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# Optimization of Sodium Alginate-Chitosan Polyelectrolyte Complex for Enhanced Gastro-Resistant Performance of Diclofenac Sodium Microcapsules

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## ABSTRACT

Diclofenac sodium (DS) is an effective nonsteroidal anti-inflammatory drug (NSAID) limited by a short half-life and gastric irritation. Microencapsulation with natural polymers enables gastric protection and controlled drug release. This study aims to formulate and optimize DS microcapsules using a combination of sodium alginate and chitosan polymers, with the addition of Tween 80, to achieve a gastro-resistant profile with ideal controlled release. The microcapsules were prepared using the ionotropic gelation method with varying concentrations of sodium alginate and chitosan: F1 (1.0%:0.05%), F2 (2.0%:0.1%), and F3 (3.0%:0.15%). Characterization included particle size analysis using a polarizing microscope, morphology using Scanning Electron Microscopy (SEM), entrapment efficiency (EE), and in vitro dissolution testing at various pH levels (1.2, 4.5, and 7.4). Data were analyzed using one-way ANOVA followed by Tukey's post-hoc test to determine significant differences. F1 exhibited the best characteristics with a particle size of 221.42 ± 39.16 µm and the highest entrapment efficiency of 91.78%. The primary endpoint for gastro-resistance was successfully achieved by F1, showing a release of 9.71% at pH 1.2 for 120 minutes, meeting the compendial criterion of <10%. In contrast, F2 (13.17%) and F3 (17.88%) exceeded this limit with statistically significant differences ($p<0.05$). SEM image analysis confirmed that F1 had the smoothest and most compact surface with minimal porosity compared to the other formulations. This study demonstrates that optimizing the polymer concentration in F1 successfully created a compact polyelectrolyte complex matrix, effectively improved entrapment efficiency, and provided stable gastro-resistant protection for safer DS delivery.

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**ABSTRAK**

Diklofenak natrium merupakan obat antiinflamasi nonsteroid yang efektif, tetapi penggunaannya masih dibatasi oleh waktu paruh yang pendek dan risiko iritasi lambung. Mikroenkapsulasi menggunakan polimer alami dapat menjadi strategi formulasi untuk meningkatkan perlindungan lambung dan mengendalikan pelepasan obat. Penelitian ini bertujuan untuk memformulasikan dan mengoptimasi mikrokapsul diklofenak natrium menggunakan kombinasi polimer natrium alginat dan kitosan, dengan penambahan Tween 80, untuk menghasilkan profil gastroresisten dan pelepasan obat yang terkendali. Mikrokapsul dibuat menggunakan metode gelasi ionotropik dengan variasi konsentrasi natrium alginat dan kitosan, yaitu F1 1,0%:0,05%, F2 2,0%:0,1%, dan F3 3,0%:0,15%. Karakterisasi meliputi analisis ukuran partikel menggunakan mikroskop polarisasi, evaluasi morfologi menggunakan *Scanning Electron Microscopy* (SEM), efisiensi penjerapan, serta uji disolusi *in vitro* pada pH 1,2; 4,5; dan 7,4. Data dianalisis menggunakan *one-way ANOVA* yang dilanjutkan dengan uji *post-hoc* Tukey untuk menentukan perbedaan bermakna antarformula. Hasil penelitian menunjukkan bahwa F1 memiliki karakteristik terbaik dengan ukuran partikel 221,42 ± 39,16 µm dan efisiensi penjerapan tertinggi sebesar 91,78%. Formula F1 juga berhasil memenuhi kriteria gastroresisten dengan pelepasan obat sebesar 9,71% pada pH 1,2 selama 120 menit, sesuai dengan persyaratan kompendial yaitu kurang dari 10%. Sebaliknya, F2 dan F3 menunjukkan pelepasan masing-masing sebesar 13,17% dan 17,88%, yang melebihi batas tersebut dan berbeda bermakna secara statistik ($p<0,05$). Analisis SEM menunjukkan bahwa F1 memiliki permukaan paling halus, padat, dan minim pori dibandingkan formula lainnya. Temuan ini menunjukkan bahwa optimasi konsentrasi polimer pada F1 mampu membentuk matriks kompleks polielektrolit yang kompak, meningkatkan efisiensi penjerapan, serta memberikan perlindungan gastroresisten yang stabil untuk penghantaran diklofenak natrium yang lebih aman.

