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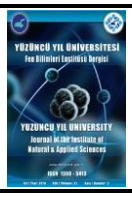

Research Article

In Vitro Evaluation of Film Hydrogels for Transdermal Drug Delivery of Paracetamol and Metformin HCl

Şebnem ŞENOL [1]

[1] Yildiz Technical University, Faculty of Chemical and Metallurgical Engineering, Department of Chemical Engineering, 34210, Istanbul, Türkiye

*Corresponding author e-mail: sebnemsenol_@hotmail.com

Abstract: This study aims to prepare sodium alginate/gelatin-based delivery systems for paracetamol ($C_8H_9NO_2$) and metformin HCl ($C_4H_{11}N_5 \cdot HCl$). Twelve sodium alginate/gelatin-based hydrogel films were synthesized using the casting method with the addition of hydroxyapatite, starch, and clinoptilolite. The drug release properties of the hydrogels were investigated in a pH 7.4 medium. Based on drug release performance, model hydrogels containing paracetamol and metformin HCl were selected. The selected hydrogels were characterized using Fourier Transform Infrared Spectroscopy (FT-IR) and Scanning Electron Microscope (SEM). It was determined that the selected hydrogels are suitable delivery systems for the active pharmaceutical ingredients.

Keywords: Polymeric Hydrogels, Paracetamol, Metformin HCl, Drug delivery

Parasetamol'un ve Metformin HCl'nin Transdermal İlaç Salımı İçin Film Hidrojellerin *In Vitro* Değerlendirilmesi

Öz: Bu çalışmanın amacı, parasetamol ($C_8H_9NO_2$) ve metformin HCl ($C_4H_{11}N_5 \cdot HCl$) için sodyum aljinat/jelatin tabanlı taşıyıcı sistemler hazırlamaktır. Hidroksipatit, nişasta ve klinoptilolit kullanılarak 12 adet sodyum aljinat/jelatin tabanlı hidrojel, plakaya dökme yöntemiyle sentezlenmiştir. pH 7.4 ortamında hidrojellerin ilaç salım özellikleri incelenmiştir. İlaç salım performansı dikkate alınarak parasetamol, metformin HCl içeren model hidrojeller seçilmiştir. Seçilen hidrojellerin Fourier Dönüşümlü Kızıl Ötesi Spektrometresi (FT-IR) ve Taramalı Elektron Mikroskobu (SEM) yardımıyla karakterizasyon işlemi gerçekleştirilmiştir. Seçilen hidrojellerin ilaç etken maddeleri için uygun taşıyıcı sistemler olduğu tespit edilmiştir.

Anahtar Kelimeler: Polimerik Hidrojeller, Parasetamol, Metformin HCl, İlaç salımı

1. Introduction

Diabetes mellitus, characterized by insufficient insulin production or impaired insulin utilization and associated with hyperglycemia, is increasingly prevalent in low- and middle-income countries. Metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), the first-line oral therapy, demonstrates efficacy in metabolic and cardiovascular disorders; however, its gastrointestinal adverse effects have stimulated interest in alternative delivery methods, particularly transdermal systems (Suryasa et al., 2021; Senol, 2023; Salem et al., 2022).

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Pain, affecting 15–25% of individuals over a three- to six-month period and increasing with age and socioeconomic disadvantage, poses substantial psychological and physical health burdens (Freo et al., 2021). Paracetamol (acetaminophen) ($C_8H_9NO_2$), listed on the WHO Essential Medicines List, remains one of the most widely used, affordable, and over-the-counter analgesics (Abdel Shaheed et al., 2021; Senol, 2025).

Paracetamol and metformin hydrochloride (metformin HCl) display distinct physicochemical properties influencing absorption and formulation. Paracetamol contains a phenolic hydroxyl group and an acetamide moiety, providing moderate polarity and hydrogen-bonding potential. Metformin hydrochloride is a highly hydrophilic biguanide derivative with multiple ionizable amine groups affecting membrane permeability and excipient interactions. These structural features emphasize the critical role of drug properties in transdermal delivery. They support the development of alternative formulations to enhance therapeutic efficacy and patient compliance (Metry et al., 2021; Miotke-Wasilczyk et al., 2021; Senol & Akyol, 2022; Senol, 2023). Moreover, advances in pharmacology and pharmacokinetics have emphasized the importance of drug release in therapeutic outcomes, leading to controlled-release strategies. Drug Delivery Systems (DDS) enhance systemic bioavailability and enable precise pharmacological control, emerging as effective tools for disease treatment and overall health improvement (Ezika et al., 2023; Senol & Akyol, 2022; Mutlu & Akyol, 2024).

Hydrogels, three-dimensional networks of natural or synthetic polymers, are widely employed in drug delivery, particularly in patch formulations and transdermal systems (Capan & Cingöz, 2025; Ahsan et al., 2020). Alginate, an anionic polysaccharide from brown algae, forms a crosslinked “egg box” structure through chelation with divalent cations (Hu et al., 2023; Yang et al., 2024). Gelatin, a natural biopolymer with amine, carboxyl, and hydroxyl groups, is commonly used in drug delivery, wound dressings, surgical applications, and tissue engineering (Singh et al., 2024; Andreazza et al., 2023).

