DOI: https://doi.org/10.31351/vol34iss2pp184-196

Preparation of Film Containing Polyelectrolyte Complex for Topical Delivery of Penciclovir

Mina Emaad Taha [1] and Nidhal Khazaal Maraie [*,2]

[1] Department of Pharmaceutics, College of pharmacy, Mustansiriyha University, Baghdad, Iraq.
[2] Department of Pharmaceutics, College of Pharmacy, Al- Farahidi University, Baghdad, Iraq.

[*]**Corresponding Author**

Received 12/10/2023, Accepted 11/3/2024, Published 25/6/2025

Abstract

A thin film refers to a pliable polymer layer, with or without a plasticizer. In this study, penciclovir (PCV) was used as a model drug, which is class III according to biopharmaceutical classification system. It has low oral bioavailability (5-10%) and limited half-life of 2hours. The aim of this work was preparation and evaluation of polyelectrolyte complex containing penciclovir as a bioadhesive film for the treatment of skin viral lesions. The method used for the preparation of the films was solvent casting method, using acacia gum (as negative charged polymer) and chitosan (as positive charged polymer) as the main components. PEC films were prepared with different molar ratio and concentration of acacia and chitosan, different pH, and type of chitosan (according to molecular weight). The prepared films undergo evaluation in terms of their percent encapsulation efficiency (%EE), film thickness, folding endurance, swelling index, and drug release. The results showed that the best film (F10) had 90 % entrapment efficiency, suitable swelling index, pH (5.5), good bioadhesion force(0.133N±0.015), and showed 57.3% drug release after 6 hours, and continued to reach 100 % after 12 hours. The Fourier Transform Infrared (FT-IR) investigation confirm the formation of PEC between the chitosan and acacia. Finally, F10 film could be considered as a suitable prolong release topical drug delivery system that may improve patient compliance compared to the available topical cream.

Key words: acacia gum, chitosan, penciclovir, polyelectrolyte complex, skin administration.

Introduction

A thin film refers to a pliable layer of polymer material, which might or might not contain a plasticizer. Thin films have demonstrated the ability to speed up the beginning of medication action, lower the frequency of doses, and increase drug effectiveness. Ideal thin films should have desirable characteristics like rapid rate of dissolution or a prolonged residence period at the administration site, and appropriate formulation stability [(1)]

Chitosan (CS) is an amino polysaccharide that occurs naturally in a linear form and possesses cationic properties. It is characterized as a positively charged biopolymer that is nontoxic, biodegradable, mucoadhesive, and biocompatible, and available in a broad range of molecular weights (generally between 10 and 1000 kDa) and levels of deacetylation (normally between 70% and 95%) [(2,3)]. Chitosan have bacteriostatic and bioadhesive characteristics[(4)]. The solubility of Chitosan-based delivery systems may be a possible factor contributing to uncontrolled water absorption or inadequate physical, rheological, or physicochemical qualities, which is reliant on pH , therefore it is preferable to physically modify CS with polyanions such as acacia gum (AG) to get PEC, since this preserves its biocompatible behavior and its multifunctional biological features [(2)]. PEC techniques can improve bioavailability of the active compound via skin through bioadhesion property of the used polymers [(5)], as well as the residence time to enhance its local effectiveness [(6)].

Chitosan-based polyelectrolyte complexes are highly tolerated, biocompatible, and ideal for wound care, tissue regeneration, and drug administration [(7)]. Many factors influence this system , including temperature, pH, chain stiffness, polymer concentration, and the availability of ionic sites [(8)].

Penciclovir, referred to by its chemical name, 9-[4-hydroxy-3-(hydroxymethyl) butyl] guanine , its exhibits efficacy in the treatment of multiple viral infections, including herpes simplex virus, varicella zoster virus, Epstein-Barr virus , and cytomegalovirus [(9)]. It is class III according to biopharmaceutical classification system, however, penciclovir has a very low oral bioavailability (5–10%) due to its limited absorption and hence limited therapeutic applicability, therefore, topical application is one potential method of penciclovir

administration. It binds 20% of plasma proteins, has a distribution volume of 1.5L/kg, and a limited half-life of approximately 2 hours [10].

The aim of this research is to prepare a topical bioadhesive film using chitosan-based polyelectrolyte complex to have sustained release of penciclovir (PCV) as a model drug that can be used to treat viral skin lesion.

