Characterisation and Optimization of Hydrogel Films Loaded with a Hydrophobic Drug

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Abstract

Hydrogel dressings are most often accessible in gel and film forms and are totally fabricated of hydrophilic, expandable, and biodegradable constituents. Since they contain only 70-90% moisture, they should only be applied to top of wounds to soak up superfluous exude. They have numerous advantages in drug delivery, bioengineering, sanitation products, farming, wastewater treatment, textiles, and packaged food. Hydrogels generated from biodegradable polymers and their analogues have been extensively exploited in medication delivery and bioengineering purposes in recent years. In this work, hydroxyethyl cellulose (HEC) hydrogel films were designed using citric acid as a crosslinking agent for the extended delivery of a modelled hydrophobic drug (cannabidiol). The tensile performance and liquid uptake capacity of dressing were augmented by crosslinking. Assessment and comparisons of the swelling, biomechanical, and mucoadhesive characteristics of drug-free and drug-incorporated films was conducted. The swelling and adhesive characteristics of CBD-incorporated films were enhanced. Furthermore, it reflects that citric acid might be utilized to synthesize HEC hydrogel films. The observations taken as a whole hint to the excellent drug-loading and organised emission of poorly soluble therapeutics adopting HEC hydrogel sheets. These results provide promising evidence for the use of hydrogel films as potential wound healing products.

Keywords: Wound healing, wound dressings, hydrogels, hydroxyethyl cellulose, citric acid, cannabidiol, swelling property, tensile strength, adhesion

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1. Introduction

A wound is an opening in the skin, mucous membrane, or muscle that has been induced by an injury. It's significant to ensure wounds are treated and dressed appropriately to minimize the chances of infection and other consequences, which may ensue from a broad array of wounds. Wounds are reported to afflict roughly 1% of the worldwide population. The primary factors are diabetes, cardiovascular events, and vascular illness (1,2). Considering the fact that chronic wounds afflict individuals all over the globe, with a significant number of seniors over the age of 65, mitigating wound complications is imperative in the current healthcare system. Following the first 6 hours, most wounds (especially burns and slits) may remain uninfected; but, with no precautions to protect the site, cutaneous pathogens will gradually permeate and lead to infections. Given that this is case, the very first step in addressing a wound is to disinfect the area using an antiseptic or even merely with plain water and afterwards applying a sterile dressing (3). It is conceivable for some wounds to become infected at the point of their damage immediately, including those engendered from animal bites or those that have debris or grit carried into the area. To minimize the risk of infection, it may be better to leave these wounds uncovered until it has been determined that they have been cleaned thoroughly. When wounds are not properly cleaned before being bandaged, additional infections may occur (4).

Numerous communities of aerobic and anaerobic microbes are present in the majority of wound infections. Bacteria that reside on skin surface include diphtheroid bacilli, gram +ve spore-forming bacteria and gram -ve coliform bacteria, alpha-hemolytic Streptococci, and enterococci, and Acinetobacter. Infections like gangrene that affects the cutaneous and other soft tissues are brought on by the synergistic interactions of such anaerobic and aerobic microbes. These microorganisms usually make up the typical microbial flora (5,6). As a result, numerous skin lesions are often caused by a variety of bacteria. On acute wounds, these pathogenic bacteria create biofilm, which leads to chronic illness. A biofilm is made up of a motile population of several bacterial strains and is surrounded by a robust polymer network rich in carbohydrates and impervious to the penetration of antimicrobials and immune cells. When these microbes reach a crucial colonization stage, whether they are free-moving or included in a biofilm, they are very harmful to wound healing (7).

Cannabidiol (CBD) is among the biological substances known as cannabinoids that have been extracted from Cannabis plant. It is the second most prevalent cannabinoid found in the plant and makes up around 40% of the plant's cannabinoids. Given its ability to reduce inflammation and modulate the immune system, CBD has recently been the subject of the most research (8,9). The pharmacological characteristics of CBD, which include anti-inflammatory and immunomodulatory effects, have paved the way for its usage as a natural remedy for autoimmune conditions including diabetes, multiple sclerosis, and rheumatoid arthritis. Nevertheless, only one CBD drug, Epidiolex, has received FDA approval yet. Innovative hydrogel dressings are anticipated to have the capacity to eliminate ROS as well as lessen inflammatory reactions throughout the wound healing cycle in along with preventing infections and encouraging vasculature. Depending on the ionic cross-linked association of Zn^{2+} ions with alginate polymer (Alg), Zheng et al. devised and created a CBD-based hydrogel dressing (CBD/Alg@Zn) (10,11). According to in vivo research, the CBD/Alg@Zn hydrogel greatly sped up the healing of wounds by preventing inflammatory intrusion, encouraging collagen accumulation and scar tissue, and assisting neovascularization. In

an in vivo study, the impacts of CBD were evaluated on oral chronic wounds (12,13). A 5 mm diagnostic punch was used to create standardized ulcers along the centre of the lower tongue in Wistar rats. Histological analysis showed that, on Day 3 post-injury, wounds treated with CBD had considerably reduced inflammatory ratings compared to control group. On Day 7, though, no indication of this change was noticed. Overall, these results show that CBD possess an anti-inflammatory activity in the initial stages of wound healing, unfortunately, it did not sufficiently ameliorate the clinical condition of oral traumatized ulcers.

Hydrogel films containing a hydrophobic medication (CBD) were the focus of the present investigation, with the goal of characterizing and optimizing their performance.

2.1 Materials

Chemicals used in the experiments are 2-Hydroxyethyl cellulose, β- Cyclodextrin, minimum 98%, Cannabidiol, CBD isolate From Sigma-Aldrich, u.k. provacan, Potassium chloride, KH_2PO_4, Citric acid, Calcium chloride,96%, extra pure powder, anhydrous. Fisher Scientific U.K.

2.2 Preparation of Hydrogel films

2.2.1 Preparation of CBD grafted HEC Hydrogel films

Two beakers were taken and citric acid was added in one and beta cyclodextrin in other, followed by addition of hydroxyethyl cellulose (2% w/v) in each beaker. The beaker was then placed on a magnetic stirrer with 800 rpm at ambient temperature for 3 hours. It was then allowed to rest for 1 hour in order to allow air bubbles to escape before proceeding to the next step. The same procedure was repeated for 3% w/v HEC (14,15). For casting hydrogel films, the above mixtures (20mg of 2% w/v HEC, 30gm of 2% w/v HEC, 20gm of 3% w/v HEC and 30 gm of 3% w/v HEC) were poured into a petri dish of 9cm diameter and films were casted as described below.