Glycerin, a natural humectant capable of retaining moisture, is also utilized as a denaturant, fragrance, hair and skin conditioning agent, and oral care ingredient, and can be obtained from both natural and synthetic sources (Bialik-Wąs et al., 2021). Hydroxyapatite (HAp), with a chemical composition similar to human bone and teeth, is widely employed in biomedical applications (Mohd Pu’ad et al., 2020; Mondal et al., 2023; DileepKumar et al., 2021). Starch, a renewable and biodegradable biopolymer, consists of microparticles containing crystalline and amorphous domains, primarily composed of amylose and amylopectin. Amylose is mostly linear with α-D-(1→4) glycosidic bonds, whereas amylopectin is highly branched, featuring α-D-(1→4) linkages and periodic α-D-(1→6) branching points (Cui et al., 2022; Qamruzzaman et al., 2022; Lee et al., 2023).

Zeolites are hydrated crystalline aluminosilicates with micro- and nanoscale features. Clinoptilolite, a natural zeolite, is widely applied in agriculture, industry, medicine, and animal husbandry due to its high availability, low cost, and large surface area. The composition and morphology of natural zeolites vary with their volcanic or sedimentary origin, and differences in Al/Si ratios and mineral content influence their antimicrobial activity and potential side effects (Samadian et al., 2023; Doğaroglu et al., 2023).

In transdermal hydrogel-based delivery systems, drug release is generally governed by a combination of diffusion through the polymer network and polymer matrix swelling. Upon contact with an aqueous environment, the hydrophilic polymer absorbs water, swells, and enlarges its mesh size, facilitating the migration of drug molecules and resulting in anomalous (non-Fickian) transport. Gradual polymer degradation or erosion can also contribute to sustained release over time, although diffusion typically predominates. The relative contributions of these mechanisms depend on polymer structure, crosslink density, and drug–polymer interactions, linking formulation properties directly to observed release behavior (Mura et al., 2018; Saha et al., 2022; Gupta & Sharma, 2022; Singh & Jain, 2023).

To date, no studies have examined the release of metformin HCl and paracetamol from a single film hydrogel. In the present study, sodium alginate/gelatin hydrogels were fabricated via solution casting and cross-linked with Ca^{2+} ions, and hydroxyapatite, starch, and zeolite were incorporated as functional additives to investigate their influence on drug release at pH 7.4. The novelty of this work lies in evaluating two clinically relevant drugs with distinct physicochemical properties within the same transdermal hydrogel system, providing new insights into how additives modulate release profiles. This study thus fills a critical gap in the literature by investigating the release profiles of paracetamol and metformin HCl from the same sodium alginate/gelatin-based hydrogel films.

2. Material and Methods

2.1. Materials

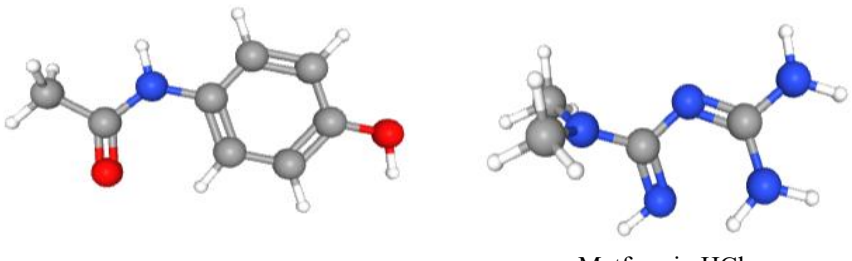
Sodium alginate (Protonal LF 10/60, FMC Biopolymer) was kindly provided by IMCD. Gelatine was obtained from Carlo Erba, while hydroxypropyl methylcellulose (HPMC) was purchased from Ashland. Starch and calcium chloride were supplied by Merck. Clinoptilolite was kindly provided by Gördes Zeolit. Glycerine was procured from Tekkim. Metformin HCl was generously gifted by Ali Raif Pharmaceutical Company, and paracetamol was kindly gifted by Atabay Pharmaceutical Company. Sodium hydroxide and monobasic potassium phosphate were obtained from J.T. Baker. All chemicals employed in this study were of analytical grade and were used without any further purification.

2.2. Methods

The film hydrogel fabrication and analysis workflow is schematically illustrated in Figure 1(b). Gelatin was dissolved in distilled water using a magnetic stirrer at 40 °C until a homogeneous solution was obtained. The gelatin solution was then allowed to cool to room temperature with continuous stirring. Subsequently, sodium alginate was added to the mixture to prepare a sodium alginate/gelatin-based solution. Depending on the formulation, either Metformin HCl or paracetamol was incorporated into the hydrogel matrix. Glycerol was then added to the mixture, which was stirred at 50 rpm for 1 hour. Following this, starch, clinoptilolite, and hydroxyapatite were sequentially added to the solution according to the formulation. The resulting mixture was stirred for an additional 3 hours to ensure homogeneous dispersion of all components.