Materials and Methods

Materials

Chitosan (CS) low molecular weight (<200 Da) and medium molecular weight (between 200-400 Da), (with acylation degree 95%) (Rhawn®, China), acacia gum (AG) (kindly gifted from SDI), acetic acid, penciclovir (PCV) (Meyer Biochemical technology Co, ltd, China), propylene glycol (PG). The rest of the things used in this research were scientific and medicinal grade.

preparation of the polyelectrolyte complex film

Various films were fabricated using the solvent casting technique, using acacia and chitosan at varying ratios and concentrations of the two polymers as in (Table 1). CS (with molecular weight of < 200 Da) was dispersed in 2 % v\v aqueous solution of acetic acid under ambient conditions, while AG was dispersed in deionized water at room temperature. The necessary amount of PG (plasticizer) was added to the acacia dispersion while mixing to form homogeneous dispersion. AG dispersion was added drop by drop to CS dispersion with stirring for 30 minutes to form PEC dispersion [11]. Formulas (F7-F10) pH was adjusted to 5.5 by acetate buffer. PCV (10 mg) was added and mixed for 10 minutes to form homogeneous dispersion. The polymer gel undergoes a homogenization process (Vanguard USA) for 30 minutes in order to eliminate entrapped air bubbles. The resulting dispersion was poured onto a mold and subsequently exposed to a drying process at a temperature of 40°C for a duration of 10 hours and the film cut in 2X2 cm. The work was repeated for F10 utilizing CS with a medium molecular weight.

Characterization of the prepared PEC films

Entrapment Efficiency

The amount of PCV encapsulated in the prepared PEC films (F1- F10) was calculated by immersing the film in 10 mL deionized water , and exposed to ultrasonic water bath (Vanguard USA) at 25 ºC for 10 min., then centrifuge for five minutes [12], the supernatant was subjected to UV spectrophotometer analysis (Shimadzu –UV -1650 pc) at a wavelength of 252 nm.

Film thickness and folding endurance

Regarding the prepared films formula (F1–F10); the film's thickness was quantified by using a digital micrometer (Shanghai, China) to measure five distinct sites both around and at the center of the films. The folding durability of the film was assessed by subjecting it to repetitive folding at a consistent location until it reached a point of fracture or had undergone 300 folds [4].

Surface pH

A piece of each prepared film (F1- F10) sample was subjected to hydration by adding 1 ml of deionized water and allowing it to incubate for a duration of one hour. The measurement of surface pH was conducted using an electronic pH meter [13].

Table 1 . Content of the prepared PEC films .

Formula no.	Penciclovir (mg)	Polymer ratio (CS:AC)	Low molecular weight chitosan (LCS)wv %	Chitosan amount (mg)	Medium molecular weight chitosan (MCS) w\v%	Acacia (AC) w\v%	Acacia amount (mg)	Propylene glycol (PG) (mL)	pH
F1	10	1:1	1	0.3	----	1	0.3	1	4.5
F2	10	1:0.75	1	0.3	----	0.75	0.225	1	4.5
F3	10	1:0.5	1	0.3	----	0.5	0.15	1	4.5
F4	10	1:0.25	1	0.3	----	0.25	0.075	1	4.5
F5	10	1:1	2	0.6	----	2	0.6	1	4.5
F6	10	1:1	3	0.9	-----	3	0.9	1	4.5
F7	10	1:1	1	0.3	-----	1	0.3	1	5.5
F8	10	1:1	2	0.6	-----	2	0.6	1	5.5
F9	10	1:1	3	0.9	-----	3	0.9	1	5.5
F10	10	1:1	---		3	3	0.9	1	5.5

Swelling index

Each of the prepared PEC films (F1-F10) were immersed in phosphate buffer pH 7.4 at ambient temperature, and at specified time interval the films removed from the buffer solution and excess solution was removed, subsequently accurately weighed again. The swelling ratio (SR) is determined using the equation [14] :

$$SR\% = \frac{Wwet - Wdry}{Wdry} X100 \qquad \text{- 1-}$$

The variable Wdry represents the mass of the film at derides phase, while Wwet denotes the mass of the film during the swelling phase.

In vitro drug release study

The drug release characteristics of the medication from the produced polymeric electrolyte complex (PEC) films (F1-F10) was preformed using USP apparatus II (paddle type). The film fixed on a glass plate with the aid of cyanoacrylate adhesive (The glass plate or glass sild put at the bottom of the dissolution jar with the releasing surface to the bottom of the jar). The dissolving medium used in this study consisted of a phosphate buffer solution with a pH of 7.4, the total volume of the dissolving media was 400 mL. The apparatus set at speed of 50 rpm and the temperature maintained at 37 ºC ±0.5. At predetermined time interval (10,30 min,1,2,4,6,8,10,12 hr) aliquots of 5 mL withdrawn and substitute 5 mL of phosphate buffer (pH 7.4), and use a spectrophotometer to measure the drug concentration at 253 nanometers [15].