- Hydrogel mixtures were poured into a petri dish and placed in an oven for 24 hours at 50 ℃.
- This was followed by curing of dried films for 5 minutes at 145 ℃. They were washed using distilled water and pH was brought to neutral. They were washed again with ethyl alcohol for an hour to remove unreacted elements.
- The films were further dried for a day at ambient temperature and stored in a desiccator for future use. Four different HEC films were obtained:

Table 1: Preparation of four different HEC films

HEC-1 = 20g of 2% w/v HEC
HEC-2 = 30g of 2% w/v HEC
HEC-3 = 20g of 3% w/v HEC
HEC-4 = 30g of 3% w/v HEC

2.2.2 Preparation of drug loaded films:

The hydrogel films are loaded with CBD before being tested for tensile strength, adhesion, water vapour transport rate, swelling capacity, and evaporated water loss. CBD-loaded films were obtained by immersing 3 squares of each film for 1 hour in a mixture of ethanol: distilled water in 8:2 ratios containing 0.05 g of CBD and covering the beaker with parafilm to prevent evaporation of the mixture (16). After an hour, squared films are placed in their correspondingly labeled petri dishes, where tests are carried out at 24, 48, 72, and 96 hours. The drug-loaded films were weighed using a weighing balance and weights obtained are as follows:

Table 2: Weights of drug-loaded films

HEC-1 = 0.346g
HEC-2 = 0.575g
HEC-3 = 0.572g
HEC-4 = 0.869g

These films were then squared by compressing in a square maker; a paper was placed under each film to prevent it from sticking to the square maker and breaking. The resultant squared films had the diameter of 20mm x 20mm. These films were then stored in a desiccator for future use. These squared films were again weighed and weights obtained are as follows:

Table 3: Weights of squared drug-loaded films

HEC-1 = 0.028g
HEC-2 = 0.048g
HEC-3 = 0.040g
HEC-4 = 0.066g

2.3 Preparation of Simulated wound fluid (SWF)

8 grams of sodium chloride, 0.2 grams of potassium chloride, 1.44 grams of Monosodium phosphate, 2.4 grams of potassium phosphate, and 1000 milliliters of de-mineralized water were amalgamated to produce the simulated wound fluid and pH was sustained at 7.5. In order to make certain that all of the constituents were diluted, the beaker was set on a mechanical stirrer and rotated at 400 rpm while being kept at room temp. The obtained liquid was placed in the fridge for subsequent utilization.

2.4 Methods Used for Testing the Blank and Drug Loaded Films

2.4.1 Swelling study

For swelling study, 12 petri dishes are used. Each petri dish is labelled as follows in the table below

Table 4: Swelling studies

HEC-1			**HEC-2**			**HEC-3**			**HEC-4**		
A	B	C	A	B	C	A	B	C	A	B	C

Every square of film was individually weighted in a petri plate, with the weight denoted as W_d. After that, film was submerged in SWF (pH 7.5, at 40°C), sealed, and left uninterrupted for next 24 hours. After removing the films, we wiped out any remaining SWF with some paper towels. Each film's W_s value, representing its inflated weight, was recorded. The films were soaked in SWF for a further 24 hours, and this method was performed again at 48-, 72-, and 96-hour intervals. The equation below was used to determine the capacity for swelling.

$$R_s(\text{g/g}) = \frac{(W_s - W_d)}{W_d}$$

Where, R_s is swelling ratio

W_s is weight of swollen film

W_d is weight of dry film

Measurement is done triplicate to minimise the errors.

2.4.2 Water vapour transmission rate (WVTR)

Twelve scintillated glass vials of 25ml volume and 8mm size were used. Three films of each type were used in this method and labelled as: HEC-1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B, 3C, 4A, 4B and 4C. Every vial was packed with 20 mL of SWF, and then opening was sealed with a flat sheet by applying adhesive. The W_b weight of each vial was assessed to estimate how long each one was heated at 40 degrees Celsius. Each vial was re-weighed as W_{af} before being re-heated in the oven for the next 24 hours. At 48-, 72-, and 96-hour times, the same method was performed once again (17,18). For the purpose of determining the WVTR, the mathematical methodology was used:

$$WVTR = \frac{W_b - W_{af}}{A} \times 10^6 \frac{g}{m^2} day^{-1}$$

Where, W_b is the weight of vial before placing in oven

W_{af} is the weight of vial after taking out of oven

A is the area of mouth of vial

2.4.3 Evaporative Water Loss (EWL):

Twelve square films, three of each type were taken in a petri dish. Every petri dish had 1.5 mL of SWF poured onto it and left at room temp. for 24 hours. After 24 more hours of drying time, the films were weighed as W_i to record their final dry weight. The process was carried out again at 48-hour, 72-hour, and 96-hour intervals, with weights recorded at every interval (19,20). The below equation was applied to determine EWL:

$$EWL\ (\%) = \frac{W_t}{W_i} X\ 100$$

where, W_t is the weight of film after a specific time 't'

W_i is the weight of film after 24 hrs (initial incubation)

2.4.4 Adhesion Test:

2.4.4.1 Preparation of gelatine for adhesion test of the blank and drug loaded films.

A beaker containing 300 mL of de-mineralized water was heated on a stovetop. Once the beaker had achieved the ideal temp., 20.01g of gelatin was poured gently and set down to melt (21). Finally, 20g of this gel was placed onto a petri plate, given a cooling period over 10 minutes, and afterwards refrigeration until it solidified. Adhesive testing was conducted using the resulting gelatin.

2.4.4.2 Method of adhesive test:

Films' adhesive properties and bioadhesion were measured using a texture analyser (TA.HD.plus) (stable microsystem Ltd) equipped with texture exponent 32 software. To emulate the wound surface, 1.5 ml of SWF was put on a gelatin petri plate before being placed on the texture analyzer's fixed apparatus. Film samples were attached to the cylindrical shape probes, which measured 35 mm diameter, by utilizing double-sided scotch tape (22,23).

Films with and without the drugs were put through the test. Throughout the study, three of both types of HEC films were employed. By analyzing the average and standard deviation, we can determine the adhesive characteristics of the films.

2.4.5 Tensile Strength:

The tensile properties of the films were determined using the TA. HD analyzer (Stable Microsystem Ltd, Surrey, U.K.), which has a maximum load of 5 kg for data graphing and makes use of the texture Exponent 32 software for data representation. The films were sized down to 60 mm x 10 mm with a 3D rectangular bar so that they would fit into the texture analyzer grips. The grips were scaled in millimeters, with 10mm

markings at either end. A 40 mm separation is maintained in the center of the film to test its elongation resistance (24,25). The normal thickness of the film is measured. Drug loading property was calculated by examining the tensile strength of drug-incorporated hydrogel films.

2.4.6 Thickness of the films:

Thickness of all the prepared films (20mg of 2% w/v HEC, 30gm of 2% w/v HEC, 20gm of 3% w/v HEC and 30 gm of 3% w/v HEC) were measured using a screw guage and three different readings obtained for each film are tabulated below (26).

Table 5: Thickness of the films

	HEC-1	**HEC-2**	**HEC-3**	**HEC-4**
A	0.7 mm	0.11 mm	0.13 mm	0.125 mm
B	0.75 mm	0.9 mm	0.10 mm	0.17 mm
C	0.8 mm	0.10 mm	0.09 mm	0.15 mm

3 Results and Discussion

Hydrogel films made from HEC, β-CB and citric acid as cross-linking compounds and then loaded with cannabidiol (CBD). Both blank and drug-loaded films were evaluated for swelling capacity, mechanical properties, evaporative water loss (EWL), water absorption (AW), Equilibrium water content (EWC), and mucoadhesive properties

3.1 Swelling test:

After placing the films in SWF (pH 7.5), their swelling behavior was measured, and the medication's influence was examined. For blank films, 2% 30 g HEC films demonstrated minimal swelling capacity of 233.4667 ± 26.85086 at 24 hr interval and 2% 20 g HEC films exhibited maximum swelling index of 459.9333 ± 102.6371 at 24 hr interval. When comparing the swelling capacities of CBD-loaded films, 2% 20 g HEC was found to have the lowest of all at 24th hour (126.8633 ± 38.3022) and the highest among all at 48th hour (696.7767 ± 369.4763). The CBD-incorporated films expanded more effectively than the blank films. The proportions of polymer and citric acid determines the film's ideal swelling capacity. Extensive prior study shows that the presence of hydrophilic COOH moieties in the polymer significantly boosts the composition's swelling index owing to the hydrophilicity of such hydroxyl groups. The increased swelling capacity may be due to the addition of citric acid (27). The chemical composition of β-CD also suggests that cross-linking may improve the 3D network architecture, leading to greater swelling index. The hydrogel's swelling capacity also maximizes as its pores develops. The high porosity of the hydrogel may be accountable, since it creates a sizable volume capable of entrapping a lot of water inside the gel network.