**Kata Kunci:** Diklofenak natrium; Mikrokapsul; Gelasi ionotropik; Natrium alginat; Kitosan; Gastroresisten

## 1. Introduction

Diclofenac sodium (DS) is a nonsteroidal anti-inflammatory drug (NSAID) widely used in the management of chronic pain and inflammatory conditions such as rheumatoid arthritis [1]. However, its clinical use is limited by a short biological half-life of approximately 1–2 hours, which requires repeated dosing to maintain therapeutic plasma concentrations [2]. In addition to pharmacokinetic limitations, NSAIDs carry a significant risk of gastrointestinal side effects, as weak acids, they can cause gastric mucosal irritation either directly or through systemic inhibition of the Cyclooxygenase-1 (COX-1) [3]. Chronic exposure and long-term use without an adequate protective system can trigger ulceration, perforation, and fatal gastric bleeding [4]. Therefore, the development of a delivery system capable of protecting the stomach has become a priority in pharmaceutical technology.

The conventional DS tablet formulation often fails to provide an optimal therapeutic response with an immediate-release mechanism, as it tends to disintegrate rapidly in the acidic conditions of the stomach (pH 1.2) [5]. Consequently, the active ingredient may be released prematurely in the stomach, which can increase the risk of gastric irritation while simultaneously reducing the efficiency of drug absorption in the small intestine, where absorption is intended to occur [6]. Therefore, to overcome this

limitation, a more controlled and targeted drug delivery system is required, one of which involves the use of natural polymer-based matrices using microencapsulation techniques [7].

Microencapsulation is a potential strategy for the development of controlled-release drug delivery systems. In this approach, drug particles are coated at the micrometer scale using a protective polymer material, with the aim of controlling drug release, improving stability, and masking undesirable tastes [8]. Compared to conventional tablet formulations, microcapsules tend to provide a more uniform drug distribution throughout the gastrointestinal tract, which can reduce local irritation and potentially increase bioavailability [9]. Ionic gelation encapsulation techniques have garnered attention as an alternative to methods such as spray drying, which typically requires high energy input, and solvent evaporation, which involves the use of organic solvents [10].

The ionotropic gelation method is an encapsulation technique based on electrostatic cross-linking between anionic polymers, such as sodium alginate, and multivalent cations, forming a three-dimensional hydrogel network with a characteristic egg-box structure. Furthermore, this encapsulation approach is more efficient and environmentally friendly, as it does not require organic solvents [11]. The advantages of this method include more controlled and predictable drug release behavior, making it highly suitable for the development of advanced drug delivery systems. It also offers the advantage of relatively mild processing conditions, typically carried out at room temperature, which is crucial for maintaining the stability of sensitive active compounds [12].

The use of natural polymers such as sodium alginate in ionotropic gelation methods has been extensively studied due to their biocompatible, biodegradable, and mucoadhesive properties. Alginate forms a hydrogel matrix upon contact with multivalent cations such as $Ca^{2+}$ [13]. Previous studies have reported that the development of alginate-based particles can provide controlled drug release of DS [14]. However, a single alginate matrix has the drawback of high porosity, leading to drug leakage during encapsulation or in an acidic medium. To overcome these limitations, combining other natural polymers is an appropriate choice, such as chitosan [15].

The polymer hybridization strategy involving the formation of a polyelectrolyte complex (PEC) between alginate (anionic) and chitosan (cationic) has become highly relevant [16]. The electrostatic interaction between the carboxyl groups of alginate and the amine groups of chitosan creates an additional protective layer capable of reducing the porosity of the matrix [17]. Previous studies have reported that the combination of collagen and alginate matrices can produce an optimal DS formulation to provide better pain-relieving therapeutic effects, given the unique characteristics of the polymers used [18].

Although the use of alginate-chitosan systems has been previously reported for other types of NSAIDs [19]. The effect of optimizing the low-polymer ratio on the physicochemical stability and release kinetics of DS, with the aid of a nonionic surfactant (Tween 80) to modulate DS surface integrity, warrants further exploration. This study provides a new perspective on the formation of a more compact matrix at minimal alginate concentrations. The current research gap lies in understanding the influence of varying combinations of alginate-chitosan polymer concentrations and the addition of Tween 80 on maintaining the stability of DS microcapsules [20].

