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ORIGINAL ARTICLE / ÖZGÜN MAKALE

PREPARATION AND CHARACTERIZATION OF CARBOPOL BASED HYDROGELS CONTAINING DEXPANTHENOL

DEKSPANTENOL İÇEREN KARBOPOL ESASLI HİDROJELLERİN HAZIRLANMASI VE KARAKTERİZASTONU

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ABSTRACT

Objective: *The purpose of this study is to create dexpanthenol-loaded hydrogel formulations to alter the release patterns and enhance the physicochemical qualities of the market product.*
Material and Method: *To make hydrogel formulations, Carbopol Ultrez was utilized in concentrations of 1%, 1.5%, and 2% (w/w). The active component dexpanthenol was then added to the formulations at a concentration of 5% (w/w). pH, viscosity, texture profile analysis, spreadability, bioadhesion, and in vitro release characteristics were all assessed for the formulations.*
Result and Discussion: *The formulations were found to be suitable for cutaneous application. TPA analysis revealed that the G1 and G1-DXP formulations had the hardness value 10.185±1.219 and 30.854±1.637 g,* respectively. *That formulations' bioadhesion strength has grown because they are more flexible than previous formulations while having low hardness values. As such, it has been observed that the formulations release more than 50% of DXP in three hours while the market preparation was not even reach the 10% drug release. In the in vitro release kinetics study, it was calculated that all formulations fit the Higuchi model. As a result, a more effective drug delivery*

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system has been developed compared to the market preparation. The currently prepared formulations are also promising formulations in terms of their use in treatment.
Keywords: *Carbopol, characterization, dexpanthenol, hydrogel*

ÖZ

Amaç: *Bu çalışmanın amacı, salım modellerini değiştirmek ve piyasa ürününün fizikokimyasal özelliklerini geliştirmek için dekspantenol yüklü hidrojel formülasyonları oluşturmaktır.*
Gereç ve Yöntem: *Hidrojel formülasyonları yapmak için, %1, %1.5 ve %2 (a/a) konsantrasyonlarında Carbopol Ultrez kullanıldı. Aktif bileşen dekspantenol daha sonra formülasyonlara %5 (a/a) oranında ilave edildi. Formülasyonlar için pH, viskozite, doku profili analizi, yayılabilirlik, biyoadezyon ve in vitro salım özelliklerinin tümü değerlendirildi.*
Sonuç ve Tartışma: *Formülasyonların cilt uygulaması için uygun olduğu bulundu. TPA analizi, G1 ve G1-DXP'nin formülasyonların düşük sertlik değerinin sırası ile 10.185±1.219 ve 30.854±1.637 g sahip olduğunu ortaya koydu. Bu formülasyonların biyoadhezyon mukavemeti, önceki formülasyonlardan daha esnek oldukları ve düşük sertlik değerlerine sahip oldukları için arttı. Geliştirilen formülasyonlar ilk üç saatte %50'nin üzerinde DXP salımı gözlenirken piyasa preparatı %10'un üzerine bile çıkamamıştır. İn vitro salım kinetiği çalışmasında tüm formülasyonların Higuchi modeline uyduğu hesaplanmıştır. Sonuç olarak piyasadaki ürünlere göre daha etkin bir ilaç salım sistemi geliştirilmiştir. Halihazırda hazırlanan formülasyonlar, tedavide kullanımları açısından da umut vadeden formülasyonlardır.*
Anahtar Kelimeler: *Dekspantenol, hidrojel, karakterizasyon, karbopol*

INTRODUCTION

The skin, the largest organ of our body, has many important roles such as creating a barrier between the outside world and our internal organs, providing thermal balance, and taking a role in vitamin synthesis [1]. The skin is basically divided into epidermis, dermis, hypodermis. This multi-layered structure undertakes the task of protecting the body against physical, chemical, radiological, and traumatic damages [2]. Many diseases such as skin urticaria, fungal infections, eczema, psoriasis, skin damage are seen. Wound is one of the most common skin injuries [3]. Wound healing is quite complex and includes 4 different processes. These are: hemostasis, inflammation, profiling, and remodeling [4]. Platelets are activated in order to close the wound opened as a result of the damage to the skin and to prevent blood loss. Monocytes and neutrophils reach the damaged tissue and initiate the inflammation phase. Cytokines are then released that stimulate endothelial cells. Revascularization occurs in the damaged tissue and wound healing is completed [5]. Conditions such as oxidative stress and excessive inflammation slow down wound healing and prevent tissue repair [6]. It is necessary to create a clean and moist environment to accelerate wound healing. For this purpose, ointments, creams, dressings, wound dressings are used. Wound dressings cut off the interaction of the wound with the external environment and protect the tissue that is open to inflammation against microorganisms. It also provides moistening of the scar tissue, thermal insulation, and gas exchange [7].

