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"Nothing exists until it is measured."

Niels Bohr

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JPharmTech

Editor's Note

Dear Pharmaceutical Technology Researchers,

We are excited to be with you in this new issue of **JPharmTech**. The purpose of our journal is to inform the all pharmaceutical scientists about all latest and important research on drug development. **JPharmTech** will publish papers that focus on the research, development and evaluation of pharmaceutical delivery systems. The journal includes topics such as preformulation, drug delivery systems and targeting, formulation design, preparation, *in vitro* and *in vivo* characterization, pharmacokinetics, pharmacodynamics, biopharmaceutics and more.

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I want to thank you to the all of my friends who studied for those processes that are mentioned above. By the valuable contribution of our friends in the publishing team, this was a successful start for our journal.

Our main goals are having a strong international editor and referee team, to increase the recognition and index number of the **JPharmTech** and to be one of the most cited journals. That's why, your contribution and support to our journal with your papers and refereeing, are really important and valuable for us.

Thank you in advance & Best regards,

Müzeyyen Demirel

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The introduction section of the articles (particularly research articles) should include the following topics;

- establish current knowledge of the field,
- summarize previous research, providing the wider context and background and the importance of the current study,
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Acknowledgments

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All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work. If no conflict exists, the authors should include the "The authors declare no conflict of interest." statement under this section.

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Citation in text must be numbered as [1] or [1-5]. Please ensure that every reference cited in the text is also present in the reference list. References should be accurate and numbered sequentially [in square brackets] in the text and listed in the same numerical order in the reference section with the DOI link. All authors must be cited and there should be no use of the phrase et al. The abbreviations of the journal names should be used. No references sould be given for the abstract section. Date of access should be provided for online citations. Furthermore, the references can easily be edited with the **JPharmTech** EndNote Style.

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Journal

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RESEARCH ARTICLE

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Preliminary study for the development of potent hydrogels for local drug delivery applications

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ABSTRACT

Currently, design and development of formulations for the oral cavity and local application is a rather challenging process since the components should be non-irritant and provide relief. Hydrogels-based drug delivery systems have been proposed as suitable candidates for oral mucosal (eg, buccal, sublingual, palatal, gingival) and local (dermal) drug delivery (eg, wound dressings). Herein, the hydrogels were prepared by Carbopol 934, Sodium carboxymethyl cellulose as well as their combination blends to develop efficient hydrogels with tunable activities. The hydrogels were characterized in terms of tensile testing, and physicochemical properties (pH, clarity). Fourier-Transformed Infrared Spectroscopy (FT-IR) was used to evaluate any possible interactions between the components or any newly developed by-products which can lead to toxicity. The F2/F5 formulation, pH (5.86±0.084), viscosity (13305±1209), firmness (39.92±0.77), consistency (356.27±9.01), cohesiveness (-28.58±0.81), and work of cohesion (-231.31±15.02) values were found to be the most suitable formulation. According to the results and the use of biocompatible ingredients, the prepared hydrogels present promising characteristics being suitable candidates for mouth application. Future studies will involve the loading of active molecules and studying their properties.

1. INTRODUCTION

Conventional formulations such as pills, tablets, capsules, etc. are suitable for specific diseases since mouth diseases and wounds require the topical application of the drug in the affected area. Moreover, conventional drug delivery systems have shown reduced therapeutic efficacy, require repeatable doses to achieve the therapeutic outcome diminishing patient compliance and resulting in possible toxicity [1]. Thus, the preparation of innovative formulations that can achieve controlled drug release and reduced toxicity is a very significant field for pharmaceutical technologists. Local drug delivery is suitable for diseases of the mouth or wounds since it acts in the desired tissue lowering the possibility of adverse effects [2-4].

There are various reported disorders of the oral cavity such as ulcers (malignant, traumatic), sores, stomatitis, oral infections from pathogens (fungi, bacteria viruses) [5-7] that should be treated to avoid any harmful events. Recurrent aphthous stomatitis is among the most common mouth diseases which affect many people; it is a painful condition described as sores of grayish-white pseudomembrane surrounded by an erythematous halo [8,9]. It has been reported that its pathogenesis is unknown and thus aphthous stomatitis treatment options mostly aim to reduce the symptoms and their duration. Various drugs have been proposed for therapeutic management as antibacterial, anti-acidic, and antineoplastic agents as well as anti-inflammatory and immunomodulatory agents [8,10,11]. Semisolid, liquid and solid formulations are the most commonly used types of drug carriers designed for the oral cavity; nonetheless, they present low retention time requiring frequent installation. Thus, the gelling systems (*in situ* gels, hydrogels, etc.) are proposed as efficient carriers for oral cavity disorders since their gelling capacity can prevent them from being swallowed [3,12,13].