The novelty of this study lies in the systematic optimization of a low-polymer ratio to form a denser polyelectrolyte complex matrix. Unlike previous studies using

high polymer concentrations, this research utilizes Tween 80 as a surface-integrity modulator to minimize porosity and ensure adherence to strict compendial gastro-resistance criteria.

This study aims to formulate DS microcapsules with varying concentrations of sodium alginate and chitosan via ionotropic gelation. The novelty of this study lies in the systematic approach to evaluating entrapment efficiency and delayed-release dissolution profiles that meet compendial criteria. It is hoped that the results of this study will provide scientific information and contribute to the development of safer and more effective NSAID formulations for patients with chronic inflammatory disorders.

## 2. Methods

### Materials and Equipment

The main materials include sodium diclofenac (Hanxin Pharm, China), sodium alginate, chitosan, calcium chloride, Tween 80, citric acid, and water, all of analytical and pharmaceutical grade. The main equipment used includes a magnetic stirrer (IKA SS30, Germany), a homogenizer (IKA RW 20, Germany), a UV-Visible spectrophotometer (Shimadzu UV-1800, Japan), a polarizing microscope (Olympus BX-53, Japan), a Scanning Electron Microscope (JEOL JSM-7600, USA), and a Type I Dissolution Tester (Erweka DT-720, Germany).

### Procedure for the Production of Microcapsules

The DS microcapsules were produced using the ionotropic gelation method (**Table 1**). A total of 1 gram of DS was dissolved in 100 mL of 0.1 N NaOH. In separate containers, sodium alginate at varying concentrations: F1 (1%), F2 (2%), and F3 (3%) were dissolved in distilled water, and chitosan was dissolved in 1% (v/v) citric acid at concentrations of F1 (0.05%), F2 (0.1%), and F3 (0.15%), respectively. The DS solution and the alginate solution were mixed using a homogenizer at a stirring speed of 2000 rpm until homogeneous; the mixture was then drawn up using a 26-gauge needle and dropped from a fixed distance of 10 cm into a 1% (w/v) $CaCl_2$ solution stirred at 100 rpm as a cross-linking agent. The particles were allowed to soak under continuous agitation for 10 minutes to complete the curing process, then filtered. Next, the microcapsules were soaked in a 3% Tween 80 solution for 10 minutes and placed in a chitosan solution for 10 minutes to form a polyelectrolyte complex layer, thereby enhancing the strength of the protective coating. The microcapsules were washed with distilled water and dried in an oven at 40°C [19].

**Table 1.** Formula of diclofenac sodium microcapsules.

| Material | Concentration (% w/v) | | |
|---|---|---|---|
| | F1 | F2 | F3 |
| Diclofenac sodium | 1 | 1 | 1 |
| Sodium alginate | 1 | 2 | 3 |
| Chitosan | 0.05 | 0.1 | 0.15 |
| Tween 80 | 3 | 3 | 3 |
| Calcium chloride | 1 | 1 | 1 |

### Characterization and Evaluation of Microcapsules

#### Particle Size Analysis

The particle size distribution of the prepared microcapsules was evaluated using a polarizing microscope, with 300 particles from each batch randomly selected to ensure

a representative measurement. The analysis was supported by Optilab Viewer and Image Raster software, allowing precise determination of individual particle dimensions. For each microcapsule, both maximum and minimum diameters were recorded and subsequently used to estimate the average particle size. The collected data were then processed and organized for further analysis [21].

### Analysis of Scanning Electron Microscopy (SEM)

The surface morphology and topographical characteristics of the microcapsules were examined using scanning electron microscopy (SEM). Prior to observation, dried samples were carefully mounted onto an aluminum stub using conductive adhesive tape to ensure adequate conductivity and imaging quality. The analysis was conducted at an acceleration voltage of 15 kV with a magnification of 10,000×, enabling detailed visualization of surface features, particularly porosity, while also providing supporting evidence for the formation of the polyelectrolyte complex structure [22].

### Analysis of Entrapment Efficiency (EE)

Entrapment efficiency (EE) was determined using a matrix disruption method in phosphate buffer at pH 7.4. Microcapsules equivalent to 50 mg of dry weight were accurately weighed and dispersed in 100 mL of buffer solution, then stirred at 50 rpm to ensure complete disruption of the polymer matrix and effective release of the encapsulated drug without inducing chemical degradation. After appropriate dilution, the solution was filtered a 0.45 µm nylon membrane to completely remove undissolved polymer residues and prevent light-scattering particle interference. The concentration of DS was then quantified by UV–Visible spectrophotometry at 276 nm. The percentage of entrapment efficiency was then calculated based on the ratio of the experimentally determined drug concentration to the theoretical drug content [23].