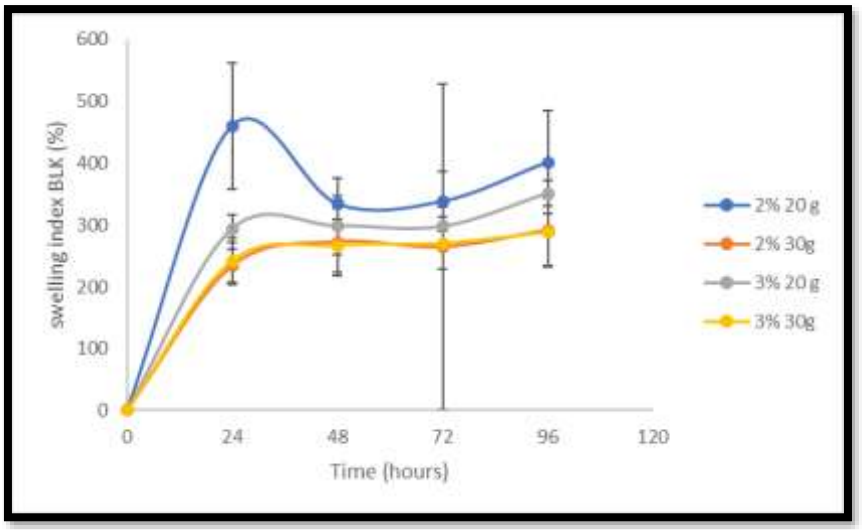

Figure 1. Swelling index for blank films with varying proportions of HEC

For preparing drug loaded films, 0.05 grams of CBD drug is added to the films of same percentages and weights and difference between the swelling index percentage of blank and drug loaded films are observed.

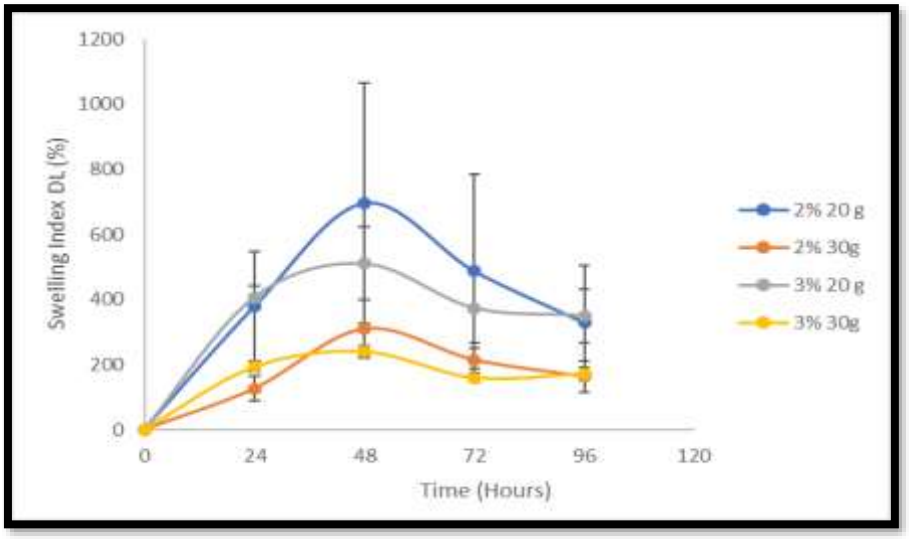

Figure 2. Swelling index drug loaded films with varying proportions of HEC. (n = 3 ± SD)

3.2 Water vapour transmission rate.

Using the mean and standard deviation of the A, B and C triplicates of 2% 20 g HEC, 2% 30 g HEC, 3% 20 g HEC and 3% 30 g HEC.

3.2.1 WVTR of blank films:

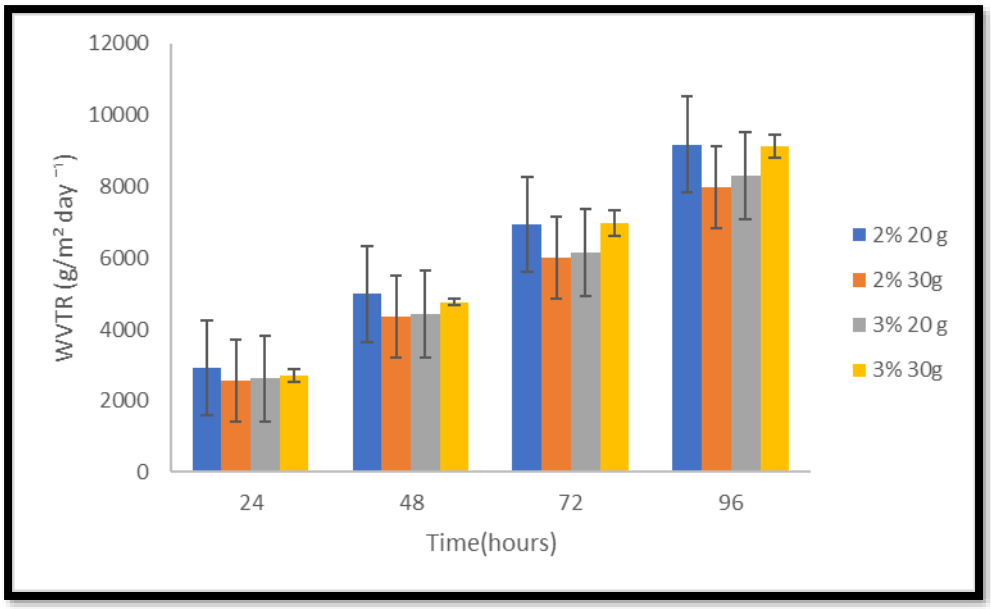

Figure 3. WVTR blank 2% 20 g HEC, 2% 30 g HEC, 3% 20 g HEC and 3% 30 g HEC n=3 ± SD

WVTR of drug loaded films

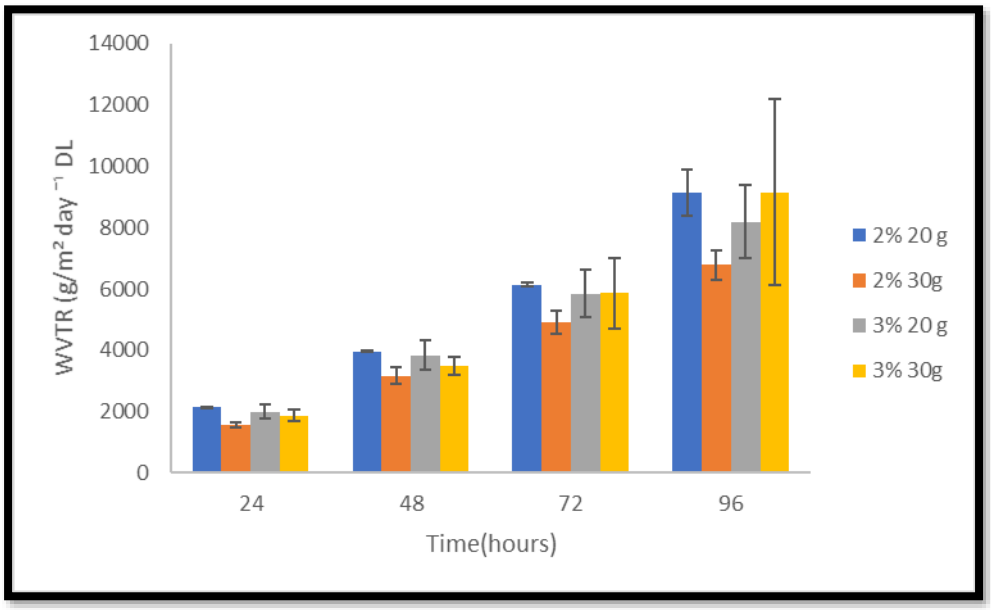

Figure 4. WVTR of drug loaded films with CBD different proportions of HEC, n=3 ± SD