Another drug delivery route that belongs to local drug delivery is that of wound or dermal delivery [14,15]. Wounds are derived from injury of the skin that normally healed. However, if the wound healing process is impaired for any reason, the wound will heal slowly or not healed at all. Chronic wounds can be colonized by fungi, bacteria, or virus resulting in medical health conditions as bacteremia, or sepsis that can be fatal [16,17]. Wound management could cost massive expenses to health systems. Consequently, medical practitioners carefully examine wounds to provide the most effective wound dressing [18,19]. Wound dressings are applied on the open wound while various dressing types

have been identified. For example, foam, gels, alginate, collagen, and other dressings are used in clinical practice [20]. Other innovative dressings might include nanoparticles, natural plants, drugs, or other biological agents that can accelerate the wound healing progress [16,21,22]. Hydrogel-based membranes are widely applied as wound delivery carriers [23,24]. The use of topical dressings derived from polymers with hydrogel properties has been studied as a prophylactic procedure to prevent systemic infection [15,25].

Gel-based systems i.e. hydrogels have been proposed for both local and systemic treatment applications due to their biocompatibility and tunable properties such as controlled release, biodegradability [26]. Hydrogels are comprised of a network of cross-linked hydrophilic chain polymer that is hydrophilic that can find as a colloidal gel in water. Water acts as the dispersion medium and should constitute at least 10% of the total volume so as the material to be a hydrogel [27]. The hydrogels can undergo a sol-gel phase or volume phase transition due to physical and chemical stimuli response. More specifically, temperature, electric and magnetic fields, solvent composition, pressure are physical stimuli, whereas pH and ion changes are chemical stimuli [28 -31]. This transition is mostly reversible since as soon as the trigger factor removes the hydrogels can return to their initial form [27]. Various synthetic and natural macromolecules have been employed for hydrogel preparation. Carbopol (CP) is a high molecular weight, hydrophilic, and cross-linked polyacrylic acid polymer which can become swollen when contacted with water [32]. CP-based hydrogels have been reported as potential systems for oral mucoadhesive drug delivery [33,34]. Carboxymethylcellulose (CMC) is an anionic hydrophilic cellulose derivative bounding with carboxymethyl groups. CMC is used in syrup and sauce formulations to increase viscosity while it has been widely found in drug delivery and tissue engineering applications [35-37]. CMC is mostly used as its sodium salt (Na-CMC). In this study, we have conducted preliminary work on the development of potent hydrogels for potential local drug delivery applications. Two polymers (CP and Na-CMC) were chosen for the preparation of hydrogels which can potentially be applied as local formulations considering their biocompatibility and toxicological safety profile. Also, the pure hydrogels blended to form mixtures with different mechanical properties and pH values.

2. MATERIALS AND METHODS

2.1. Materials

Carbopol (CP) 934 and sodium carboxymethyl cellulose (Na-CMC) were purchased from Doğa İlac, Turkey. In the study, distilled aqueous media was applied. The other chemical reagents and solvents were of analytical grade.

2.2. Methods

2.2.1. Preparation of the hydrogels

The preparation of gel formulations was conducted using different concentrations (0.5%, 1.0%, 1.5%, w/w) of CP 934 and Na-CMC. The polymers and the water were added to the beaker and mixed with magnetic stirring for 3 hours. F1/F4, F2/F5, and F3/F6 formulations (blended hydrogels) were prepared by mixing 50% w/w from each formulation and magnetically stirred for 3 hours. **Table 1** depicts the composition of the developed hydrogels.

Table 1. *Composition of the developed hydrogels*

Code	Concentration % (w/w)		
	Carbopol (CP) 934	Carboxymethyl-cellulose (Na-CMC)	Water
F1	0.5	-	99.5
F2	1.0	-	99.0
F3	1.5	-	98.5
F4	-	0.5	99.5
F5	-	1.0	99.0
F6	-	1.5	98.5

2.2.2. FT-IR spectroscopy analysis

The prepared hydrogels were subjected to FT-IR analysis using ATR-FTIR (Attenuated Total Reflection Fourier Transform Infrared) spectroscopy (FTIR-spectrometer FTIR-2000 (Perkin Elmer, USA). FT-IR spectra were recorded over a spectral region from 4000 to 400 cm^{-1} to ascribe the function groups of the hydrogel samples [38].