In-vitro evaluation of the bioadhesive property

To evaluate the bioadhesive property of the prepared films (F1-F10), was done using sheep skin as a model skin. The bioadhesive strength was assessed using a modified physical balance (Figure 1) [16]. The two sides of physical balance were made equal level before the study by placing a beaker of water on the right-hand pan for weight balance purpose. On the left side of the balance, an inverted glass beaker was placed, on which the sheep skin tissue was glued with cyanoacrylate glue. The surface of the sheep tissue was swept with few drops of PB pH 7.4. The prepared PEC film was fixed (by cyanoacrylate glue) to the stopper of a plastic tube (which was hanged by thread). Then the film was placed on the skin tissue and gently pressed by fingers for two minutes to facilitate adhesion. Water was added gradually drop by drop to the pan in the left side of balance until the tissue just split up from the film. The force of adhesion was determined using the following equation, where the bioadhesive strength indicated the amount of water added [17]:

$$\text{adhesion force (N)} = \frac{\text{bioadhesion strenght (g)}}{1000} \times 9.8 \quad -2-$$

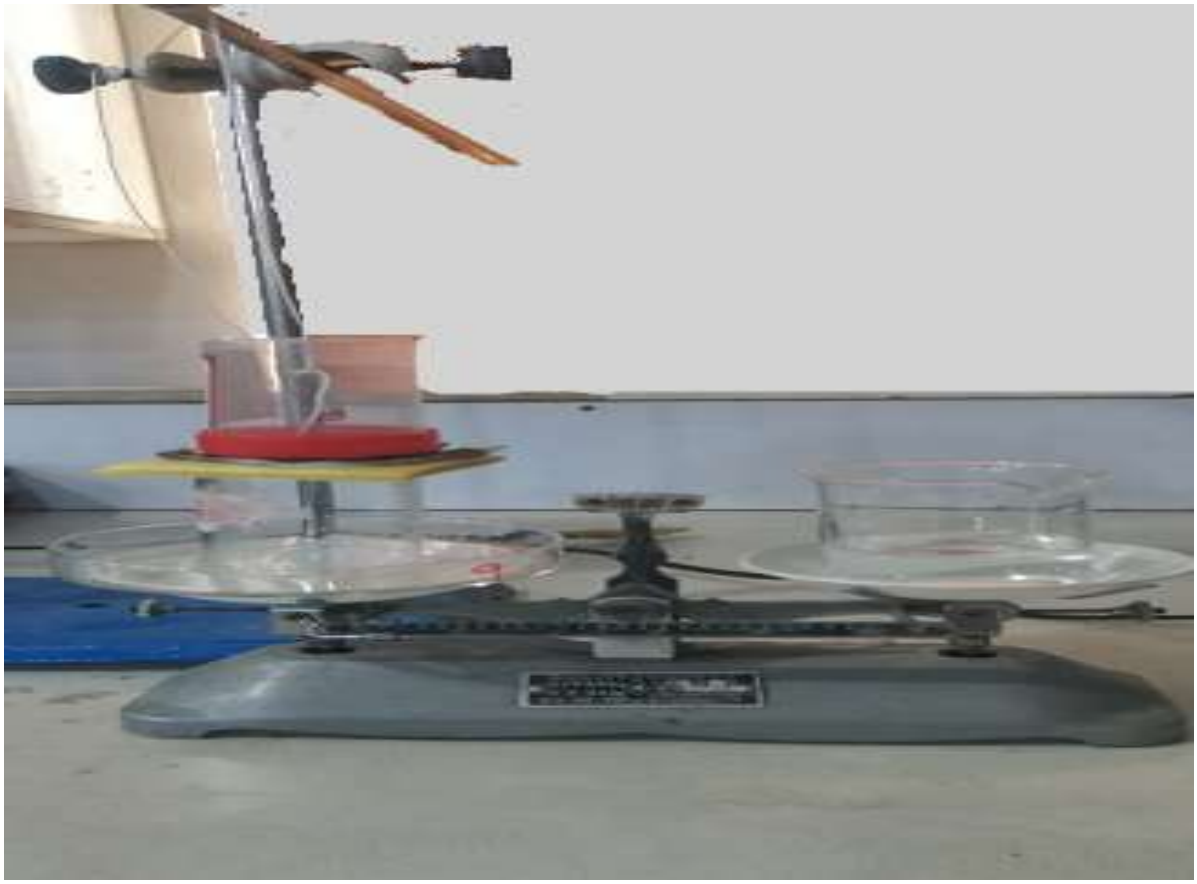

Figure 1. Bioadhesion test for the prepared PEC films.