WVTR values of blank films and CBD-loaded films were compared with the help of mean and standard deviation

Among blank films, 2% 30 g HEC films displayed minimum WVTR i.e., 2578 ± 99.83148 at 24 hours interval and 2% 20g HEC films showed maximum WVTR of 9172.76 ± 139.9204 at 96 hr interval (28). For drug-loaded films, 3% 30 g HEC films showed maximum WVTR of 9146.523 ± 3036.645 at 96 hours whereas 2% 30 g HEC films showed minimum WVTR of 1571.667 ± 85.9516 at 24th hr. CBD-

conjugated films demonstrated greater WVTR, spanning between 1571.667 ± 85.9516 at 24th hr and 9146.523 ± 3036.645 g/m2day^{-1} at 96th hr, than BLK films (varying between 2578 ± 99.83148 and 9172.76 ± 139.9204 g/m2day^{-1} at 24th hr and 96th hr, respectively). It is thought that perhaps the inclusion of the medication (CBD) improves cross chain mobility, producing a porous matrix that enables excess water to flow across it.

2.3 Evaporated Water Loss (EWL)

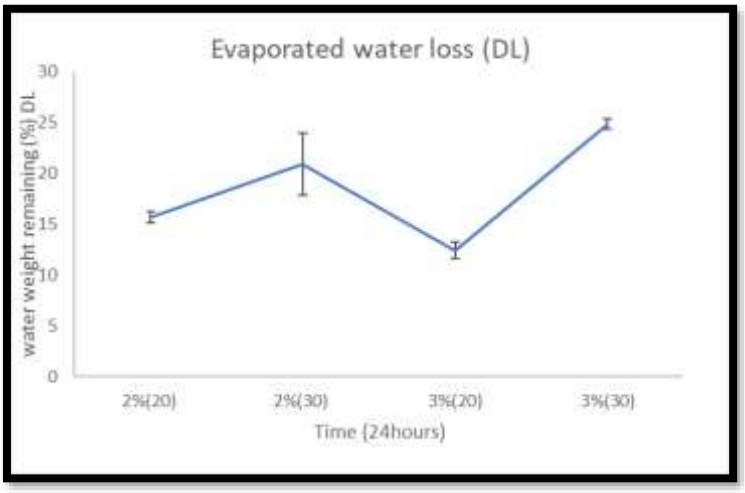

Figure 5. EWL of CBD loaded films

The flow of water molecules across the film is theorized to happen via suitably large pores which randomly develop in the film. CBD-loaded film formulations with the smallest EWL value were the 3% 20g HEC films (12.39667 ± 0.795501) and those with the strongest EWL were the 3% 30g HEC films (24.8 ± 0.509117). EWL improved as the proportion of HEC was raised; this is possibly due to the hydrophilic character of HEC; the stronger the hydrophilicity, the greater the water loss observed in a film (29).

3.4 Eqilibrium Water Content (EWC)

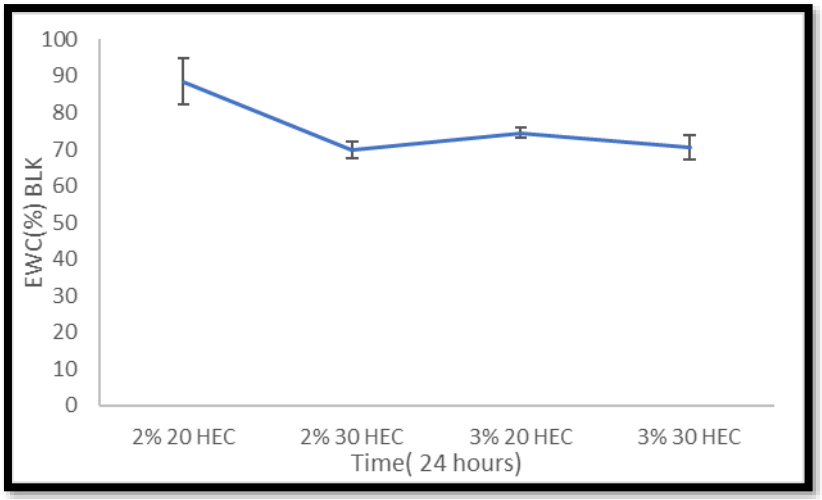

Figure 6. EWC (%) BLK For blank samples at 24 hours

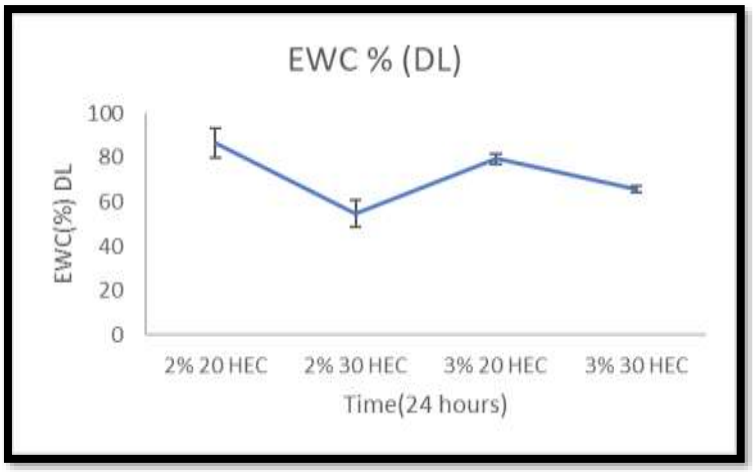

Figure 7. EWC % of CBD-loaded HEC films after 24 hours. n = 3± SD

Among blank films, 2% 20g HEC films showed maximum EWC% of 88.49 ± 6.248904 at 24 hr interval and 2% 30g HEC films showed minimum EWC % of 69.85667 ± 2.275043, as shown in Table 3.18. Among the CBD-loaded films, maximum EWC % at 24 hr interval was shown by 2% 20g HEC films ranging around 86.46667 ± 6.656492. Minimum EWC % was shown by 2% 30g HEC films (54.7 ± 5.939697). Relative to the CBD-incorporated films, the EWC% of blank films was higher, which could possibly be ascribed to the presence of more hydroxyalkyl clusters in HEC.