### In Vitro Dissolution Assay

The in vitro drug release profile of the microcapsules was evaluated using a type I (basket) dissolution apparatus maintained at 37 ± 0.5 °C and rotating at 50 rpm, under conditions designed to simulate the gastrointestinal environment sequentially. Microcapsules equivalent to 50 mg of dry substance were initially placed in 900 mL of 0.1 M HCl (pH 1.2) for 2 hours to represent gastric conditions, followed by successive replacement of the medium with phosphate buffer at pH 4.5 for 3 hours and pH 7.4 for 8 hours to mimic intestinal phases. At predetermined intervals, 10 mL samples were withdrawn, immediately replaced with fresh medium at the same temperature to maintain consistent dissolution conditions, and the released drug concentration was subsequently determined by UV–Vis spectrophotometry at 276 nm. This assay has been fully validated, demonstrating an excellent linear calibration range of 2–20 µg/mL with a high correlation coefficient ($R^2 = 0.9995$) [23].

### Statistical Analysis

Experimental data are expressed as mean ± standard deviation (n = 3). Differences among formulations were analyzed using one-way ANOVA in Minitab® Version 18, with $p < 0.05$ considered statistically significant, and followed by Tukey's post-hoc test to compare each pair of formulas.

## 3. Results and Discussion

### Preparation and Mechanism of Microcapsule Formation

Formation of diclofenac sodium (DS) microcapsules using the ionotropic gelation method based on the electrostatic interaction between anionic polymer sodium alginate and calcium cation from the crosslinking agent $CaCl_2$.

The resulting product is an egg-box structure, where $Ca^{2+}$ ions are introduced into the cavities of guluronate blocks embedded into the alginate chains, resulting in the formation of a three-dimensional hydrogel network that can entrap DS molecules [23]. Tween 80, which is a nonionic surfactant, is the key ingredient in reducing the interfacial tension between the hydrophobic DS and the hydrophilic alginate matrix. The condition makes the dispersion of the drug more even and prevents aggregation of the particles during the curing process [24].

Moreover, the stability of the subsequent microcapsules in terms of their structure seems to be additionally promoted by the development of a polyelectrolyte complex layer after immersion in a chitosan solution [25]. This is due to the electrostatic interactions of positively charged amino groups ($-NH^{3+}$) of chitosan and negatively charged carboxyl groups ($-COO^-$) of alginate at the surface of the microcapsule. The development of this new layer adds to the density of the wall, which can be an effective barrier to the diffusion process and decrease the porosity of the matrix and drug leakage, especially in acidic environments [26].

## Particle Size Analysis by Polarizing Microscope

Analysis of the particle size distribution under a polarizing microscope showed that all formulations produced DS microcapsules with diameters ranging from 196 to 310 µm. The sodium alginate concentration was gradually increased to 1% (F1), then 3% (F3) [27]. Such a trend has been attributed to the increased viscosity of the polymer solution, which is more likely to produce larger droplets during extrusion via the needle to produce larger microcapsules, finally, after cross-linkage with $CaCl_2$ [28]. One-way ANOVA showed a significant difference ($p<0.05$) in mean particle size among the formulations: 221.42 ± 39.16 µm (F1), 265.93 ± 36.85 µm (F2), and 294.21 ± 32.58 µm (F3). To further evaluate the polydispersity and size distribution of the prepared microcapsules, the $D_{10}$, $D_{50}$, and $D_{90}$ metrics and the Span index were determined. The $D_{50}$ values (median diameters) for F1, F2, and F3 were found to be 221.37 µm, 263.69 µm, and 292.75 µm, respectively. The Span Index values calculated for all formulations show a very narrow range, ranging from 0.193 to 0.251, confirming a highly homogeneous and monodisperse size distribution. This tight distribution ensures a uniform drug content and reproducible dissolution kinetics across the batches [29]. Formulation-wise, all microcapsules are an acceptable size of particles of delivery systems based on alginate-chitosan (approximately 1–2000 µm) [30]. Particle sizes in the sub-millimeter range are usually deemed as desirable since they have a good surface to volume ratio to support a good controlled drug release and sufficient physical stability in storage [31].