The polymeric formulation was cast into petri dishes with a surface area of 12,56 cm² and dried at 40 °C for 24 hours to obtain uniform films. After drying, the film hydrogels were gently removed from the petri dishes and immersed in a 5% (w/v) calcium chloride solution for 4 hours to induce ionic crosslinking. After crosslinking, the hydrogels were thoroughly rinsed with distilled water to remove any residual unreacted reagents. The washing and crosslinking solutions were analyzed for drug content, and negligible amounts of drug were detected. Therefore, for the purpose of encapsulation calculations, it was assumed that the total amount of drug initially incorporated remained in the hydrogel matrix. This approach is consistent with previous studies on alginate–gelatin hydrogels showing minimal drug leaching during similar washing and ionic crosslinking procedures (Alven & Aderibigbe, 2020; Senol et al., 2018). Finally, the film hydrogels were air-dried at 25 °C for an additional 24 hours prior to further use. Franz diffusion cells were used to investigate the release profile of the formulation at 37°C. The release studies were carried out using a phosphate buffer solution (pH 7.4) as the release medium (Mutlu & Akyol, 2024; Senol et al., 2018).

Table 1. presents the compositions of hydrogel formulations H1–H10, detailing the formulations of sodium alginate, gelatin, glycerol, the active drugs (paracetamol and metformin HCl), and selected excipients (HAp, starch, and zeolite). Paracetamol was included in formulations H1, H2, H5, H6, and H7, while metformin HCl was present in H3, H4, H8, H9, and H10; HAp, starch, and zeolite were incorporated in specific formulations at low quantity to investigate their effects on the hydrogel properties.



Paracetamol Metformin HCl

Figure 1. Visual representation of the paracetamol and metformin HCl structures (NCBI, 2024).

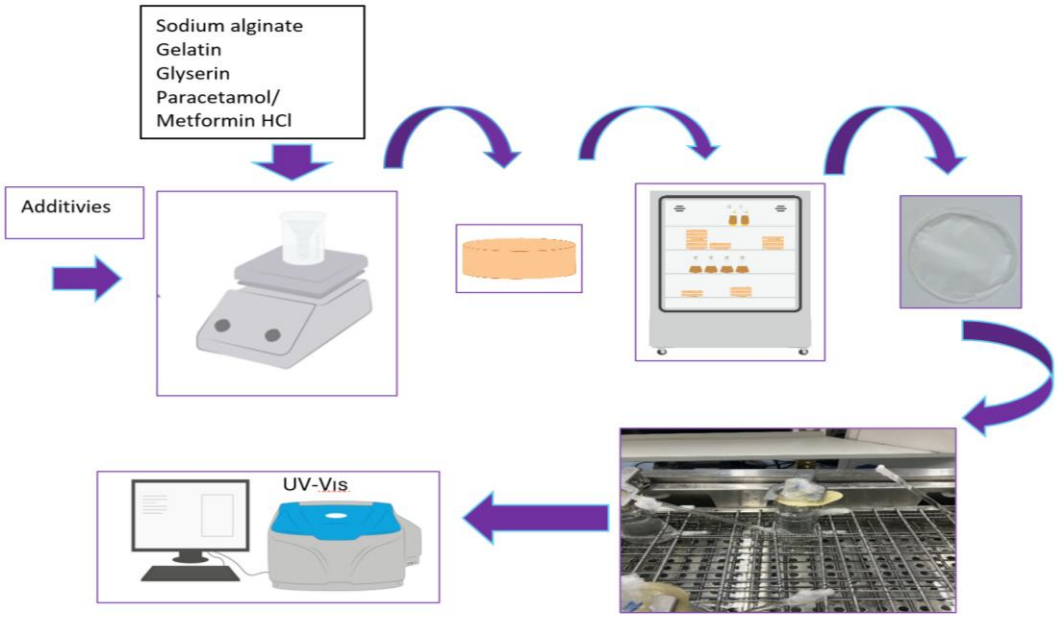


Figure 2. Visual representation of the analysis process.

Table 1. Formulation of films, (w/w, %).

	Sodium alginate	Gelatin	Glyserol	Paracetamol	Metformin HCl	HAp	Starch	Zeolit
H1	0.5%	0.3%	3%	0.05%	-	-	-	-
H2	0.5%	0.5%	3%	0.05%	-	-	-	-
H3	0.5%	0.3%	3%	-	0.05%	-	-	-
H4	0.5%	0.5%	3%	-	0.05%	-	-	-
H5	0.5%	0.5%	3%	0.05%	-	0.0125%	-	-
H6	0.5%	0.5%	3%	0.05%	-	-	0.0125%	-
H7	0.5%	0.5%	3%	0.05%	-	-	-	0.0125 %
H8	0.5%	0.5%	3%	-	0.05%	0.0125%	-	-
H9	0.5%	0.5%	3%	-	0.05%	-	0.0125%	-
H10	0.5%	0.5%	3%	-	0.05%	-	-	0.0125%

2.3. Characterization

The chemical functionalities of the prepared hydrogels were systematically analyzed using Fourier Transform Infrared (FT-IR) spectroscopy (PerkinElmer, Spectrum 100). Spectra were recorded using the Attenuated Total Reflectance (ATR) method and a diamond internal reflection element mounted on a dedicated sample holder. Measurements were performed over a wavenumber range of 4000–650 cm^{-1}.