Hydrogels, known as hydrophilic gels, are 3-dimensional structures. The high amount of water they contain keeps the wound moist. It also helps to relieve pain and pain by keeping the wound cool. Since they do not contain fibers, they do not stick to the damaged tissue and do not cause irritation [8,9]. Hydrogels can be produced with polymers such as chitosan, carbomer, carboxymethyl cellulose. Carbomers are cross-linked polyacrylic acid polymers and are very good drug carriers for transdermal applications [10,11]. Hydrogels are also used in cosmetics. It is especially preferred for moisturizing, anti-aging and cellulite problems [12]. The bioadhesive properties of hydrogels make their use in the cosmetic field widespread. The cooling effect, bioadhesive and non-toxic properties of hydrogels increase their potential for use, especially in skin irritations, laser burns, and sunburns. Since carbomer polymers have several benefits in pharmaceutical applications, including the ability to produce high viscosity gels at relatively low gelling agent concentrations, exhibit bioadhesive, thermostable, and organoleptic properties, and be compatible with a variety of active ingredients, Carbopol Ultrez was used as the gelling agent in this study [13]

Dexpanthenol is an enantiomeric compound with D and L forms. Although both enantiomers have moisturizing properties in topical application, only D-panthenol is a biologically active compound. After D-panthenol is absorbed topically, it is metabolized to pantothenic acid [14]. D-panthenol reduces ROS production and induces tissue regeneration by minimizing tissue damage [15,16]. In a study examining wound healing of D-panthenol, cream containing nebivolol and cream containing dexpanthenol were applied to rats, and as a result of the analyzes, the effects of nebivolol and dexpanthenol on wound healing were found to be comparable [17]. In another study, a multilayered dressing loaded with dexpanthenol was produced. In the *in vitro* study, it was observed that the wound scratches were completely occluded 24 hours after tissue damage was created [18].

In this study, dexpanthenol-loaded hydrogel formulations are made in an effort to change the release patterns and improve the physicochemical properties of the commercial product. As a result, Carbopol Ultrez was used as a gelling agent at various concentrations, and the formulations were assessed for pH, viscosity, textural profile analysis, spreadability, and bioadhesion. Additionally, *in vitro* release investigations were carried out, and the release mechanism was assessed using the mathematical models.

MATERIAL AND METHOD

Materials

Propylene glycol was purchased from Yasin Teknik (Turkey). Glycerin, triethanolamine, Carbopol Ultrez were purchased from Tekkim (Turkey). Propyl paraben was purchased from Doga Ilac (Turkey). Ethanol (EtOH) distilled water and acetonitrile were analytical grade. Acetonitrile and ortho-phosphoric acid were purchased from Sigma (USA). Dexpanthenol (DXP) was a kind gift from BASF (Germany).

Methods

Determination of Dexpanthenol

Dexpanthenol was quantified using an HPLC method. A UV detector, gradient pump, and thermostable column unit are features of the HPLC device (Agilent 1200 Series, USA). The study made use of C18: 4.6x250 mm, 5 micron column (Phenomenex Gemini C18, USA). The HPLC method was modified from previously performed experiments [19]. Briefly, the mobile phase was a mixture of acetonitrile: 0.01 M ortho-phosphoric acid (10:90, v/v). The flow rate, injection volume and UV wavelength were set at 1 ml/ min at 25°C, 10 µl and 205 nm, respectively. Calibration curve was obtained and then the HPLC method was validated in terms of linearity, accuracy and recovery, precision, limit of detection (LOD) and limit of quantification (LOQ).

Preparation of Blank and DXP Loaded Hydrogels

Hydrogels were prepared using 3 different concentrations of Carbopol Ultrez (1%, 1.5%, 2%). Carpobol Ultrez and distilled water were added to the beaker and mixed. Then propylene glycol, ethanol and glycerin were added. Neutralization and cross-linking were achieved by adding 0.5 ml of triethanolamine. Then propyl paraben was added as a preservative. Table 1 shows the formulation components and their amounts.

Preparation of Dexpanthenol Loaded Hydrogels

Dexpanthenol (5%) was dissolved in a 1:1 mixture of distilled water and ethanol. Then, a mixture of distilled water, ethanol, propylene glycol and glycerin were added. Different concentrations (1%, 1.5%, 2%) of Carbopol Ultrez were added to the prepared mixture and mixed. Triethanolamine was added to provide crosslinking.

Characterization of Blank and Panthenol Loaded Hydrogels

pH measurement was performed with a Mettler Toledo S220-K (Switzerland) device. First, pH measurement of the gels without active substance was made. Then, the pH of the active substance loaded

gels was measured. The viscosities of the hydrogels were measured at room temperature (25±2°C) with the Brookfield DV1-LV viscosimeter (UK).

Table 1. Components of the blank and drug loaded formulations.