Choice of the best formula

The best formula was selected according to the highest EE%, suitable folding endurance, swelling index, bioadhesive property, and release profile.

Further characterization for the best film formula

Mechanical strength

The mechanical features include two key parameters: tensile strength and % elongation at break. The tensile strength (TS) refers to the highest level of stress that is exerted on a specific location, resulting in the fracture of the strip specimen. The computation requires the division of the applied load at rupture by the cross-sectional area, yielding a value representing the force exerted per unit area (in MPa) on the strip, as shown by the following equation [18]:

$$Ts = \frac{\text{force at break}}{\text{cross-section area}} \qquad \text{-2-}$$

The percentage elongation at the point of fracture, defined as %EB, is used as a means to evaluate the extent of elongation shown by the film compositions. To determine this, the measurement of the space between the tensile clamps of the tensile strength apparatus (Tinius Olesn H50KT,UK) is performed both before to and after the fracture of the film. Film specimen with the dimensions 2 X 8 cm and empty of air bubbles or any other defects were firmly affixed using a pair of clamps. The top clamp was adjustable, while the lower clamp remained stationary. The experiment was carried out at a head speed of 10 millimeters per minute, with a cell load of 50 kilo Newton. In order to reduce the potential damage to the film caused by the grooves of the clamp, a cardboard piece was securely attached to the surface of the clamp. During the measuring procedure, the strips were subjected to tension by the top clamp until the film reached its breaking point. The measurements of force and elongation were conducted during the fracture of the films [19] :

$$\%EB = \frac{D2-D1}{D1} X100 \qquad \textbf{(Equation 4)}$$

The symbol %EB represents the percentage elongation at the break. D1 refers to the space between tensile clamps before film fracture. D2 refers to the space between the tensile clamps after the occurrence of film fracture.

Morphology study

The morphology of the prepared PEC film studied with scanning electron microscope (SEM Inspect S50, Netherlands) operated at 20 Kv accelerating voltage. The study was applied for the selected film formula before (blank)and after loading with drug.

FT-IR study

The interactions between polymers - polymers, and polymer - drugs were studied by FT-IR spectroscopy (Shimadzu FT-IR 8040, Japan). The spectra were recorded for the pure polymers(chitosan ,and acacia), pure drug, blank PEC films, and for the chosen formula. The samples were grinded and combined with potassium bromide (KBr), afterwards compressed to a disc. These discs were subjected to analysis within a spectral range spanning from 400 to 4000 cm^{-1}.

Statistical analysis

One-way analysis of variance (ANOVA) was used to do the statistical analysis of the formulations. The observed discrepancy when the p-value is less than 0.05, it is considered statistically significant.

Result and discussion

Entrapment Efficiency EE%

The EE % relates to the amount of drug molecules that are successfully encapsulated inside a delivery system. that are encapsulated inside the PEC film and calculated for all the prepared formulas (F1-F10) as presented in Table 2. There are different variables affecting EE% including:

1.Influence of acacia ratio on EE%

The result showed that as the ratio of AG decreased from 1% to 0.25% in formulas (F1-F4) , the amount of encapsulated PCV significantly decreased ($P< 0.05$) from 59.5±5.7 for F1 to 42.6±5.03 for F4 . The potential consequence of a decrease in the amount of AG is a reduction in the ionic interaction between the amine group of CS and the carboxylic acid group of AG, thereby leading to a decrease in the agglomeration of polyelectrolyte complexes (PECs) [20]. These results were similar to another study used PEC technique to encapsulate Ibuprofen [21].

2.Influence of polymer concentration on EE%

Upon increasing the concentration of CS and AG from 1% (F1) to 2% (F5), there were no significant difference in EE% ($p = 0.453$, $p>0.05$), but upon further increase to 3% (F6) there was a significant ($p<0.05$)increase in EE% (67%), this can be explained on the basis that increasing polymers concentration caused increase in agglomeration of PEC resulting in high EE of drug ,and similar results were observed in PEC for ginger volatile oil upon increasing polymers concentration from 0.5% to 3% w\w [22].