3.5 Water Absorption (AW) %

3.5.1 AW% of Blank Films After 24 Hours

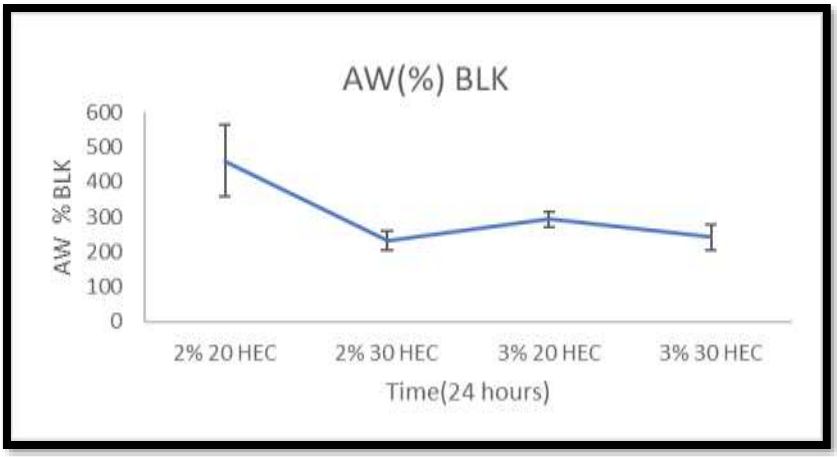

Figure 8. AW% OF blank films at time interval after 24 hours

3.5.2 AW% of CBD-loaded films

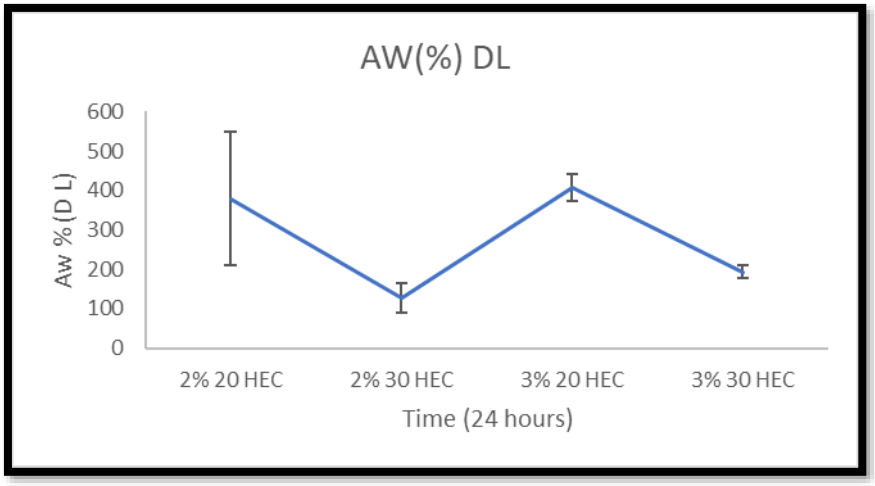

Figure 9. AW (%) of CBD loaded films.