2.2.3. Appearance

The developed hydrogels were inspected visually for their clarity, color, and particle content.

2.2.4. pH measurement

The pH values of the hydrogel formulations were determined by a digital pH-meter (Mettler Toledo, Switzerland). The electrode was inserted into the hydrogel and constant value was noted. The measurements were repeated three times at 25±0.5 °C.

2.2.5. Viscosity

The viscosities of hydrogel formulations were measured using Brookfield RV-10 viscometer at 25°C (Brookfield, USA).

2.2.6. Mechanical properties

The mechanical properties tested using a software-controlled penetrometer TA-XT Plus Texture Analyzer (Stable Micro Systems, Surrey, UK) equipped with a 5 kg load cell. Each formulation (50 g) was transferred to a 100 mL beaker and left in an ultrasonic bath for about one hour to remove air bubbles. In the study using a Perspex probe of 10 mm diameter; the test was carried out at a pretest speed of 2 mm/s, post-test speed of 2 mm/s, test speed of 2 mm/s, trigger force of 0.001 N, compression depth to the gel in each operation of 10 cm, delay period between two compressions of 10 s. The mechanical properties of all hydrogels were calculated using the Texture Exponent 4.0.4.0 software package of the instrument [25,26]. All experiments were repeated three times at 25±0.5°C [39-41].

3. RESULTS AND DISCUSSION

CP and CMC were chosen to prepare hydrogel formulations due to their hydrophilicity, biocompatibility-biodegradability as well as mucoadhesion properties [31,42,43]. Throughout the literature, various concentrations of the polymers were used for the preparation of hydrogels; herein, we decide to choose three different concentrations

(0.5%, 1%, 1.5%, w/w) for pure hydrogels while the blends of hydrogels were developed using 50% of the pure hydrogels. The blending procedure has been identified as a suitable process for obtaining formulations with different properties. Most of the physicochemical values of the blends were between the initial values.

3.1. FT-IR Spectroscopy Analysis

The evaluation of pharmaceutical formulations using FTIR spectroscopy is a very significant process since FTIR can show possible interactions between the components. Such interactions can affect the release process, physicochemical even *in vivo* behavior of the formulations. Herein, the hydrogels follow the typical spectrum of their original compositions. Two different polymers known to develop hydrogels when contacted with water were used, herein: Na-CMC and CP 934. Na-CMC is the sodium salt of carboxymethyl cellulose while CP 934 is a high molecular weight of cross-linked polyacrylic acid.