Components	G1 (%)	G1-DXP (%)	G2 (%)	G2-DXP (%)	G3 (%)	G3-DXP (%)
Propylene Glycol	5	5	5	5	5	5
EtOH	2	2	2	2	2	2
Glycerin	2	2	2	2	2	2
Propyl Paraben	0.03	0.03	0.03	0.03	0.03	0.03
Triethanolamine	0.5	0.5	0.5	0.5	0.5	0.5
Distilled Water	89.47	84.47	88.97	83.97	88.47	83.47
Carbopol Ultrez	1	1	1.5	1.5	2	2
Dexpanthenol	-	5	-	5	-	5

Textural Profile Analysis

The mechanical properties such as hardness, compressibility, adhesiveness, cohesiveness, and elasticity of gels were detected using a Texture Analyzer. The test was performed with Perspex probe having 25 mm diameter (P/25P, θ: 25 mm). The pre-test speed was 2.00mm/s, test and post-test speeds were 2 mm/s each with trigger force of 0.001N. The compression depth in each operation was 10.00 mm and the delay period between two compressions was 10 seconds [20,21]. All experiments were performed in triplicates at 25 ± 0.5°C.

Spreadability

The spreadability of blank and loaded gel formulations was determined by using TA-XT Plus Texture Analyzer. Test sample was placed within the female cone. Male cone was moved toward the female cone up to 23 mm at a specified test speed of 3 mm/s and the post-test speed of 10 mm/s. The spreadability of gels was determined in terms of firmness, stickiness, work of shear and work of adhesion.

***Ex vivo* Bioadhesion Experiments**

The mucoadhesion strength was evaluated by using a TA-XT Plus Texture analyzer following the previously described method with some modifications. Dorsal skins of rats sacrificed in previous ethical committee-approved studies were used in this study (Ethical Committee Permission, Kobay Deney Hayvanları Laboratuvarı San. ve Tic. A.Ş., Date: 25.02.2023). Mucoadhesion strength was determined as the detachment force needed to separate the formulation from the skin after applying a force of 0.5 N for 200 seconds with the rate of 0.5 mm/sec. [22]. In summary, 1g of the formulation was placed in the beaker. Rubber has been used to firmly secure animal tissue to the probe. The formulation was then applied to the tissue for the designated amount of time and strength before being removed. Software was used to evaluate the results that were obtained.

***In vitro* Release Studies**

In vitro release studies were performed by using dialysis bag method for the formulations G1, G2, G3 and marketed product (MP, Bepanthol Derma©). Briefly, one gram of accurately weighed gel or MP, containing 5% w/w DXP, was placed inside the dialysis membrane and fixed at both ends. Then, the dialysis bags containing formulations were put in a beaker containing 100 ml of PBS (pH7.4) solution and it was gently stirred on a magnetic stirrer maintained at 32±1°C at 100 rpm. To avoid evaporation, beakers were covered with aluminum foil and parafilm. At each regular interval of time (0.5, 1, 2, 4, 6, 8,10, 12, 24 h), 0.5 ml of sample was removed and replaced with 0.5 ml of new diffusion

medium. Sink condition was maintained during the experiments [23]. Finally, the samples were analyzed by HPLC-UV method at 205 nm.

Drug Release Kinetic and Mechanism

In this study, to comprehend drug release pattern, *in vitro* drug release data were fitted to various kinetic models, including zero order, first order, Higuchi model, and Hixson-Crowell model. Large value of the coefficient of determination suggested that dissolving behavior and mathematical models were well-matched (r^2) [24].

Similarity and Difference Factors for DXP Release

Fit Factors, which were adapted by the Food and Drug Administration as industry advice for dissolution testing, were used to statistically examine and compare DXP diffusion across the membranes and DXP release patterns from formulations [25,26]. Fit factors are models that are frequently used by researchers to directly assess the variation in drug release percentage per unit time between a reference and a test formulation. Using Equations (1) and (2), the difference factor (*f1*) and the similarity factor (*f2*) were determined.

$$f1 = \left\{\left(\sum_{t=1}^{n}|Rt - Tt| \Big/ \sum_{t=1}^{n} Rt\right) x100 \right. \qquad \textbf{Eq. 1.}$$

$$f2 = 50xlog\left[\left(1 + \left(\frac{1}{n}\right)\sum(Rt - Tt)^{2}\right)^{-0.5} x100\right] \qquad \textbf{Eq. 2.}$$

Where n is the number of dissolution sample periods and Rt and Tt are the percentages of medication released from the reference and test formulations at a certain time point (t), respectively. The relative inaccuracy between the two curves is measured by the difference factor (f_1), which computes the percent difference between the reference and test curves at each time point. The sum of squared errors' logarithmic reciprocal square root translation into the similarity factor (f_2), which measures the similarity in percentage released between curves, is used to calculate the similarity. Arbitrary descriptors of difference and similarity must be selected for data analysis. Curves with $f_1 \geq 10$ and $f_2 \leq 50$ were seen as being distinct.

