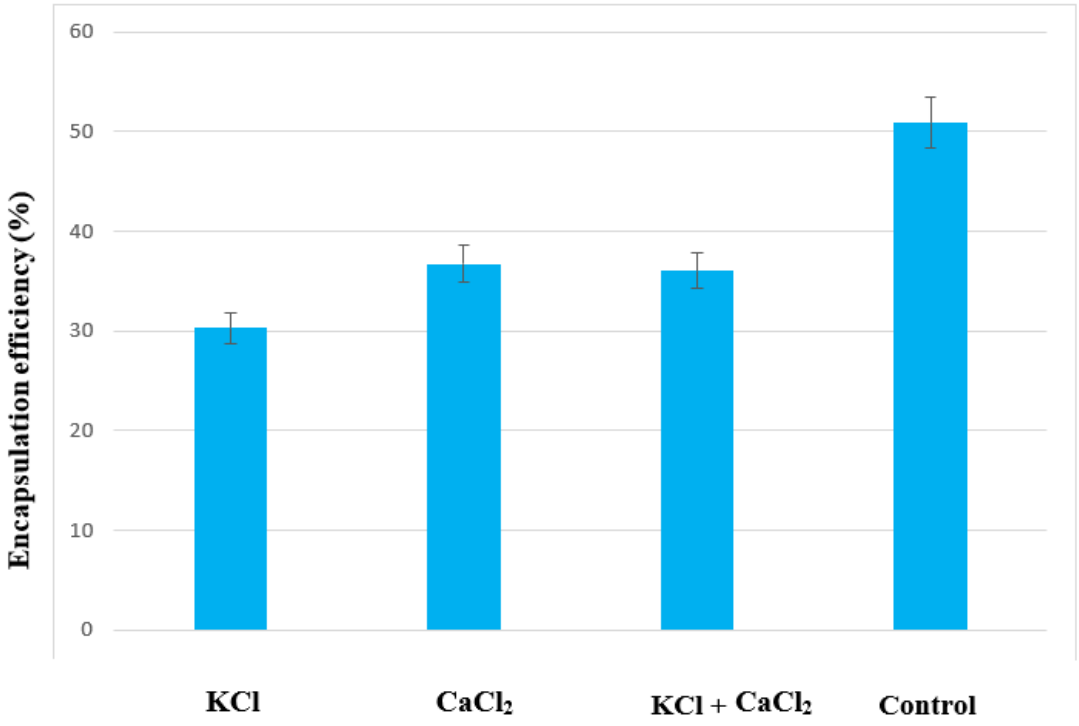


*Figure 10. Curcumin encapsulation efficiency for various crosslinked nanoemulsion based κ-carrageenan hydrogels*

## 4. Conclusion

Nanoemulsion-based drug delivery systems offer numerous advantages and have received much attention for improving active pharmaceutical mechanisms. They can overcome the complications of poor absorption and low miscibility of hydrophobic drugs. We synthesized κ-carrageenan-based hydrogels using KCl and $CaCl_2$ as crosslinkers. The nanoemulsion was first prepared, followed by formulating hydrogels containing curcumin. The hydrogels exhibited significant swelling and acceptable mechanical properties required for an ideal drug carrier. The hydrogels' *in vitro* curcumin release behavior indicated efficient drug delivery prospects. Furthermore, *in vivo* studies could be significant in evaluating the clinical efficacy of curcumin-loaded nanoemulsion-based κ-carrageenan hydrogels in drug delivery.

## 5. Conflict of interests

No conflict of interest existed concerning this research.

## 6. Acknowledgments

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