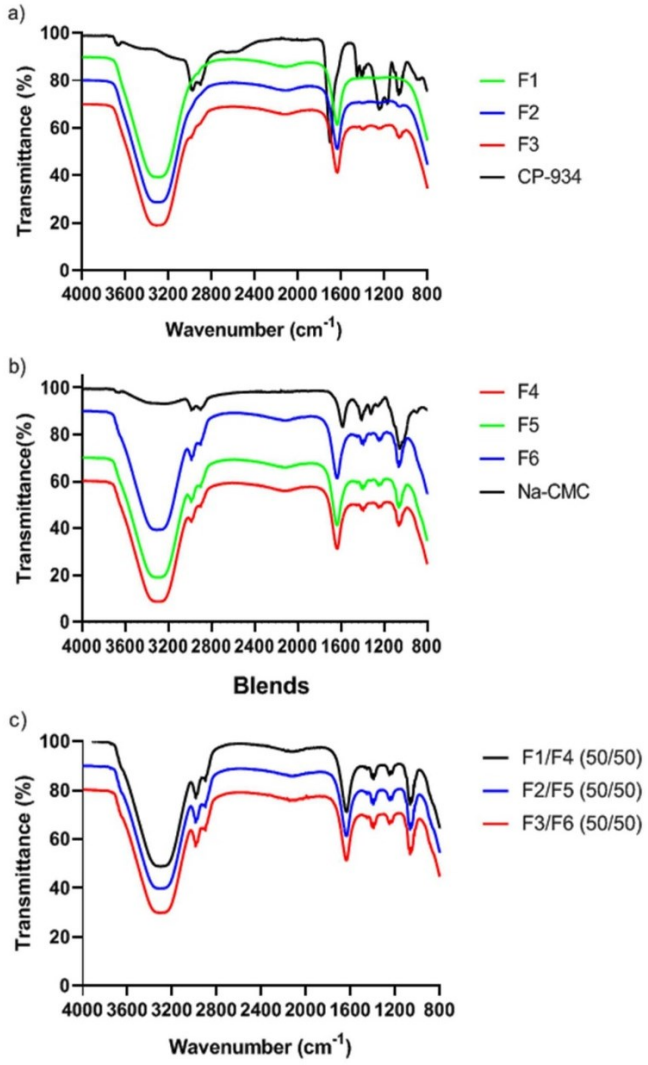

Figure 1. *FT-IR spectroscopy analysis of (a) F1, F2, F3 hydrogels and pure CP 934; (b) F4, F5, F6 and pure Na-CMC; (c) blends between F1 and F4, F2 and F5 as well as F3 and F6*

Figure 1a shows the spectra of CP 934 and the hydrogels of different concentrations of CP 934 (F1, F2, and F3). As was expected, the F1, F2, F3 formulations mostly follow the spectrum of pure CP 934. Pure CP 934 depicts at 3000-2950 cm^{-1} the OH stretching vibration whereas at 1717 cm^{-1} was assigned the carbonyl C=O stretching band. Moreover, the band at 1237 cm^{-1} represents the C-O-C peak for acrylates [25,44]. The hydrogels present a broad sharp band at 3300 cm^{-1} due to water content. **Figure 1b** exhibits the FTIR spectrum of carboxymethyl cellulose sodium salt and F4, F5, F6 Na-CMC spectrum demonstrated a band at 2920 cm^{-1} representing the C-H anti-symmetrical stretching while at 1600 and 1408 cm^{-1} the bands due to carboxylate groups stretching vibrations (symmetric and asymmetric) are seen. At 3400 cm^{-1} the presence of OH band is also depicted. In the case of the formulations, F4, F5, and F6 represent a similar spectrum with Na-CMC with the only difference that the band at 3400 is sharp due to water presence [45]. It can be said that the prepared hydrogels did not exhibit any new peaks indicating stability and compatibility. **Figure 1c** depicts the spectra of the blends between F1 and F4, F2 and F5, F3, and F6. It is well reported that blends are widely used in pharmaceutical technology since they can be useful for enhancing the properties of each component. Also, the blending can differentiate drug release and *in vitro/in vivo* performance of the formulation (**Figure 1c**) [46,47]. Herein, 50% of each hydrogel was blended with another hydrogel to produce blends of them and examine their mechanical properties. The blends did not exhibit any interesting differences or any new peaks. The blends mostly followed the spectra of both excipients while the absence of new peaks indicates that new bonds were not depicted. Thus, the prepared blends would be stable and by-products being harmful to the oral mucosa or skin were not detected.

3.2. Appearance and pH Measurement

All gels were described as transparent when visually checked. **Table 2** summarizes the pH and clarity values of the hydrogels. As was expected, the formulations developed by CP (F1, F2, F3) presented pH values around pH 4 and the Na-CMC (F4, F5, F6) were around pH 8.

Table 2. *pH and clarity values of the hydrogels and their blends*

Code	pH	Clarity
F1	4.45±0.091	Transparent
F2	4.15±0.042	Transparent
F3	3.78±0.021	Transparent
F4	8.18±0.106	Transparent
F5	8.42±0.007	Transparent
F6	8.38±0.247	Transparent
F1/F4 (50/50)	5.94±0.007	Transparent
F2/F5 (50/50)	5.86±0.084	Transparent
F3/F6 (50/50)	6.05±0.120	Transparent

The blends of the hydrogels exhibited higher pH values than CP-based hydrogels and lower than Na-CMC values. The pH of the blends was found between the values of initial polymers. F1, F2, and F3 have acidic pH values and F4, F5, F6 have basic pH values. Normal pH value of oral cavity is 6.8 [48,49]. The normal skin pH is 5.0-5.5 [50], but depending on the area, it may vary [51]. Generally, the pH values of the blended hydrogels were similar to that of human skin pH and oral cavity pH indicating that the hydrogels could be applied as topical wound dressings and oral cavity applications. So F1/F4, F2/F5, and F3/F6 (blended hydrogels) were more appropriate for local application due to their better pH values.