Morphological evaluation of the hydrogels was performed using Scanning Electron Microscopy (SEM) using a Thermo Scientific Apreo 2S LoVac system. Complementary microstructural observations at lower magnifications were obtained using a Veho VMS-004 USB digital microscope, providing detailed visualization.

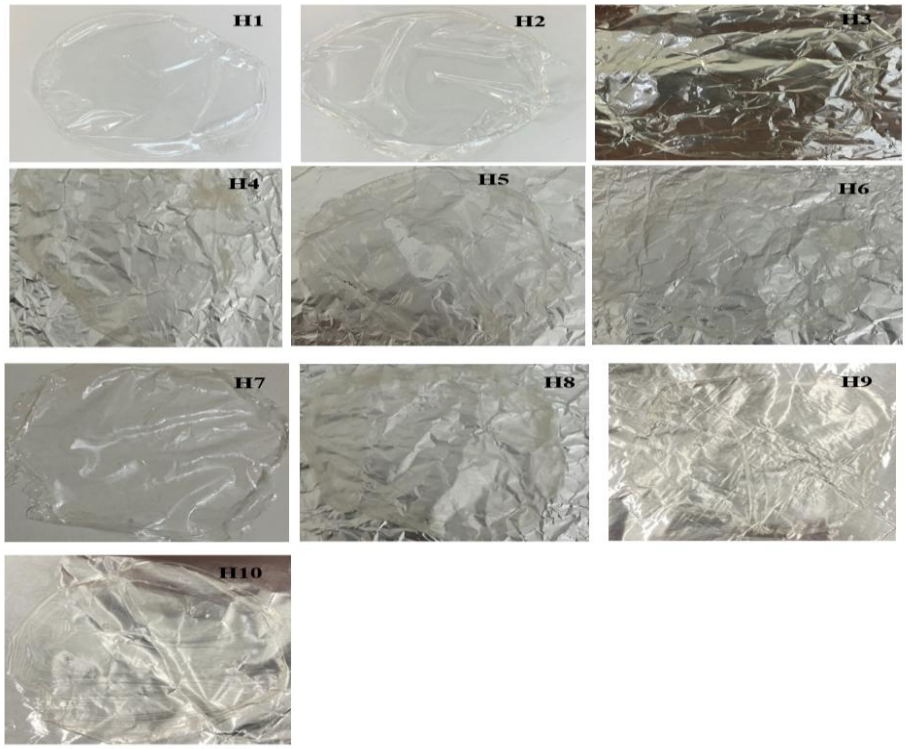


Figure 3. Photographic images of synthesized films.

3. Results and Discussion

3.1. FT-IR and SEM Analysis of Films

The hydrogel films were characterized using SEM and FT-IR. The digital microscope images in Figure 3, along with other SEM analyses demonstrated that all hydrogel formulations formed smooth, uniform, single-layered films with interconnected microstructures. In Figure 4, SEM images of selected samples (H2, H7, H8, and H10) confirmed homogeneous surface morphologies consistent with single-layer structures, with no observable cracks across the examined areas.

These findings are in agreement with previous studies on sodium alginate–gelatin hydrogels, which reported well-defined and crack-free surfaces in composite systems (Ameli et al., 2025), uniform porous morphology in lyophilized gelatin–alginate biomaterials (Skopińska-Wiśniewska et al., 2024), preservation of smooth morphology after bioactive incorporation (Hossainpour et al., 2025), and maintained microstructural integrity in radiation-synthesized SA/GL hydrogels (El-Diehy et al., 2024). The hydrogels exhibited an interconnected framework. Overall, the present results support the consistent structural integrity reported in the literature.

FT-IR analyses were conducted using a Perkin Elmer Spectrum 100 instrument, and the obtained results are summarized in Table 2. The FT-IR spectra of the selected hydrogel formulations are presented in Figure 5. Fourier Transform Infrared spectroscopy of the hydrogels exhibiting the most effective active pharmaceutical ingredient release performance revealed characteristic absorption bands for sodium alginate, including the symmetric stretching vibration of carboxylate groups (COO^-) at 1411 cm^{-1}, the asymmetric stretching vibration of COO^- in the range of 1606–1639 cm^{-1}, and broad –OH stretching vibrations between 3200 and 3600 cm^{-1} (Bulut, 2011; Senol et al., 2017). For gelatin, distinct peaks were observed at 1547 cm^{-1} and 1243 cm^{-1}, corresponding to the amide II and amide III bands, respectively (Paul Das et al., 2017; Bulut, 2011). FT-IR analysis of clinoptilolite demonstrated absorption bands in the range of 3400–3500 cm^{-1}, attributed to –OH stretching vibrations, as well as bands between 1240–1250 cm^{-1} associated with the structural units of the alumino-silicate framework (Zendelska et al., 2018). Characteristic phosphate group vibrations of hydroxyapatite were observed in the range of 1590–1600 cm^{-1} (Senol & Akyol, 2018; Eslami et al., 2010). Paracetamol showed a C=C