RESULT AND DISCUSSION

Preparation of Blank and Drug Loaded Hydrogels

In this study, we have formulated hydrogels that can be easily spread on the skin surface, suitable for use in minor skin wounds and cosmetic purposes. Prepared hydrogels contain 5% dexpanthenol. Hydrogel formulations were prepared in 3 different concentrations of Carbopol Ultrez (1%, 1.5%, 2%). Carbopol Ultrez is regarded as a viable candidate for the development of various polymeric systems, particularly controlled drug-delivery systems, and plays a crucial role in the delivery of drugs to a specified location of the body [27]. Because carbomer polymers are known to have bioadhesive, thermostable, and organoleptic qualities, they may be made into very viscous gels at relatively low concentrations, making these systems appealing from both a pharmacological and patient acceptability perspective. Additionally, Carbopol Ultrez hydrogels' compatibility with a variety of active substances and strong bioadhesiveness are benefits [28]. In our study, transparent, non-irritating, non-sensitizing, and non-gritty hydrogels were produced.

Characterization of Blank and DXP Loaded Hydrogels

Carbomers are acrylic acid homo- and copolymers with high molecular weight that have been cross-linked with a polyalkenyl polyether. They are acidic in their unneutralized condition and anionic in nature, so in order to have the potential to thicken, they must be neutralized with the proper base. Water soluble gel that has been neutralized with inorganic bases is stable. Gels made with triethanolamine may withstand high alcohol concentrations [29]. When our results are examined, it is

observed that in the empty formulation, with the addition of a fixed amount of triethanolamine, the viscosity increases when the concentration of Carbopol Ultrez increases and reaches the plateau level after a concentration. On the other hand, the addition of DXP to the formulation led to a decrease in viscosity, although the concentration of Carbopol Ultrez increased (G2-DXP and G3-DXP). Triethanolamine was used to gel the carboxyl groups of Carbopol Ultrez, which were present in low quantity in the G1-DXP formulation. However, in the G2-DXP and G3-DXP formulations, a fixed quantity of triethanolamine caused some carboxyl groups of Carbopol Ultrez to gel. The alcohol structure of DXP, however, resulted in a decrease in the remaining carboxyl groups' ability to form hydrogen bonds, which in turn reduced viscosity. Because aqueous gels have higher viscosity than hydroalcoholic gels [30].

There is naturally a chemical layer on the skin. This barrier at acid pH is called the acid mantle of the skin [31]. This mantle provides hydration of the stratum corneum. The natural skin pH is between 4.1 and 5.8 in adults. Formulations with this pH range are considered to be compatible with the skin. In our study, the pH values of DXP loaded formulations were between 3.760 ±0.034 and 5.416±0.335. Additionally, the pH values were slightly raised by adding DXP to the formulations, although they are still within the permissible range for dermal applications. The pH ranges of all formulations prepared are shown in Table 2.

Table 2. pH and viscosity measurement results

Formulations	pH	Viscosity (P)
G1	5.043±0.117	14.180±0.288
G1-DXP	5.416±0.335	25.333±1.973
G2	4.560±0.095	40.266±4.004
G2-DXP	5.393±0.379	38.880±22.788
G3	3.760±0.034	37.440±1.499
G3-DXP	5.357±0.054	26.466±12.608
MP	6.767±0.029	22.267±0.115

Rutin-loaded hydrogels were investigated in one research for the treatment of wounds in rats. The pH values of the formulations were 5.7, which was determined to be appropriate for dermal applications because the pH of skin is slightly acidic [32]. Another research examined dexamethasone-loaded nanocapsules incorporated in hydrogels. Carbopol Ultrez was used to create the formulations, which had a pH value of about 5.5. The use of these formulations on the skin's surface was also accepted [33].

Viscosity determines the application time of formulations to the skin and the residence time after application. Although the residence time of the formulations with high viscosity increases, the penetration rate of the active substance into the skin slows down. Table 2 shows the viscosity values of the formulations developed. According to the literature on topical administration, at optimal viscosity, the gel neither flowed immediately after its application to the skin nor resisted application [34]. The viscosity of formulations was determined to be within the permitted range for topical use.