3.3. Viscosity

The viscosity of hydrogels is a very significant feature for patient compliance, so the hydrogel is given for oral mucosa and local application should not be too fluid. A low viscosity product may spread in the application area and leak out. Too high viscosity can cause application difficulties [52]. Different viscosity values were presented in **Table 3**. In general, CP polymers are polymers of acrylic acid, cross-linked with polyalkenyl ethers or divinyl glycol. In several experiments, their neutralized aqueous dispersions demonstrated a high viscosity. It was found that a pH range of 5.0-9.0 usually leads to the formation of highly viscous systems [53]. In a study, the increase of pH in various concentrations of CP gels showed increased viscosity. Also, CP gels showed the highest viscosity when neutralized to pH 6.0 [54]. Because of these reasons, F3/F6 had the highest viscosity (the reason is the highest and alkaline pH value that comes from the polymer of Na-CMC) in our study. On the other hand, the viscosity of F4 was found to be very low. Şenyiğit et al. has reported that the viscosity of hydrogels increased as polymer concentration increased [41]. In our study, as the polymer concentration increases, the viscosity found high, as expected. When Arpa et al. compared gels containing CP and Na-CMC in the same ratio, they found that the viscosity of hydrogels containing CP was higher [31]. Similarly, in our study, CP hydrogels (F1 and F2) showed higher viscosity values when compared to Na-CMC hydrogels (F4 and F5). Based on the viscosity and visual assessment, Gull et al. concluded that the hydrogel prepared with 1.0% w/w CP 940 (4412 cP) was less viscous to be called a gel, and hydrogel prepared with 2.0% w/w CP 940 (28197 cP) was a stiff gel which can create a problem during the topical application and handling. Hence, these two formulations were not considered for further studies and they selected hydrogel prepared with 1.5% w/w CP 940 (14097 cP) [55]. Similarly, in our study F1, F4, F5, and F1/F4 were less viscous to be called a gel. F3/F6 was a stiff gel that can create a problem during the application and handling. So, we selected F2, F3, F6, and F2/F5 due to their better viscosity values.

Table 3. *Viscosity values of the hydrogels and their blends*

Code	Viscosity (cP)
F1	4670±310
F2	10647±255
F3	15157±692
F4	444.8±11.5
F5	4272±40
F6	19087±51
F1/F4 (50/50)	1056±62
F2/F5 (50/50)	13305±1209
F3/F6 (50/50)	138667±1858

3.3. Mechanical Properties

The mechanical properties such as firmness (hardness), consistency, cohesiveness, and work of cohesion of gels that contain different ratios of CP 934 and Na-CMC were examined in this study. Mechanical parameters in texture studies are known to provide information on the performance of hydrogel formulations and have been used to identify formulations that may be suitable for applications. Texture analyses provide knowledge on transferring or applying the semi-solid formulations from the measured parameters of a pharmaceutical formulation [56].

The amount of gelling agent in a formulation is extremely important for its textural properties [57]. Gel firmness, which expresses the applicability of the gels to the skin, is directly correlated to the polymer concentration [57]. Hydrogels should possess specific mechanical properties since they should easily apply to the administration site, remain in the tissue for the desired time, and be easily removed from the package. Subsequently, mechanical testing properties should be evaluated. **Table 4** summarizes the mechanical properties of hydrogels. The difference is very rational given that CP has been reported to produce firm hydrogels [58]. The firmness and consistency of CP and Na-CMC hydrogels seem to increase with increasing polymer concentration. Similarly, Yang et al., Cevher et al., and Arpa et al. found an increase in gel firmness by increasing Carbopol concentration [31,57,59]. Also, the firmness values of the Na -CMC gels prepared by Jones et al. and Arpa et al. increased as the Na-CMC concentration increased [31,60]. Also, the formulations consisted of Carbopol (F1, F2, F3) exhibited a higher firmness value than the formulations based on Na-CMC (F4, F5, F6). Consequently, blending CP hydrogels with Na-CMC can improve the low firmness values of Na-CMC hydrogels. Similar to our study, the firmness of the formulation containing Carbopol was found higher than the formulation containing the same proportion of CMC in previous studies [31,61]. Besides, it has been claimed that the firmness values of Na-CMC hydrogels are enhanced by enhancing carboxymethyl substitution, molecular weight, and polymer concentration [62]. For this reason, F6 is the firmest amongst F4, F5, and F6. Also, Abouhussein et al. reported that an increase in consistency for gels prepared at higher concentrations of CP and Na-CMC and the consistency value higher in gels containing CP than gels containing Na-CMC at the same rate, similarly to our study [63]. Similarly, one study found that the consistency of the formulation containing CP was higher than the formulation containing the same proportion of Na-CMC [64]. Cohesiveness and work of cohesion of CP and Na-CMC hydrogels seem to decrease with increasing polymer concentration. Cohesiveness is expressed as the structural reconstitution of the gel after application. If the gel-forming polymers are capable of attracting their molecules, they show high cohesiveness values [40]. According to the results of the studies, it was found that the cohesiveness values of the hydrogels decreased by increasing polymer concentration. Similarly, Cevher et al. and Tan et al. reported a reduction in gel cohesiveness for CP gels with increasing concentration of the polymers [59,65]. The adhesive properties of the polymers used in the preparation of gels are of great importance in this respect. It was concluded that as the polymer concentration increased, the adhesive properties of the gels increased [40,41,66]. In general, it has been observed that the work of cohesion value increases as the concentration of polymers increases.