stretching vibration at 1609 cm^{-1} (Senol, 2025; Obeidat et al., 2015), whereas metformin HCl exhibited an N–H wagging vibration at 945 cm^{-1} (Senol, 2023). The FT-IR spectrum of glycerine exhibited a broad O–H stretching vibration in the range of 3000–3600 cm^{-1}, attributed to hydroxyl groups, while asymmetric and symmetric $–CH_2$ stretching vibrations were observed around 2937 cm^{-1}. Furthermore, C–O stretching vibrations corresponding to secondary alcohol groups were identified between 1100 – 1107 cm^{-1}.

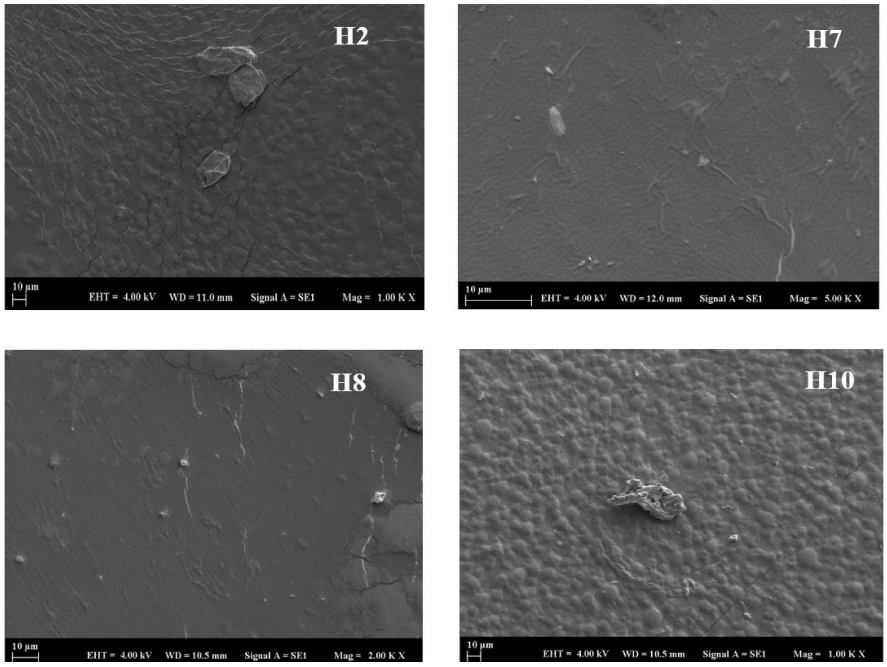


Figure 4. SEM micrographs illustrating the hydrogels structure

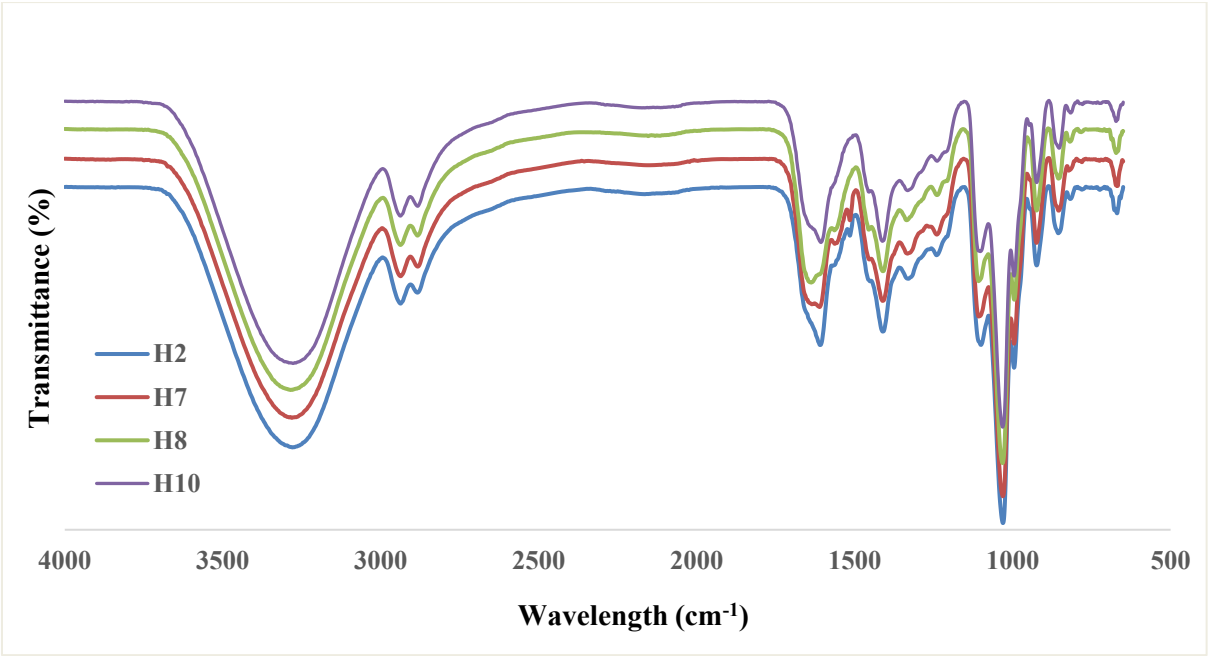


Figure 5. FT-IR characterization of hydrogels.