Polarized light microscopy (**Figure 1**) revealed that all formulations displayed birefringence, indicating that the crystalline structure of DS is maintained in the alginate-chitosan matrix. Particle size growth and subsequent growth of F1 to F3 with increasing polymer concentration were consistently observed, and all formulations exhibited uniform ovoid morphology. F1 was selected as the most desirable of the tested formulations because it had a smaller particle size and lower opacity than F2 and F3, suggesting a more homogeneous distribution of the active compound in the matrix. Conversely, the increased opacification of F3 can probably be attributed to the fact that a denser and thicker network was formed. This feature of the structure can, in its turn, affect the entrapment efficiency, as well as the drug release behavior of the system [32].

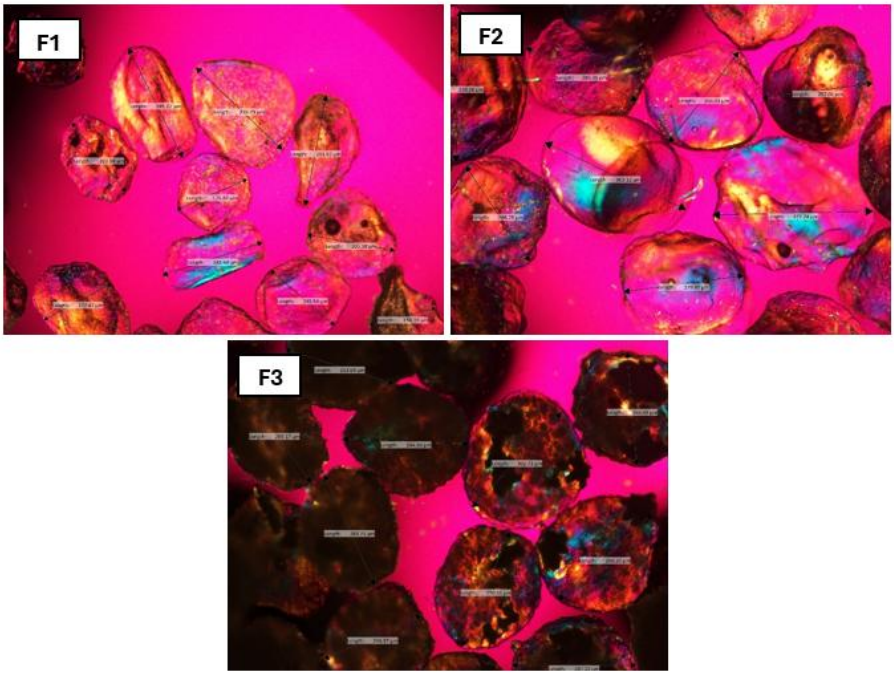


**Figure 1.** Polarized light micrographs of sodium diclofenac microcapsules (F1, F2, and F3) showing the particle morphology and birefringence properties of the DS crystals.

## Analysis of SEM

According to SEM micrographs, the three formulations exhibit distinct surface topographies (**Figure 2**). F1 has a smoother, denser surface with fewer pores than F2 and F3. The compact surface layer of F1 demonstrates that a more organized alginate-chitosan polyelectrolyte complex forms at lower polymer concentrations, which correlates with the highest adsorption efficiency. F2 exhibits a transitional morphology; its particle surface appears more porous than F1, suggesting that a further increase in polymer viscosity has triggered a reorganization of the alginate-chitosan polyelectrolyte complex network at the interface. It is claimed that at excessively high alginate concentrations (F3), the polymer network becomes stiffer and more porous due to distortions during drying, as evidenced by microcracks in SEM images [33]. The surface of F3 was further examined and found to contain trapped DS crystal deposits, indicating that the 3% alginate matrix was overly saturated, preventing the microcapsule core from fully retaining the drug on its surface [34]. On the other hand, visualization of F1 showed a continuous microcapsule wall without large pores, which should theoretically prolong the diffusion of the drug molecule. These morphological characteristics are directly related to F1's ability to maintain formulation integrity under gastric pH conditions, as reported in a previous study [35].