3.6 Adhesion Test

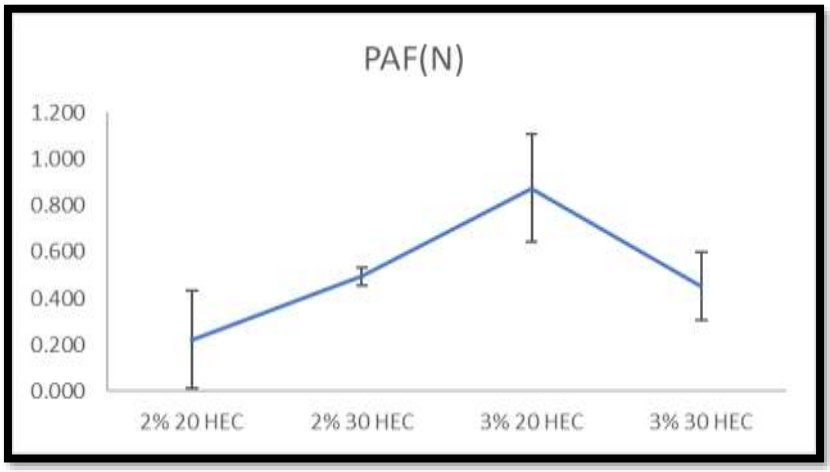

Figure 10. Peak adhesive force of blank films

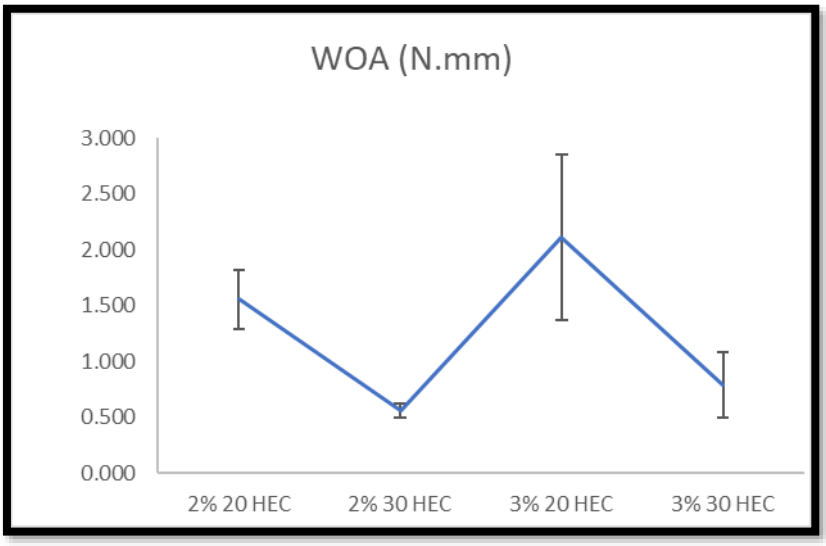

Figure 11. Work of adhesion (WOA) for blank films

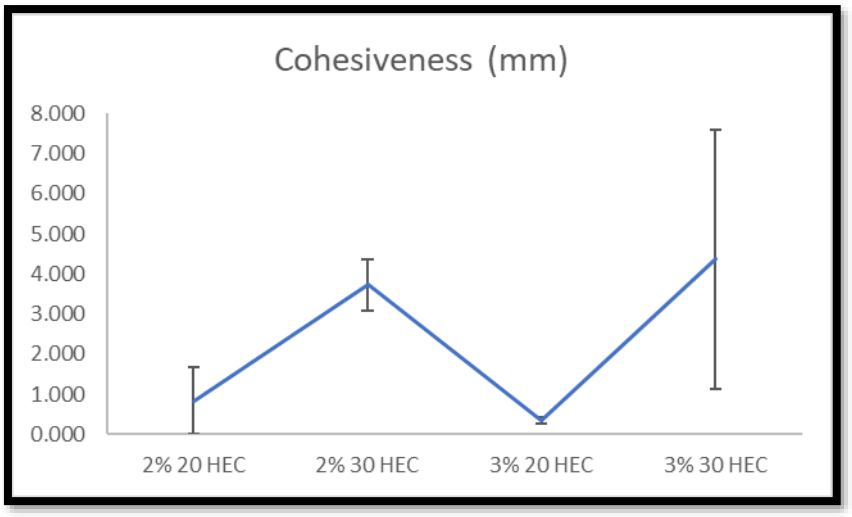

Figure 12. Cohesiveness of blank films

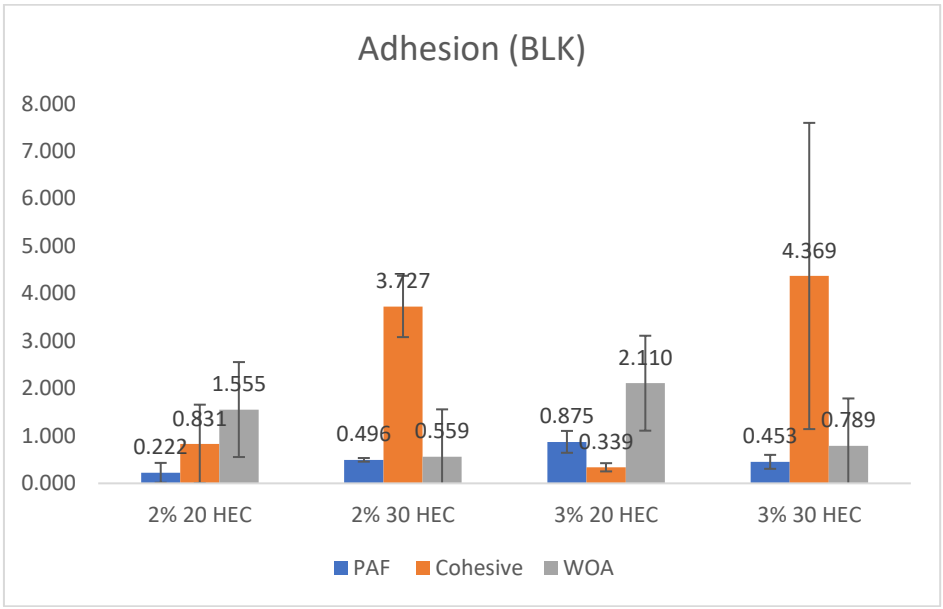

Figure 13. Bar graph showing adhesion of blank films

For the blank films, 3% 20g HEC films showed maximum PAF values of 0.875 ± 0.230 and minimum by 2% 20g HEC films (0.222 ± 0.209). WOA values were maximum for 3% 20g HEC films (2.110 ± 0.746) and minimum for 2% 30g HEC films (0.559 ± 0.066). Cohesive values were maximum for 3% 30g HEC film (4.369 ± 3.226) and minimum for 3% 20g HEC film (0.339 ± 0.087). PAF, WOA and cohesiveness of blank HEC films. The physicochemical features of the hydrogel films, including their distribution of pore sizes and resultant ability to absorb water have a direct effect on these three parameters (30,31). Specifically, PAF was utilized as a metric of in vitro wound adhesion efficacy.

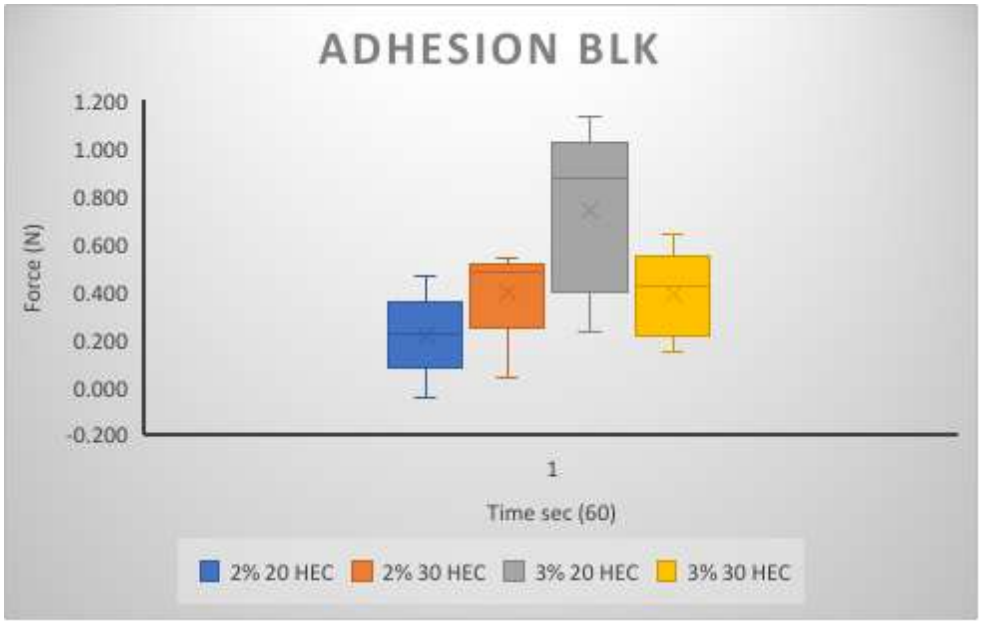

Figure 14. Box plots of peak positive force for blank samples

For CBD-loaded films, PAF values were maximum for 2% 20g HEC (0.582 ± 0.046) and minimum for 3% 30g HEC (0.215 ± 0.176). WOA values were maximum for 2% 20g HEC films (0.955 ± 0.644) and minimum for 3% 20g HEC films (0.132 ± 0.128). Maximum Cohesiveness was seen in 3% 20g HEC films (8.504 ± 0.710) and minimum was seen in 2% 20g HEC films (3.474 ± 2.870). Table 3.24 shows the PAF, WOA and cohesive values of 2% 20g HEC and 3% 20g HEC films. The considerable adhesion of the films signifies that they may definitely affix to the injured surface for a long duration, consequently perhaps minimizing the need for periodic dressing replacement that cause patient non - compliance owing to the pain experienced during replacing the wound dressings (32). The disparities in all three metrics may be attributable to the hydrophilic nature of HEC, which enhances the couplings between the film and the SWF, most presumably because of the film's higher overall fluid intake (33).

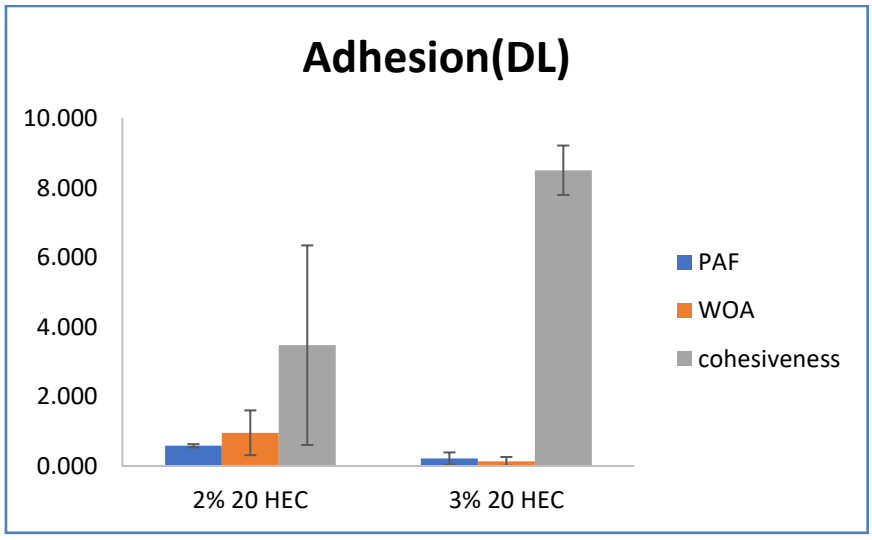

Figure 15. Bar graph representing adhesions for drug loaded films 2% 20g HEC and 3% 20g HEC

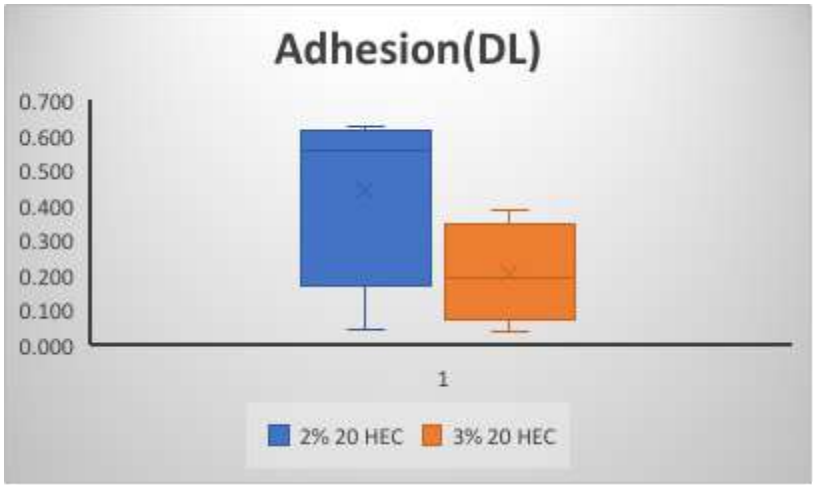

Figure 16. Box plot showing positive adhesive force for drug loaded samples 2% 20 HEC and 3% 30 HEC

Adhesion tests for 2% 30 g HEC and 3% 30 HEC films could not be performed further because drug loaded films rolled and didn't support for the testing.