Firmness is the maximum positive force required to attain a given deformation [67]. It introduces the necessary force to

Table 4. *Mechanical properties of hydrogels*

Code	Firmness (g.Force)±SD	Consistency (g.sec)±SD	Cohesiveness (g)±SD	Work of Cohesion (g.sec)±SD
F1	112.33±3.25	854.62±5.92	-72.48±4.16	-590.65±14.27
F2	262.41±10.63	1715.54±158.58	-160.65±11.00	-1041.73±69.88
F3	335.10±9.06	2457.13±143.48	-220.52±2.45	-1518.12±128.15
F4	15.54±0.01	186.69±4.64	-11.93±0.15	-15.04±0.68
F5	21.71±0.03	196.63±0.46	-17.13±0.02	-38.11±0.57
F6	48.05±0.93	429.61±6.10	-33.33±0.41	-410.98±6.67
F1/F4 (50/50)	19.19±0.14	187.42±0.81	-15.38±0.19	-28.56±0.96
F2/F5 (50/50)	39.92±0.77	356.27±9.01	-28.58±0.81	-231.31±15.02
F3/F6 (50/50)	109.19±1.89	891.32±7.12	-61.64±0.86	-728.78±9.03

ensure the formation of gels. It expresses the applicability of the gel to the desired site [40]. Firmness values should be low so that gel can be easily removed from the container and administrated to the skin surface easily [56,59]. The topical formulations should preferably have high consistency in the container but quickly pour or distribute during the application [68]. Hydrogel formulations are soft consistency and contain excess water [64]. Cohesiveness is described as the work required to deform the hydrogel in the downward movement of the probe [57]. It is a parameter related to the structural reformation following successive shearing stress during application [65]. It is the distance hydrogel travels before detachment [69]. Texture also provides an opinion on cohesiveness, which is a guess of the extent of structural reformation after the utilization of the formulation. Cohesiveness improves the performance of the formulation in the application area. Also, a lower cohesion value is preferred as it indicates that the formulation spreads [56]. If the hydrogel is extremely cohesive and hard, it will be difficult to apply to the skin surface [70]. The work of cohesion represents the work needed to overcome the internal bonds of the material [67]. Accordingly, F4 (15.54±0.01), F5 (21.71±0.03), F6 (48.05±0.93), F1/F4 (19.19±0.14), and F2/F5 (39.92±0.77) have a low firmness value. Among them, F4 (186.69±4.64), F5 (196.63±0.46), F1/F4 (187.42±0.81), and F2/F5 (356.27±9.01) have a soft consistency. Also, F4 (-11.93±0.15), F5 (-17.13±0.02), F1/F4 (-15.38±0.19), and F2/F5 (-28.58±0.81) have low cohesion value that showed the formulation spreads.

4. CONCLUSION

Herein, hydrogel formulations were developed and studied for their mechanical properties so as their potential application for local delivery. Two biocompatible polymers, Carbopol and carboxymethyl cellulose were used from the preparation of the hydrogels. Apart from the pure hydrogels, blends of the Carbopol and carboxymethyl cellulose hydrogels were developed to obtain better physicochemical and mechanical properties. The preliminary results demonstrated that hydrogels can be used for oral mucosa and wound drug delivery in future studies. After all tests were completed, the F2/F5 formulation, pH (5.86±0.084), viscosity (13305±1209), firmness (39.92±0.77), consistency (356.27±9.01), cohesiveness (-28.58±0.81), and work of cohesion (-231.31±15.02) values were found to be the most suitable formulation.

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CONFLICT OF INTEREST DECLARATION

The authors report no conflict of interest. The authors alone are responsible for the content and the writing of the paper.

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