To provide a semi-quantitative validation of these morphological observations without automated digital scoring, a comparative correlation with the empirical formulation metrics was established. The compact and minimally porous surface observed visually in F1 directly corresponds to its significantly higher entrapment efficiency (91.78%) and its strict compliance with the compendial gastric resistance limit (<10% release at pH 1.2). Conversely, the visible microcracks and surface deposits in F3 provide physical evidence of matrix oversaturation, which mathematically aligns with its reduced entrapment efficiency (70.94%) and pronounced drug leakage (17.88%). This

direct inter-evaluation alignment provides a robust, scientifically cross-validated proof that surface density is inversely proportional to premature drug diffusion, validating the structural superiority of the F1 polyelectrolyte complex network.

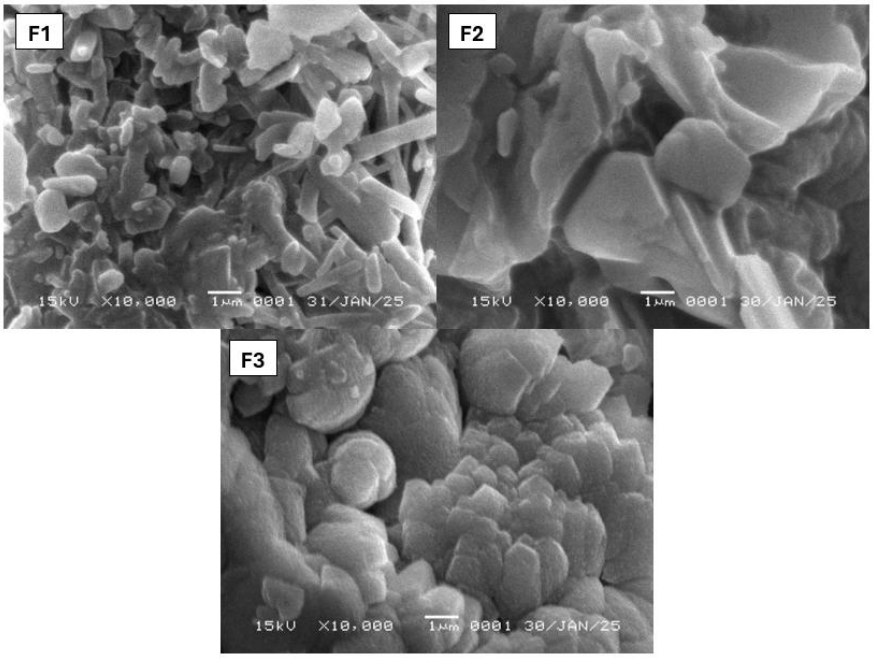


**Figure 2.** SEM micrographs of the surface of diclofenac sodium microcapsules (F1, F2, and F3) at 10,000x magnification.

## Entrapment Efficiency (EE)

The results of the entrapment efficiency determination showed that F1 had the highest value at 91.78%, followed by F2 (83.18%) and F3 (70.94%), can be seen in **Figure 3**. To evaluate these differences comprehensively, a multiple pairwise statistical comparison using Tukey's post-hoc test was performed. The analysis revealed that the differences were statistically significant across all formulation pairs: F1 vs F3 ($p<0.01$), F2 vs F3 ($p<0.05$), and F1 vs F2 ($p<0.05$). F1 performed better because the low concentrations of alginate and chitosan created an ideal viscosity balance, allowing the formation of a denser, more homogeneous polyelectrolyte complex matrix that perfectly traps DS within the core. In F2, the increased viscosity began to cause stiffness in the polymer network, hindering even drug distribution. Upon further examination, the decrease in drug loading efficiency in F3 indicates that excessively high concentrations of alginate and chitosan create a rigid polymer chain density, which limits the diffusion space for the active substance into the matrix core and triggers drug leakage during the ionotropic gelation process [36]. This reduced entrapment efficiency was visually confirmed by polarized light microscopy and SEM. These results align with previous research stating that entrapment efficiency in polyelectrolyte complex systems is significantly influenced by the stoichiometric ratio between the anionic and cationic polymers used [37]. The relationship between polymer concentration and entrapment efficiency is determined by the optimal matrix viscosity and the density of the polyelectrolyte complex network. Low polymer concentrations minimize steric hindrance, thereby allowing electrostatic interactions between alginate and chitosan to

form a tighter, more homogeneous network. Conversely, increasing polymer concentration increases matrix stiffness, which actually leads to leakage [38].