3.7 Tensile Strength

Among the blank films, 3% 20g HEC films showed maximum tensile strength i.e., 37.4025 ± 6.460865388 and 2% 30g HEC films showed minimum strength (12.523 ± 2.626994523), as shown in Table 3.26. Among CBD-loaded films, 2% 20g HEC film showed maximum tensile strength (23.444 ± 4.0099502) and 2% 30g HEC films showed minimum strength (11.806 ± 7.56445193), as shown in Table 3.27. Relative to CBD-incorporated films, the tensile strength of blank films was greater. In addition to HEC polymer, citric acid and β-CD were incorporated as crosslinking compounds in the gel matrix, which might also serve as additives to improve the mechanical nature of the gel matrix (34). However, tensile strength decreased after adding CBD to the films; this was due to a significant decrease in polymer crystallinity driven by the cannabinoid. (35).

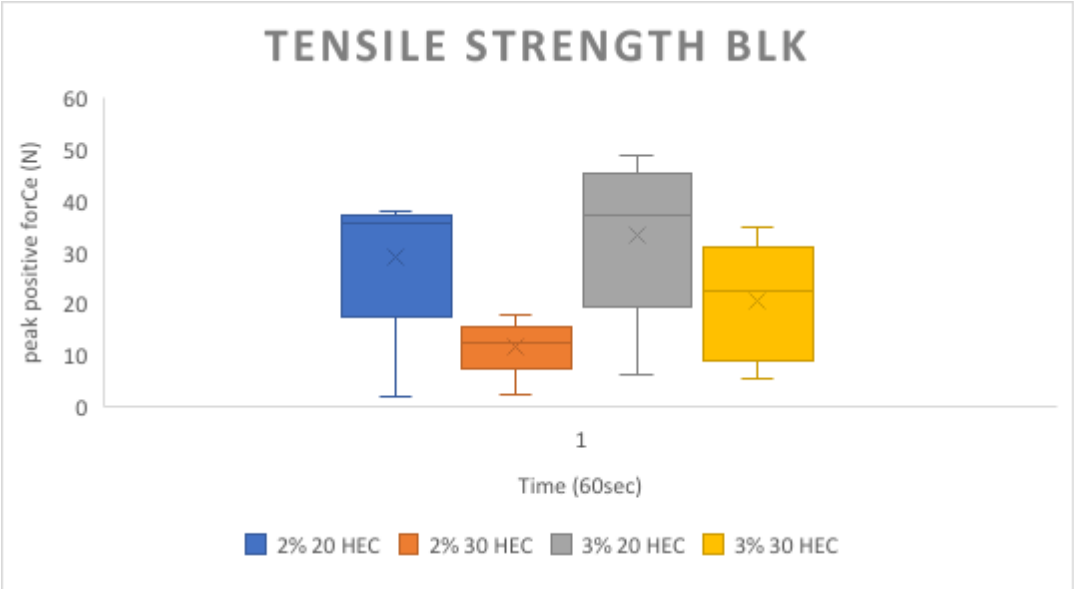

Figure 17. Box plot of blank films

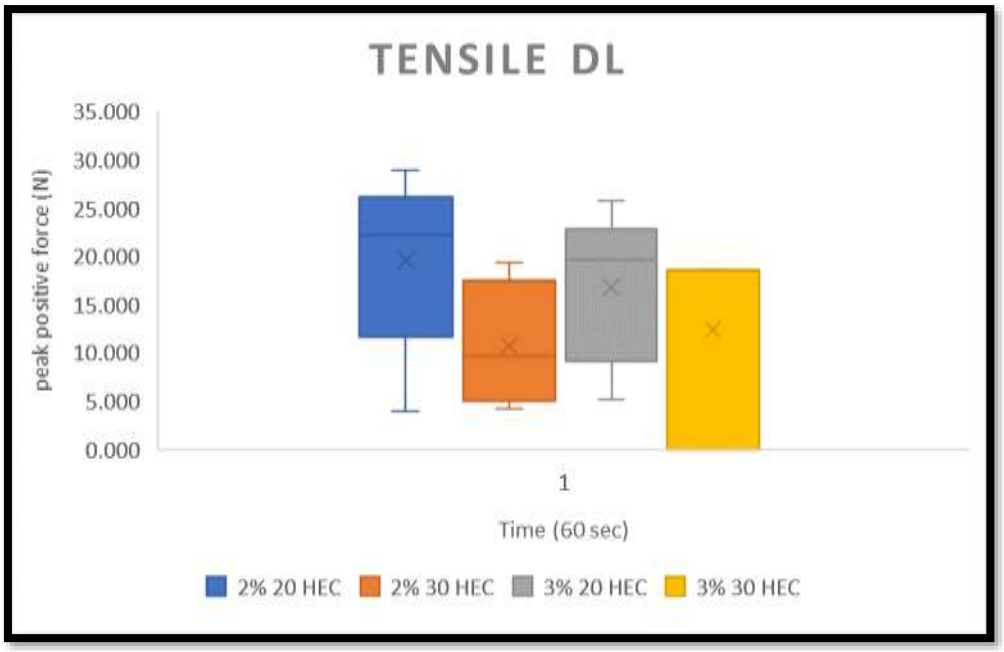

Figure 18. Peak positive force (N) of mean of triplicates a, b, and c of different samples.

For this 3% 30 g HEC it has done with only one A because of shortage of films.

Conclusion

The experimental findings suggest that citric acid has the capacity to interlink HEC and build hydrogel. Featuring improved mechanical characteristics and fluid retention property, HEC films were discovered to be the most efficient. In comparison with blank films, CBD-attached HEC films showed improved expansion, moisture content, and diffusion. Consequently, it might be assumed that films containing drugs have significant ballooning and bioadhesive properties. Unfortunately, they lacked the mechanical qualities of blank films. As a result, the HEC hydrogel films prepared are appropriate for the prolonged release of poorly water - soluble medications.

REFERENCES

1. Percival, N.J. (2002). Classification of wounds and their management. *Surgery* (Oxford), 20(5), 114-7.

2. Abd Alla, S.G., Sen, M., El-Naggar, A.W. (2012). Swelling and mechanical properties of superabsorbent hydrogels based on Tara gum/acrylic acid synthesized by gamma radiation. *Carbohydr Polym.*, 89(2), 478-85. doi: 10.1016/j.carbpol.2012.03.031.
3. Aderibigbe, B.A., Buyana, B. (2018). Alginate in Wound Dressings. *Pharmaceutics*, 10(2), 42. doi: 10.3390/pharmaceutics10020042.
4. Alexiadou, K., Doupis, J. (2012). Management of diabetic foot ulcers. *Diabetes Therapy*, 3(1), 1-5.
5. Argueta, D.A., Ventura, C.M., Kiven, S., Sagi, V., Gupta, K. (2020). A balanced approach for cannabidiol use in chronic pain. *Frontiers in pharmacology*, 11, 561.