Additional peaks at 993 cm^{-1}, 852–855 cm^{-1}, and 667–672 cm^{-1} were assigned to C–C skeletal vibrations, C–C–O symmetric stretching, and –OH wagging vibrations, respectively (Guo et al., 2023; El-Banna & El-Dakroury, 2024; Chatzisymeon & Dimirkou, 2015). Overall, FT-IR analysis enabled the identification of characteristic peaks corresponding to the different components of the hydrogel system.

Table 2. Essential function group of hydrogels.

Wavenumber [cm^{-1}]	Essential Functional Group	References
Sodium alginate		
1411 cm^{-1}	COO^- (symmetrical) stretching	Senol et al., 2017; Bulut, 2011
1606-1639 cm^{-1}	COO^- (asymmetric) stretching	
3200-3600 cm^{-1}	-OH stretching	
Gelatine		
1547 cm^{-1}	Amide II peak	Paul Das et al., 2017; Bulut, 2011
1243 cm^{-1}	Amide III peak	
Clinoptilolite		
3400–3500 cm^{-1}	-OH groups of the water	Zendelska et al., 2018
1240–1250 cm^{-1}	Structural units of the alumino-silicate lattice	
Hydroxapatite		
1590-1600 cm^{-1}	Phosphate group	Senol & Akyol, 2018; Eslami et al., 2010
Paracetamol		
1609 cm^{-1}	C=C stretching	Senol, 2025; Obeidat et al., 2015
Metformin HCl		
945 cm^{-1}	N–H wagging vibrations	Senol, 2023
Glycerine		
3000–3600 cm^{-1}	Broad O–H stretching (hydroxyl groups, H-bonded OH)	Guo et al., 2023; El-Banna & El-Dakroury, 2024; Chatzisymeon & Dimirkou, 2015
~2937 cm^{-1}	Asymmetric and symmetric $–CH_2$ stretching	Ü El-Banna & El-Dakroury, 2024
~1100-1107 cm^{-1}	C–O stretching (secondary alcohol)	Guo et al., 2023
993 cm^{-1}, 852-855 cm^{-1}, 667-672 cm^{-1}	C–C skeletal stretch, C–C–O symmetric stretch, OH wagging	Guo et al., 2023

3.2. Drug Release Analysis

The release studies were carried out using Ultraviolet–Visible spectroscopy (UV-Vis, Perkin Elmer Lambda 35 / PG Instruments T80+). In Figure 6, the results for hydrogels containing paracetamol are presented. The produced hydrogels are based on sodium alginate and gelatin. While H5 contains hydroxyapatite (HAp) as an additive, H6 and H7 are supplemented with starch and zeolite, respectively. When comparing hydrogels H1 and H2, the H2 hydrogel, which contains a higher amount of gelatin (72.32%), exhibited a higher release profile compared to H1 (38.76%). An increase in the gelatin ratio led to enhanced swelling, which in turn resulted in an increased drug release rate (Aljawahiry et al., 2023; Senol, 2022). Among the additive-containing hydrogels (H5, H6, H7), the zeolite-based H7 hydrogel demonstrated the highest release profile (95.58%), followed by the HAp-containing H5 hydrogel (62.32%). The starch-based H6 hydrogel showed the lowest release rate among them (54.60%). In the study by Dinu et al., the synthesis and drug release properties of chitosan-based biocomposite cryogels containing clinoptilolite were investigated. It was observed that increasing clinoptilolite content enhanced water uptake and drug release (Dinu et. al., 2016). These results indicate that clinoptilolite provides better drug release in hydrogels compared to starch and hydroxyapatite. Bahulkar et al. evaluated starch-based hydrogels loaded with hydroxyapatite for drug release in maxillofacial bone

regeneration. Hydrogels containing hydroxyapatite showed enhanced drug release compared to the control group, which consisted of starch-based hydrogels without any additives (Bahulkar et.al., 2017). These results highlight their potential for biomedical applications. Overall, when comparing all paracetamol-loaded hydrogels, H1 exhibited the lowest release rate, while H7 had the highest release profile.