3.Influence of pH adjustment on EE%

The pH of the prepared PEC solutions was about (4.5). In order to investigate the impact of the pH level of the PEC (polyelectrolyte complex) solution on the drug's encapsulation efficiency (EE%) , the pH was adjusted to 5.5 (using acetate buffer) in formulas F7, F8 and F9. The data given in Table 2 indicate that EE% in F7 (containing 1% of CS and 1% AG in 1:1 ratio) was not significantly different ($p>0.05$) from %EE in F1 that contain the same concentration and ratio of both polymers but with pH of 4.5. While the EE% in F8 (containing 2%of CS and 2% AG in 1:1 ratio and the pH was adjusted to 5.5) showed significantly ($p<0.05$) higher EE% (81%) in

comparison with F5 (contain the same concentration and ratio of both polymers but with pH of 4.5).Same results were observed upon comparing EE% of F9 (prepared with 3% of both polymers with pH 5.5) with F6 (prepared with the same polymer concentration but pH 4.5) and had 53.5% EE. The macromolecule's stiffness will diminish as a consequence of chitosan's charge density decreasing concurrently, it is anticipated that the conformational modification required for charge matching will be assisted by the decrease in repulsive electrostatic interactions, resulting in the formation of more compact complexes [23].

Comparable findings were noted in the PEC matrix for the delivery of curcumin where changing the pH at high polymer concentration resulted in a significant variation in the encapsulation efficiency [24].

4.Influence of chitosan molecular weight on EE%

In order to investigate the impact of CS molecular weight on EE%, the formula F10 prepared containing 3% CS of medium molecular weight and 3% AG in comparison to F9 where low molecular weight CS was used. The EE% was increased significantly ($p < 0.05$) to 90% in F10 because medium molecular weight CS has longer chain lead to increase entanglement of the polymers resulting in more pours structure [7]. Similar results were observed in PEC for lung delivery of levofloxacin hydrochloride using chitosan [25].

Thickness and folding endurance of the prepared films

The thickness of the film varied from 0.12 ± 0.02 to 0.38±0.015mm (Table 2), which increased with the increase in polymers concentration. Topical film should be thinner than human skin (depending on characteristics including sex, age, and anatomical differences, may be anywhere from 0.5 to 2 mm thick). The films created in this work are thought to be useful for skin lesions because their thickness is less than 0.5 mm [26].

Results showed that all films are sufficiently flexible without breaking, and folding endurance values were determined to be adequate (> 300).

Table 2. Thickness, drug content, EE%, folding endurance and surface pH for the prepared PEC films.

Formula code	Thickness	EE%	Folding endurance	Surface pH
F1	0.14±0.006	59.5±5.7	>300	4.5±0.05
F2	0.12±0.02	60±2	>300	4.5±0.15
F3	0.12±0.006	44±18.5	>300	4.5±0.058
F4	0.11±0.006	42.6±5.03	>300	4.5±0.25
F5	0.29±0.015	53.5±11.5	>300	4.5±0.15
F6	0.37±0.015	67±2.5	>300	4.5±0.05
F7	0.13±0.01	55±5	>300	5.5±0.05
F8	0.31±0.021	81±5	>300	5.5±0.2
F9	0.38±0.015	85.3±1.5	>300	5.5±0.05
F10	0.35±0.015	90±1.4	>300	5.5±0.35

Surface pH

The measured surface pH ranged from 4.5 ± 0.05 to 5.5 ± 0.05, this pH value is acceptable, and non- irritating to the skin (where the skin surface pH range from 4.1 -6.7) [27].

Swelling index

All the prepared films pass swelling test successfully without disintegration and reached plateau after about 4hours, except F4 which gave the high swelling index and disintegrated after 2 hours which might be due to high amount of unreacted chitosan and low acacia gum concentration (Figure 2), these results meet the results of PEC membrane for encapsulation of thyme oil for topical use [14].