6. Aswathy, S., Narendrakumar, U., Manjubala, I. (2020). Commercial hydrogels for biomedical applications. *Heliyon*, 6, e03719.
7. Biswas, A., Maiti, P., Sahu, M. (2022). Polymeric Vehicles for Controlled Delivery of Ayurvedic Drugs for Wound Management. *InBiomedical Translational Research*, (pp. 585-599). Springer, Singapore.
8. Blacklow, S. O., Li, J., Freedman, B. R., Zeidi, M., Chen, C., & Mooney, D. J. (2019). Bioinspired mechanically active adhesive dressings to accelerate wound closure. *Science advances*, *5*(7), eaaw3963.
9. Bort, A., Alvarado-Vazquez, P. A., Moracho-Vilrriales, C., Virga, K. G., Gumina, G., Romero-Sandoval, A., & Asbill, S. (2017). Effects of JWH015 in cytokine secretion in primary human keratinocytes and fibroblasts and its suitability for topical/transdermal delivery. *Molecular pain*, *13*, 1744806916688220.
10. Brumberg, V., Astrelina, T., Malivanova, T., Samoilov, A. (2021). Modern wound dressings: Hydrogel dressings. *Biomedicines*., 9(9), 1235.
11. Zheng, Z., Qi, J., Hu, L., Ouyang, D., Wang, H., Sun, Q., Lin, L., You, L., Tang, B. (2022). A cannabidiol-containing alginate-based hydrogel as novel multifunctional wound dressing for promoting wound healing. *Biomaterials Advances*., 134, 112560.
12. Demidova-Rice, T.N., Hamblin, M.R., Herman, I.M. (2012). Acute and impaired wound healing: pathophysiology and current methods for drug delivery, part 1: normal and chronic wounds: biology, causes, and approaches to care. *Adv Skin Wound Care*., 25(7), 304-14.
13. Klein, M., de Quadros De Bortolli, J., Guimarães, F.S., Salum, F.G., Cherubini, K., de Figueiredo, M.A. (2018). Effects of cannabidiol, a Cannabis sativa constituent, on oral wound healing process in rats: Clinical and histological evaluation. *Phytotherapy Research*., 32(11), 2275-81.
14. Ghorpade, V. S., Yadav, A. V., & Dias, R. J. (2017). Citric acid crosslinked β-cyclodextrin/carboxymethylcellulose hydrogel films for controlled delivery of poorly soluble drugs. *Carbohydrate polymers*, *164*, 339–348.
15. Dini, V., Oranges, T., Rotella, L., Romanelli, M. (2015). Hidradenitis Suppurativa and Wound Management. *Int J Low Extrem Wounds*, 14(3), 236-44.
16. George Broughton II, Janis, J.E., Attinger, C.E. (2006). Wound healing: an overview. *Plastic and reconstructive surgery*, 117(7S), 1e-S.
17. Thomas, S. (2007). Fluid handling properties of Allevyn dressing. *Wound Management Communications*, 1-8.
18. Ferrari, F., Bertoni, M., Caramella, C., Waring, M.J. (1994). Comparative evaluation of hydrocolloid dressings by means of water uptake and swelling force measurements I. *Int J Pharm.*, 112, 29–36.
19. Catanzano, O., Docking, R., Schofield, P., & Boateng, J. (2017). Advanced multi-targeted composite biomaterial dressing for pain and infection control in chronic leg ulcers. *Carbohydrate polymers*, *172*, 40–48.
20. Firlar, I., Altunbek, M., McCarthy, C., Ramalingam, M., Camci-Unal, G. (2022). Functional Hydrogels for Treatment of Chronic Wounds. *Gels*, 8(2), 127.
21. Pan, Z., Ye, H., Wu, D. (2021). Recent advances on polymeric hydrogels as wound dressings. *APL bioengineering*, 5(1), 011504.
22. Patil, P.S., Fathollahipour, S., Inmann, A., Pant, A., Amini, R., Shriver, L.P., Leipzig, N.D. (2019). Fluorinated methacrylamide chitosan hydrogel dressings

improve regenerated wound tissue quality in diabetic wound healing. *Adv. Wound Care*, 8, 374–385.
23. Boateng, J. S., Pawar, H. V., & Tetteh, J. (2013). Polyox and carrageenan based composite film dressing containing anti-microbial and anti-inflammatory drugs for effective wound healing. *International journal of pharmaceutics*, *441*(1-2), 181–191.
24. Momoh, F. U., Boateng, J. S., Richardson, S. C., Chowdhry, B. Z., & Mitchell, J. C. (2015). Development and functional characterization of alginate dressing as potential protein delivery system for wound healing. *International journal of biological macromolecules*, *81*, 137–150.
25. Fan, L., Yang, H., Yang, J., Peng, M., Hu, J. (2016). Preparation and characterization of chitosan/gelatin/PVA hydrogel for wound dressings. *Carbohydr Polym*., 146, 427-34.
26. Jin, S.G., Yousaf, A.M., Kim, K.S., Kim, D.W., Kim, D.S., Kim, J.K., Yong, C.S., Youn, Y.S., Kim, J.O., Choi, H.G. (2016). Influence of hydrophilic polymers on functional properties and wound healing efficacy of hydrocolloid based wound dressings. *Int J Pharm*., 501(1-2), 160-6.
27. Ghorpade, V. S., Yadav, A. V., & Dias, R. J. (2016). Citric acid crosslinked cyclodextrin/hydroxypropylmethylcellulose hydrogel films for hydrophobic drug delivery. *International journal of biological macromolecules*, *93*, 75-86.
28. Hafezi, F., Scoutaris, N., Douroumis, D., & Boateng, J. (2019). 3D printed chitosan dressing crosslinked with genipin for potential healing of chronic wounds. International journal of pharmaceutics, 560, 406-415.
29. Catanzano, O., D'Esposito, V., Formisano, P., Boateng, J. S., & Quaglia, F. (2018). Composite alginate-hyaluronan sponges for the delivery of tranexamic acid in postextractive alveolar wounds. Journal of pharmaceutical sciences, 107(2), 654-661.
30. Dharmalingam, K., & Anandalakshmi, R. (2019). Fabrication, characterization and drug loading efficiency of citric acid crosslinked NaCMC-HPMC hydrogel films for wound healing drug delivery applications. International journal of biological macromolecules, 134, 815–829.
31. Wong, R., & Dodou, K. (2017). Effect of Drug Loading Method and Drug Physicochemical Properties on the Material and Drug Release Properties of Poly (Ethylene Oxide) Hydrogels for Transdermal Delivery. Polymers, 9(7), 286.
32. Eftekharizadeh, F., Dehnavieh, R., Hekmat, S.N., Mehrolhassani, M.H. (2016). Health technology assessment on super oxidized water for treatment of chronic wounds. *Med. J. Islam Repub. Iran*, 30, 38
33. Gao, C., Xiao, L., Zhou, J., Wang, H., Zhai, S., An, Q. (2021a). Immobilization of nanosilver onto glycine modified lignin hydrogel composites for highly efficient p-nitrophenol hydrogenation. *Chem. Eng. J.*, 403, 126370.
34. Gao, Y., Peng, K., Mitragotri, S. (2021b). Covalently Crosslinked Hydrogels via Step-Growth Reactions: Crosslinking Chemistries, Polymers, and Clinical Impact. *Adv. Mater*., 33, 2006362.
35. Gholizadeh, H., Messerotti, E., Pozzoli, M., Cheng, S., Traini, D., Young, P., Kourmatzis, A., Caramella, C., Ong, H.X. (2019). Application of a thermosensitive in situ gel of chitosan-based nasal spray loaded with tranexamic acid for localised treatment of nasal wounds. *AAPS PharmSciTech*, *20*, 299.