Texture Profile Analysis

The textural parameters of the hydrogel formulations produced by TPA analysis such as hardness, adhesiveness, cohesion, resilience, and springiness were evaluated. Table 4 shows the TPA values of the formulations. Hardness (N or g) is the resistance to product deformation and is measured as the initial compression's maximum force. Gel hardness provides details on how easily gels may be applied to skin, which may be a sign of how long a gel will stay on the application site. The amount of effort needed to separate the probe from the formulation is defined by the adhesiveness value, which is related to adhesive qualities. Greater tissue surface adherence is indicated by a higher adhesiveness rating, which is a desirable property to prolong medication retention. Adhesiveness is determined using the negative force area for the first compression cycle if any attractive force acts between the gel's surface

and the probe. The formulations' response to repeated shearing loads is demonstrated by their cohesiveness. The gel sample distorted during the first compression, and the definition of the gel's reconstruction following its deformation is springiness or elasticity. A product's cohesiveness is determined by comparing how well it stays together following one deformation to how well it kept together following a subsequent deformation [35,36].

Table 3. The mechanical properties of hydrogels

Formulations	Hardness (g)	Adhesiveness (g.sec)	Cohesion	Resilience (%)	Springiness (%)
G1	10.185±1.219	-35.372±8.234	0.885±0.005	14.506±2.581	89.355±0.980
G1-DXP	30.854±1.637	-63.600±0.392	0.810±0.052	9.975±0.945	92.147±2.149
G2	26.819±0.904	-65.927±10.080	0.816±0.035	20.041±0.624	91.816±1.559
G2-DXP	41.292±1.360	-67.759±15.066	0.823±0.016	11.715±1.973	93.811±1.306
G3	24.450±0.180	-62.477±13.674	0.864±0.019	18.370±2.286	90.552±1.662
G3-DXP	43.496±3.824	-53.961±2.062	0.752±0.112	14.218±0.158	93.846±1.248
MP	-2.893±1.033	-125.761±28.063	0.866±0.139	0.026±0.008	0.996±0.001

As was already indicated, different concentrations of Carbopol Ultrez were used as a gelling agent. TPA findings show that increasing concentration has enhanced the gels' hardness as predicted, notably for drug-loaded gels [37]. It is desirable that the hardness value be low for simple administration and spreadability since it is connected to the formulation's application to the skin [36]. In contrast to other formulations, the hardness values of G1 and G1-DXP were found to be lower in our investigation. This outcome may be assessed based on how simple it was to apply the G1 and G1-DXP formulations to the skin's surface. The blank and drug-loaded G2 and G3 formulations approach a plateau at concentrations of 1.5% and 2%, whose values are not statistically different, even if the hardness corresponds with increasing concentration.

Since the formulations attained plateau values for all of the aforementioned properties as well as for adhesiveness, cohesiveness, resilience, and springiness, the results show that all created formulations are appropriate for cutaneous applications.

To correlate data from rheological investigations with textural profile analyses, Carvalho et al. created hydrogels using a variety of gelling agents. Researchers employed various types of polyacrylic polymers for this purpose. The findings showed that formulations' levels of textural analysis plateaued at various concentrations. Results were also assessed in light of how well-suited the formulations' low hardness values are for cutaneous applications [38]. In a different study, Özcan et al. developed chitosan hydrogels loaded with terbinafine hydrochloride to improve topical drug delivery. For this reason, scientists have developed chitosan hydrogels with varying molecular weights. Results indicated that other formulations had textural characteristics comparable to the one we prepared [39].

Spreadability Analysis

In terms of patient compliance, spreadability is one of the key characteristics of the topical formulation. If a product has sufficient spreadability, even applying it to the skin is simpler and more patient acceptable. Additionally, formulations that are easier to distribute might cover more skin upon application, which can enhance the therapeutic impact [40]. Spreadability results of our study are shown in Table 4.

Spreadability study reveals formulation strength (firmness), work of spreading (work of shear), stickiness, and force of extrusion by displaying the fluctuation of force as a function of time (work of adhesion). The formulation's strength may be determined by its firmness, which is the maximal positive force that can distort it. The strength of the formulation is improved by a greater firmness value. The spreadability of the formulation is demonstrated by the area up to the positive force, which is the work

of shear. The weight of the sample raised on the top surface of the male cone during the turn was mostly responsible for the negative section of the graph produced by the probe rotation. This is a result of back motion and indicates if there is resistance to the disc sticking or flowing. The adhesion force for the gel, which symbolizes the force necessary to separate the gel from the tube, is at its maximum negative value. The area of the curve's negative portion was picked to represent the adhesion work [41]**.** Spreadability is inversely related to firmness and work of shear [42]. The values of firmness and work of shear for G2 and G3 formulations were determined to be greater based on the data produced (Table 4, Figure 1). Consequently, they have less spreadability than the G1 formulation.