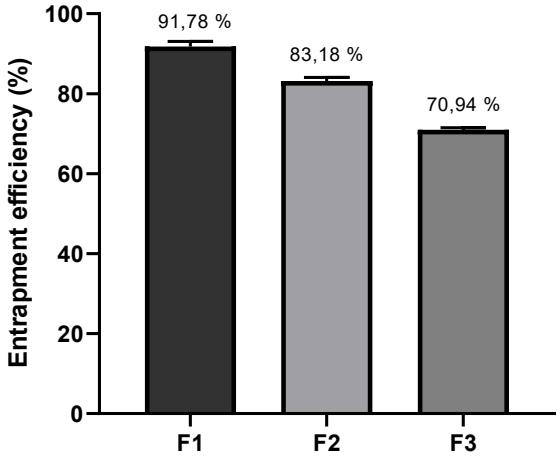


**Figure 3.** Graph showing the entrapment efficiency of sodium diclofenac microcapsules at various concentrations of alginate-chitosan polymer (F1, F2, and F3). Significant differences ($p<0.05$) across all formulation pairs.

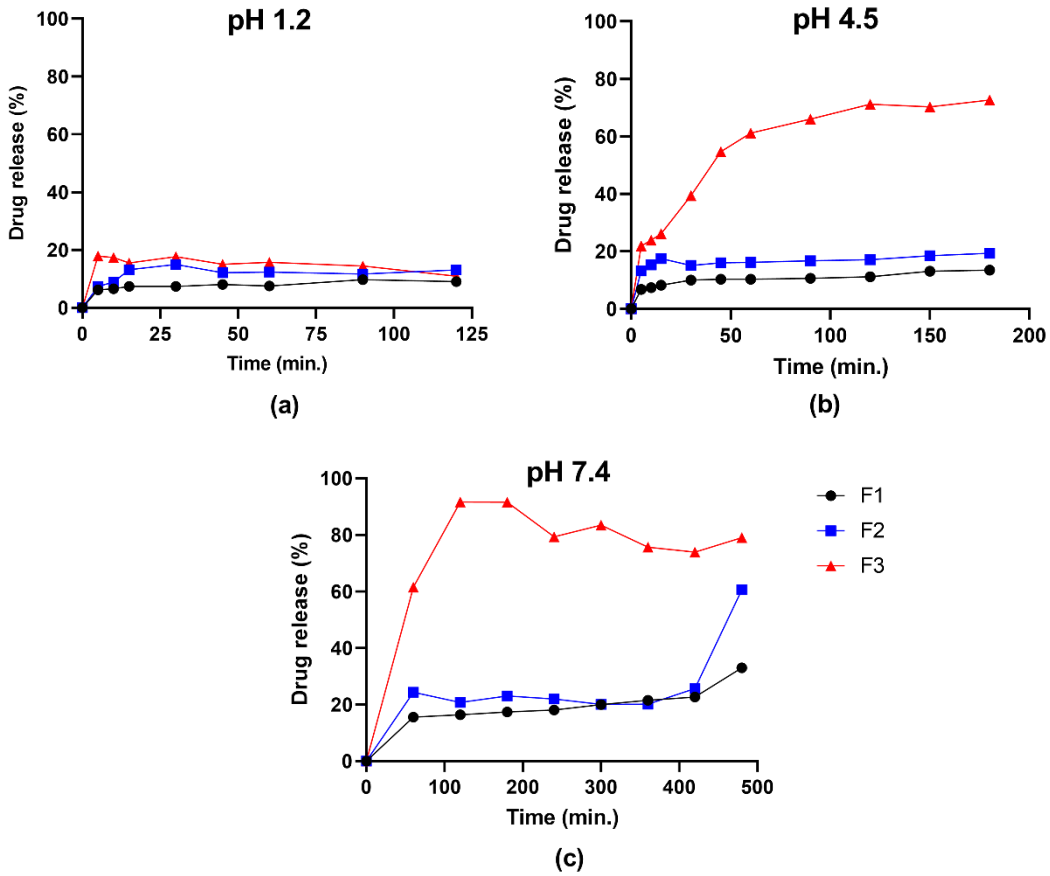


**Figure 4.** In vitro release profiles of sodium diclofenac from alginate-chitosan microcapsules in various media: (a) pH 1.2; (b) pH 4.5; and (c) pH 7.4.