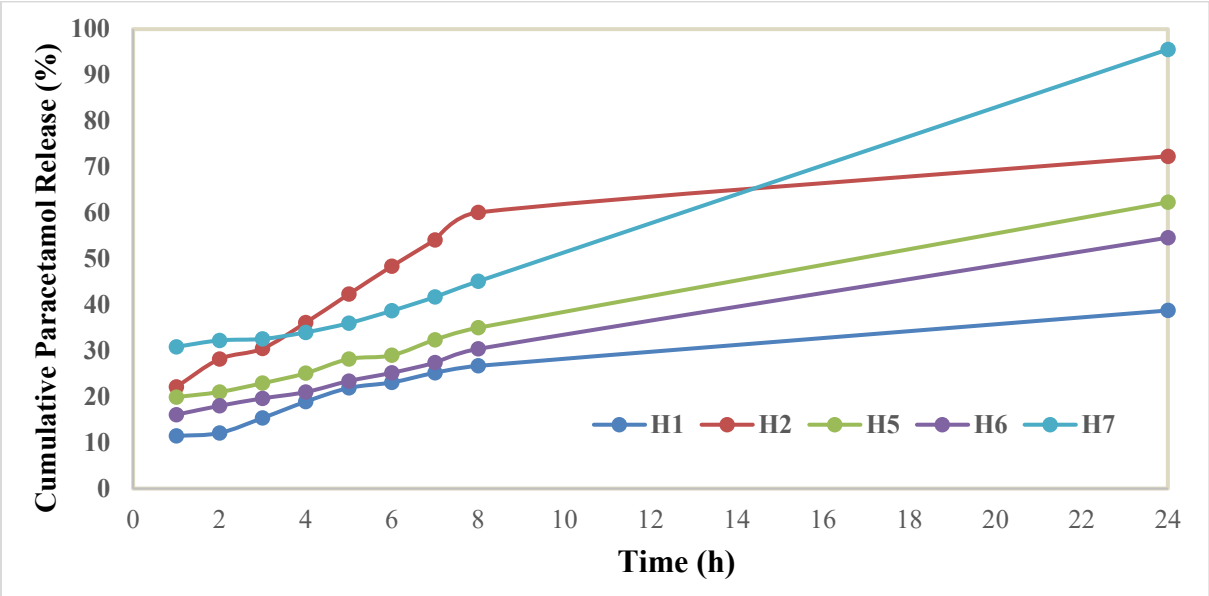


Figure 6. Cumulative release of Paracetamol.

As presented in Figure 7, the release behavior of hydrogels containing metformin HCl was investigated. Among the additive-free formulations, the H4 hydrogel - containing a higher gelatin ratio, demonstrated a significantly higher release rate (90.17%) compared to H3. Hydrogels H8, H9, and H10 were formulated with hydroxyapatite (HAp), starch, and zeolite, respectively. The zeolite-based H10 hydrogel showed the highest release percentage (94.97%), followed by H8 (92.46%) and H9 (91.88%). These findings suggest that the incorporation of additives can enhance the drug release efficiency of hydrogels. Metformin HCl-loaded hydrogels exhibited a drug release profile similar to that of paracetamol-loaded hydrogels.

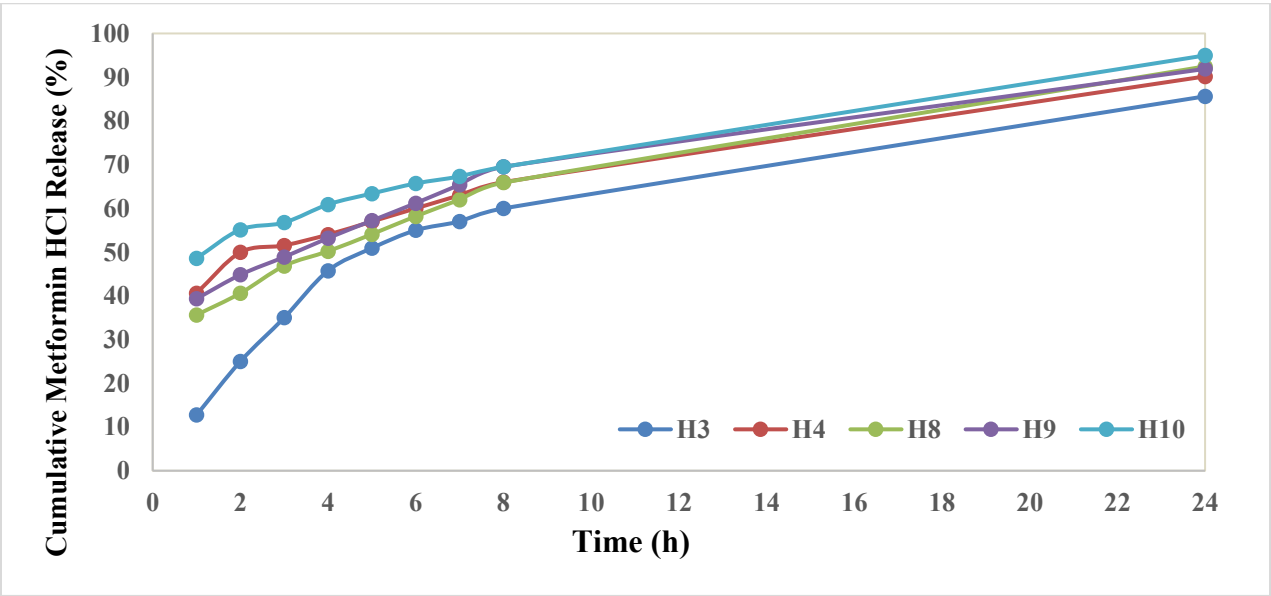


Figure 7. Cumulative release of Metformin HCl.