Table 4. Results of spreadability test

Formulations	Firmness (g)	Work of Shear (g.sec)	Stickiness (g)	Work of Adhesion (g.sec)
G1	360.40±18.39	347.25±15,20	-304.3±13.21	-85.64±7.72
G1-DXP	884.69±14.94	775.3±33,15	-700.91±9.33	-218.18±2.61
G2	917.58±18.48	895.10±43.40	-694.16± 14.06	-205.98±6.76
G2-DXP	1065.09±14.23	1008.09±27.41	-819.00±9.92	-255.52±6.69
G3	862.59±13.67	877.70±36.06	-649.37±13.86	-185.42±9.72
G3-DXP	1237.01±0.88	1256.00±53.66	-911.98±7.47	-305.53±11.49
MP	1159.78±30.67	829.01±8.55	-2122.05±96.64	-332.49±33.21

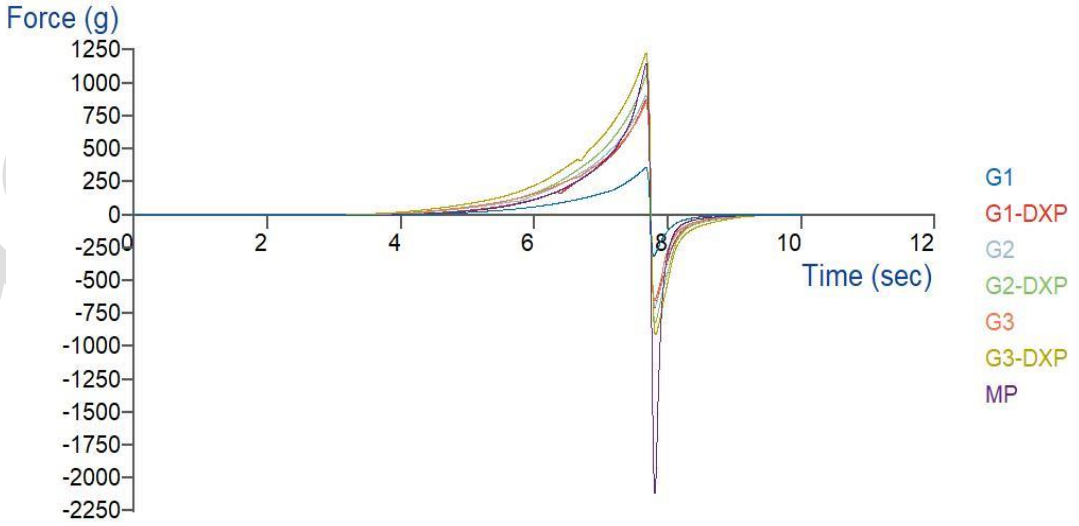

Figure 1. Graphical results of spreadability tests

In one study, scientists made fish-oil-based oleogels for the topical administration of bethametasone dipropionate. As a result, many types of oleogels were produced and described. Spreadability characteristics of produced formulations were measured and evaluated as part of a formulation characterization study. Some oleogels had enhanced firmness levels, according to the results. Results assessed as higher hardness values are associated with lower spreadability behaviors [43]. Another study utilized the loading of capsaicin into lipid-based nano colloidal topical carriers to enhance analgesic potency and lessen cutaneous irritation. Formulations were then added to the Carbopol 934 gel system. Spreadability experiments were carried out to assess the formulation's compatibility with the skin's surface. Results revealed that lower values for firmness, work of shear, and work of adhesion were considered to be more suitable for patient use [44]. Additionally, a correlation between our spreadability test results and the literature was observed. In comparison to G2 and G3

formulations, G1 formulations had lower spreadability values. G1 formulations exhibit good patient compliance because of this.

Ex vivo Bioadhesion Studies

In terms of how well a gel-based formulation adheres to a biological surface (skin), bioadhesion is a crucial component. Its foundation was the idea of measuring the force necessary to rupture the adhesive link between a model membrane and the test formulation (Table 5). Figure 2 shows the textural analysis of prepared hydrogels.

Table 5. Results of *ex vivo* bioadhesion experiments

Formulation	Peak Force (Adhesiveness) (N)	Work of Adhesion (N.sec)	Debonding Distance (mm)
G1	1.13±0.18	0.54±0.00	7.24±0.24
G1-DXP	0.74±0.12	0.65±0.18	5.39±0.06
G2	0.70±0.11	0.79±0.02	14.28±2.97
G2-DXP	0.51±0.05	0.50±0.06	8.20±3.99
G3	0.34±0.00	0.34±0.11	7.88±1.28
G3-DXP	1.05±0.06	0.52±0.02	5.02±0.34

Based on the aforementioned bioadhesion findings, it was found that G1 and G1-DXP hydrogels demonstrated substantial spreadability and bioadhesion, which is ideal for a formulation designed for dermal applications. Additionally, G1-DXP hydrogel had a longer residence time, indicating that the substance stays at the application site for a longer amount of time**.**

The establishment of hydrogen bonds between the functional groups of the bioadhesive polymers and the skin is generally thought to be what produces the adhesion force, not the interpenetration of the Carbopol Ultrez® chains into the skin, which is thought to be what produces the adhesion work. Therefore, the bioadhesiveness should enhance when Carbopol Ultrez content is increased [45]. According to our findings, the formulation with less concentration had better bioadhesive qualities. It is because drug-loaded G2 and G3 formulations and blank samples both displayed greater hardness levels. The formulations' rigidity may reduce how well the polymer interacts with the skin [38].