## In Vitro Dissolution Test

In vitro drug release profiles were conducted in three different media to simulate gastrointestinal conditions: the stomach at pH 1.2 (**Figure 4a**), the small intestine at pH 4.5 (**Figure 4b**), and the colon at pH 7.4 (**Figure 4c**). The formulation was designed to protect the stomach within the tolerance limits specified by the pharmacopeia, with active ingredient release not exceeding 10% within 120 minutes at pH 1.2 [39]. The results show that at pH 1.2, F1 met this criterion with a release percentage of 9.71%, while F2 (13.17%) and F3 (17.88%) showed statistically significant differences ($p < 0.05$). F1 has the slowest and most controlled release profile at pH 4.5 and 7.4 compared to F2 and F3. This demonstrates that the stability of the alginate-chitosan polyelectrolyte complex in F1 is highly effective in resisting medium erosion and preventing excessively rapid fluid penetration into the microcapsule core matrix.

Data analysis revealed a strong positive correlation between entrapment efficiency and dissolution profile. F1, which had the highest EE (91.78%), consistently exhibited the most uniform release, indicating a homogeneous distribution of the active ingredient within a compact matrix that minimized burst release and, consistent with previous studies [33]. Conversely, the release from F3 was very rapid and unstable, reaching its peak at pH 7.4 within a short time; this is directly related to the low EE value (70.94%) of F3 and its large-pore surface structure, as observed in the SEM images. To systematically evaluate the drug release mechanism, the dissolution data were analyzed using the Korsmeyer-Peppas kinetic model [40]. The release exponent ($n$) for the optimal formulation F1 was 0.38, confirming that the drug release strictly followed a Fickian diffusion mechanism [41]. This indicates that the dense polyelectrolyte complex layer of F1 serves as a stable physical barrier, where drug release is predominantly controlled by the diffusion of diclofenac sodium through the matrix channels rather than matrix swelling or erosion. In contrast, F2 and F3 exhibited higher $n$ values (0.52 and 0.68, respectively), representing anomalous non-Fickian transport where polymer swelling and structural erosion dominated the release profile, leading to a burst release.

Low drug loading at high polymer concentrations (F3) is often caused by the segregation of the active substance to the particle surface, which ultimately triggers uncontrolled drug release when exposed to a medium with high ionic strength [42]. At pH 7.4, the release mechanism of F3 is dominated by swelling and dissolution of the pH-responsive alginate matrix. However, the polymer composition in F1 successfully maintains the mechanical integrity of the microcapsules longer than F2 and F3. Mechanistically, the optimal density of the polyelectrolyte complex network in F1 limits the diffusion rate of DS, making it the best formulation for maintaining a stable drug concentration and potentially minimizing the risk of gastric irritation through precise release control.

Implications and Limitations: These findings have strategic implications for the development of gastro-resistant drug delivery systems, as the optimization of the sodium alginate-chitosan polyelectrolyte complex at low concentrations (F1) has been shown, through mechanistic analysis, to create a denser matrix that reduces gastric irritation caused by NSAID side effects. However, a limitation of this study is that testing has been confined to in vitro laboratory-scale testing. To support the scalability and clinical translation of this delivery system, future investigations will establish a rigorous batch-to-batch reproducibility assessment and a structured stability testing protocol under accelerated (40°C ± 2°C / 75% ± 5% RH) and long-term (25°C ± 2°C /60% ± 5% RH) conditions in accordance with ICH guidelines. Furthermore, developing a

mathematical in vitro-in vivo correlation (IVIVC) model is essential to accurately predict the physiological performance and pharmacokinetic profiles of the optimized F1 microcapsules in a complex biological environment before moving to clinical applications.

## 4. Conclusion

In conclusion, gastro-resistant diclofenac sodium microcapsules were successfully developed using an alginate-chitosan polyelectrolyte complex via ionotropic gelation. Formulation F1 (1.0% alginate and 0.05% chitosan) was optimal, demonstrating a uniform size distribution, dense surface morphology, and a high entrapment efficiency of 91.78%. Most importantly, F1 provided excellent gastric protection by restricting drug release to 9.71% at pH 1.2 within 120 minutes, followed by a controlled release at pH 7.4 via a Fickian diffusion mechanism. However, these findings are strictly limited to in vitro evaluations, and further in vivo validation is required to confirm their clinical efficacy.

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## Conflict of Interest:

All authors confirm that there are no actual or potential conflicts of interest associated with this research.

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