Considering all the formulations compared, as also shown in Figure 8, the drug release rate of the hydrogels containing Metformin HCl was found to be higher than that of the hydrogels containing paracetamol.

The high-performance films (H7-H8-H9-H10) exhibited no notable changes in appearance or drug release profiles (89.18 ± 0.4%) during three-month stability studies conducted at 25 ± 2 °C.

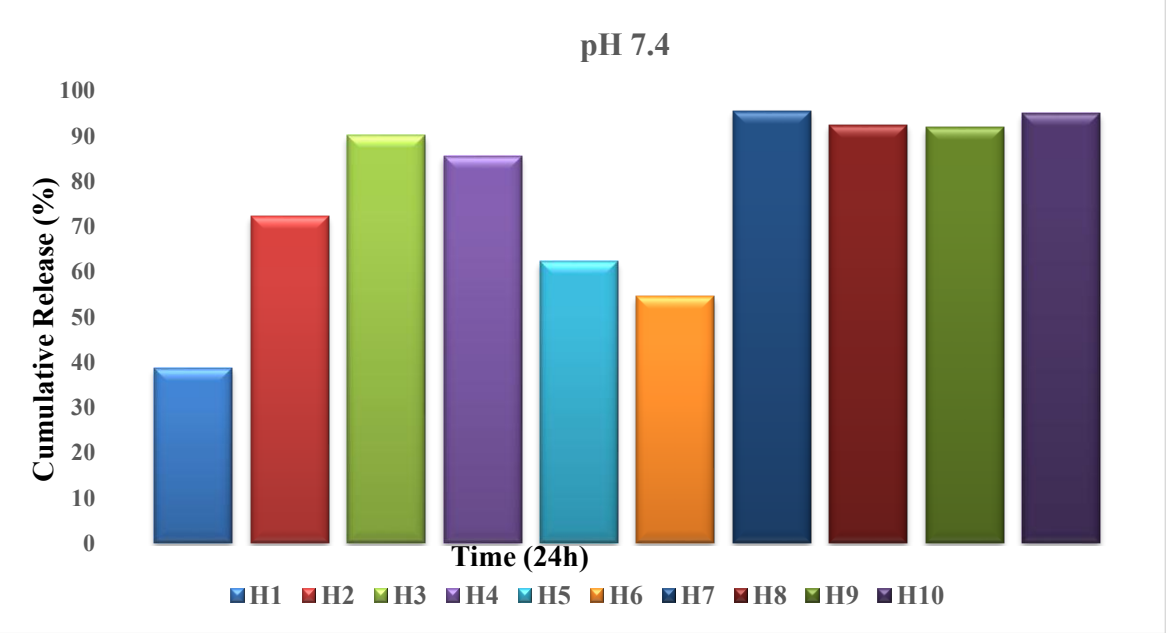


Figure 8. *In vitro* release behavior of the films.

4. Conclusion

In the present study, sodium alginate and gelatin-based film hydrogels were successfully synthesized using metformin HCl and paracetamol as active pharmaceutical ingredients. To enable application in both diabetic patients and those experiencing pain associated with diabetes, two separate hydrogel systems were developed. To enhance drug release performance, clinoptilolite, starch, and hydroxyapatite were incorporated into the formulations. Due to their porous structures, zeolite and hydroxyapatite contributed to improved release characteristics. As gelatin content was found to increase swelling behavior, formulations with higher gelatin concentrations were selected, and performance was further optimized with the addition of release-modifying agents. Stability studies supported the formulation design, and the results demonstrated that sodium alginate–gelatin-based films have potential for use in controlled drug delivery applications. While the study focused on the observed drug release profiles, detailed kinetic analysis was not performed, which could be addressed in future studies to better understand the underlying release mechanisms. Additionally, *in vivo* studies are also required to confirm the *in vitro* findings and support clinical applicability.

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Author Contribution Statement

Şebnem Şenol: Conceptualization, data curation, investigation, formal analysis, writing – original draft, writing – review & editing, supervision.

Conflict of Interest Statement

The author declares no conflict of interest.

Research and Publication Ethics Statement
The author declares that all procedures followed were in accordance with research and publication ethics.

Ethics Committee Statement
The author declares that the material and methods used do not require ethics committee approval and/or any legal or special permission.

Use of Artificial Intelligence
The author declares that no generative artificial intelligence tools were used in the writing of this manuscript or in the preparation of images, graphs, tables, or their captions.

Data Availability Statement:
The datasets generated and/or analyzed during the current study are not publicly available.

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