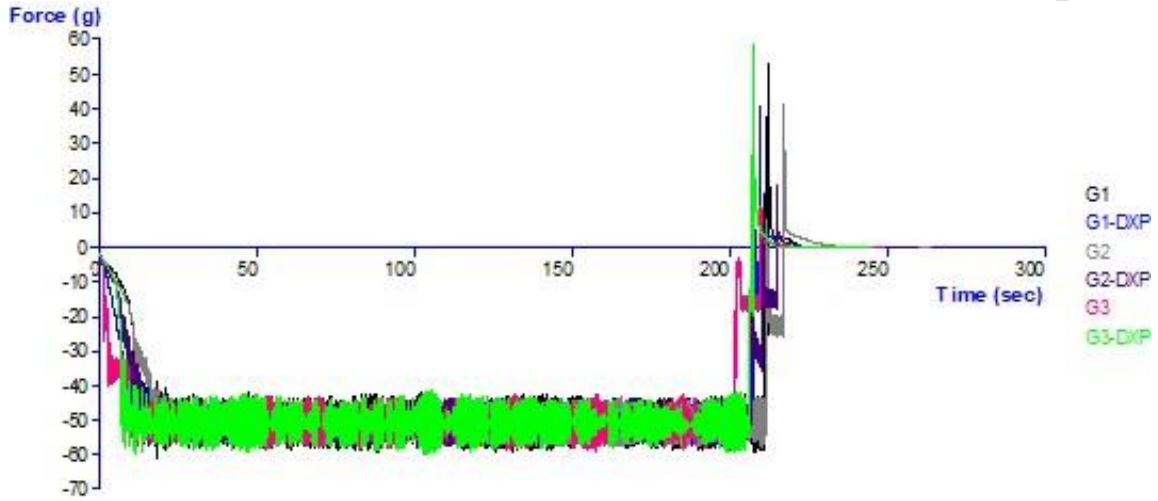

Figure 2. Graphical results of bioadhesion studies

Additionally, the results of the bioadhesion do not correlate with the adhesiveness values found from TPA analysis. It is as a result of the absence of biological membrane (skin).

In vitro Release Studies

DXP hydrogels of G1-DXP, G2-DXP, and G3-DXP as well as a commercial product had their *in vitro* release tested. The investigation was carried out at 32°C using PBS (pH 7.4) as the release medium, and Figure 3 displays the findings. The state of the sink was also preserved.

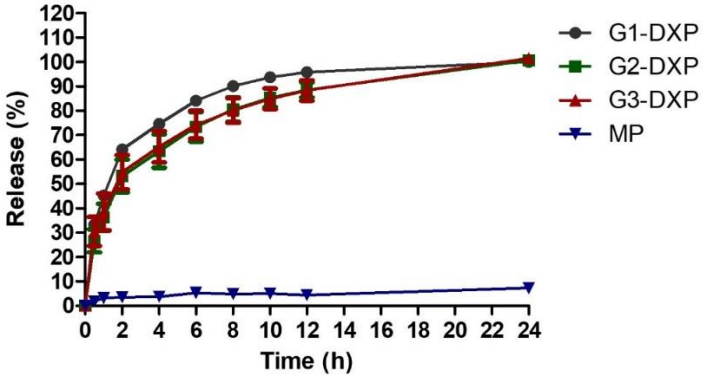

Figure 3. Results of *in vitro* release studies

The drug was released in the following amounts within the first hour: 45.237%, 36.311%, 38.570%, and 3.241% for the formulations G1-DXP, G2-DXP, G3-DXP and MP, respectively. The MP released 7.358% of the drug to the medium at the conclusion of the 24-hour period, while the remaining formulation had reached 100%. MP is a product in the ointment type. Hydrogels demonstrated enhanced release compared to commercial product since they are simple to moisten by the release medium.

To improve *in vivo* absorption characteristics, DXP loaded carboxyvinyl derivatives (Carbopol 980 and Ultrez 10) and poloxamer (Lutrol F 127) were employed as the hydrogel foundation in one research. The *in vitro* release characteristics of DXP from the gel basis were also compared to those of the commercial product (cream). The study's findings, which were consistent with our findings, demonstrated that commercial products released the least amount of DXP over the course of a 24-hour period as compared to gel formulations [46]. Another research looked at how different vehicles affected the pharmaceutical availability of different antirheumatic drugs and tried to create the best technique for cutaneous application. Due to this, the *in vitro* release of indomethacin and diclofenac sodium from several drug carrier systems, including ointment, cream, and gel, was assessed. The study's findings showed that our formulations had a comparable *in vitro* release pattern [47]. Another study looked at the skin's ability to absorb capsaicin and nonivamide from hydrogels both *in vitro* and *in vivo*. Hydrogels and a variety of commercially available capsaicin creams were also contrasted. Results demonstrated that hydrogels released drugs more effectively than cream formulations, which is consistent with our findings [48].

The calculated difference and similarity factor for pair-wise intraformulation comparisons are shown in Table 6. All formulations were found to be similar.

Table 6. Difference (f_1) and similarity (f_2) factors for DXP loaded gel formulations

Release Method	Reference Formulation	Test Formulation	f_1	f_2	*Dissolution Profile*
Dialysis Bag	G2-DXP	G1-DXP	6	59	Similar
	G3-DXP	G1-DXP	6	58	Similar
	G3-DXP	G2-DXP	1	97	Similar

In vitro Release Kinetic and Mechanism

Cojocaru et al. claim that in order to comprehend the release characteristics, the drug release data should be matched with an appropriate mathematical model. In fact, as the r2 grows with the number of included parameters, the modified coefficient of determination should be used when comparing models with numerous parameters [49]. To describe the kinetics of drug release from the test gels and the commercial product, zero-order, first-order, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas models were used. Before doing linear regression analysis for each case, the data were transformed.

Table 7. Fitting various mechanism models to the release kinetics of DXP loaded gels

Formulations	**G1-DXP**			**G2-DXP**			**G3-DXP**			**MP**		
Models	**r^2**	**n**	**m**	**r^2**	**n**	**m**	**r^2**	**n**	**m**	**r^2**	**n**	**m**
Zero-Order	0.5515	45.825	3.3052	0.6752	36.905	3.545	0.6701	38.447	3.4667	0.7002	2.3912	0.2296
First-Order	0.8001	37.682	53.03	0.8696	30.058	53.592	0.8468	32.035	51.913	0.75	2.1233	3.165
Higuchi	0.834	23.586	20.319	0.9174	15.544	20.657	0.9128	17.499	20.228	0.8686	1.1384	1.2782
Hixson-Crowell	0.2908	1.1095	-0.1029	0.3499	1.0464	-0.1077	0.3351	1.3019	-0.1069	0.3363	2.7588	-0.043
Korsmeyer-Peppas	0.9984	0.4704		0.9984	0.4704		0.9866	0.4222		0.8686	0.2884	

The Hixson-Crowell model may generally be used to examine drug formulations with a range of particle surface area and diameter. The zero-order law can be used to find drug delivery methods where the drug dissolves slowly independent of the initial drug concentration and where the medication does not increasingly deteriorate. The first-order rule, on the other hand, works better in systems where the initial drug concentration affects drug release. Finally, the release brought on by drug diffusion from the matrix via pore generation is consistent with Higuchi's hypothesis [50].

The effectiveness of each model in representing the drug release kinetics was evaluated using the r^2 calculation. The outcomes of fitting the *in vitro* release data into several kinetic models are displayed in Table 6. Our results showed that all formulations including commercial product were fitted to Higuchi's model.

In order to identify the release mechanisms for these formulations, the Korsmeyer-Peppas model was once more used in an *in vitro* DXP release behavior analysis. These mechanisms were Fickian (nonsteady) diffusional release when $n \leq 0.5$, case-II transport (zero-order) release when $n \geq 1$, and non-Fickian, "anomalous" release when n is between 0.5 and 1 [51]. As a result, in this work, all formulations including marketed product showed Fickian diffusional release processes since "n" values were smaller than 0.5.

Our project's objective was to develop topical gel formulations with quality and amount of chemicals that produce gel structures with sufficient mechanical strength and stability. According to acceptable rheological/mechanical characteristics and *in vitro* drug release, the G1-DXP formulation was discovered to be a successful topical drug delivery method. To conclude, G1-DXP may be a successful substitute for formulation for cutaneous applications. To corroborate the findings of this study, more *ex vivo* and *in vivo* research is needed.

AUTHOR CONTRIBUTIONS

Concept: E.Ş.Ç., G.K.G., N.Ü.O.; Design: E.Ş.G., N.Ü.O.; Control: E.Ş.Ç, G.K.G., N.Ü.O.; Sources: E.Ş.Ç, G.K.G., N.Ü.O.; Materials: E.Ş.Ç., G.K.G., N.Ü.O.; Data Collection and/or Processing: E.Ş.Ç., G.K.G., N.Ü.O.; Analysis and/or Interpretation: E.Ş.Ç, G.K.G., N.Ü.O.; Literature Review: E.Ş.Ç., G.K.G., N.Ü.O.; Manuscript Writing: E.Ş.Ç., G.K.G., N.Ü.O.; Critical Review: N.Ü.O.; Other:-

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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