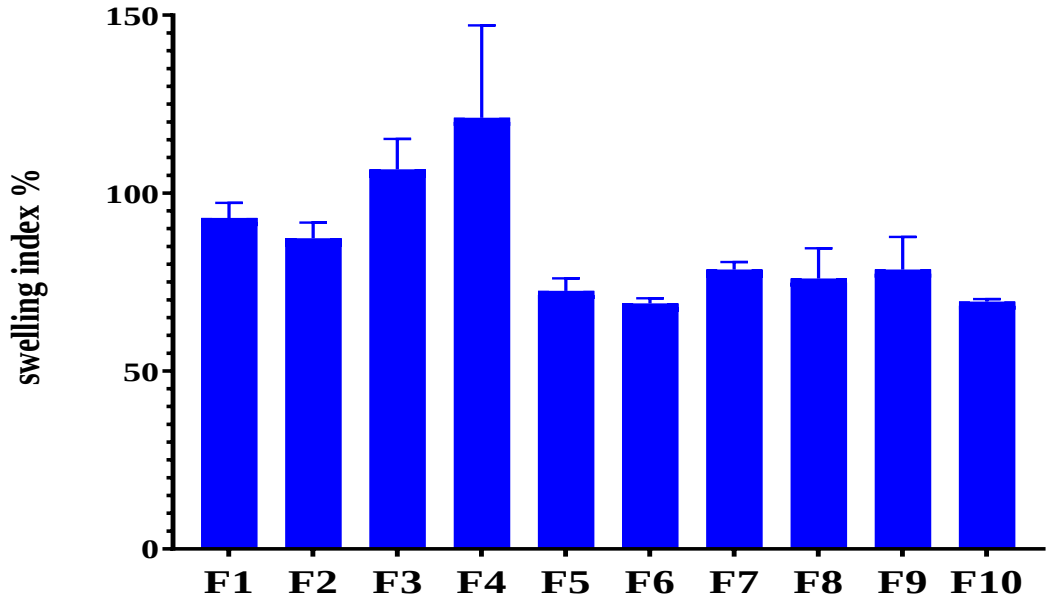

Figure 2. Swelling index of the prepared films (F1-F10).

In vitro drug release study

The patterns of drug release from the different formulas (F1–F10) are shown in (Figure 3). All formulations exhibited initial release of PCV could be due to presence of drug on the surface of the films, followed by slow continuous release attributed to the drug entrapped in PEC complex. There were many variables affecting the drug release including:

1.Impact of acacia ration on drug release

Where formula F1, F2, F3, and F4 (containing lower concentration of AG) released about 50% of the drug during the first thirty minutes that continued to 100% release after 4 hr. with no significant difference (Figure 3a), as these formulae have a high swelling index, resulting in the rapid and full release of the medication within a shorter time interval, and resembled those obtained from PEC film for topical delivery of ketotifen fumarate [4].

2.Impact of increasing polymers concentration

When increasing concentration of both polymers (keeping ratio 1:1) from 1% (in F 1) to 2% (in F5) and 3% (in F6) the drug release became slower where F5 released 56.6% of the drug after 1hr and reached 100% after 6 hr., while F 6 released 57 % after 2 hr. and reached 100% after 8 hr., as illustrated in (Figure 3b). The slow disintegration of the CS is responsible for the delayed release of the medication in F6 and also due to higher viscosity , and the reduced rate at which the solvent penetrates into the matrix [28].Similar results were observed for the delivery of 5-flurouracil from PEC matrix [29].

3.Impact of pH adjustment on drug release

As the PEC dispersion pH value adjusted to 5.5 in F7, F8, and F9 (in which the polymers concentration was 1%, 2%, and 3% respectively, in 1:1 ratio) in comparison to F1, F5, and F6 (containing the same ratio and polymers concentration in same manner to F7–F9, but with preparation pH 4.5) the drug release became more slower where F7 release 58% of the drug after 1 hr and reach 100% after 6 hr., while F8 and F9 took 2 and 4 hr to release 55% and 57% of the drug, and reached 100% after 8 and 10 hr respectively, as shown in (Figure 3c). This phenomenon occurs because when Cs molecules approach their pKa values (6.3–7), there is a decrease in their degree of ionization and solubility, furthermore, as pH approaches 7, it is observed that AG molecules have an excellent degree of solubility and ionization, so that chitosan-acacia dispersions have the greatest turbidity levels. at a pH value of 5.5 may be resulting in the formation of more compact and intensive complexes [23,30] . Similar results were observed in PEC for delivery of theophylline [31] .

4.Impact of chitosan molecular weight on drug release

when the type of CS changed from low molecular weight (in F9) to medium molecular weight in F10, the F10 film released 57.3% of the drug after 6 hr and the release reach 100% after 12 hr (Figure 3d) , this may be attributed to high complexation degree of the film (F10), as the positive charge density increased as the molecular weight of CS increase [32]. This result similar to another study in which sodium valproate incorporated in PEC based oral tablet [33].

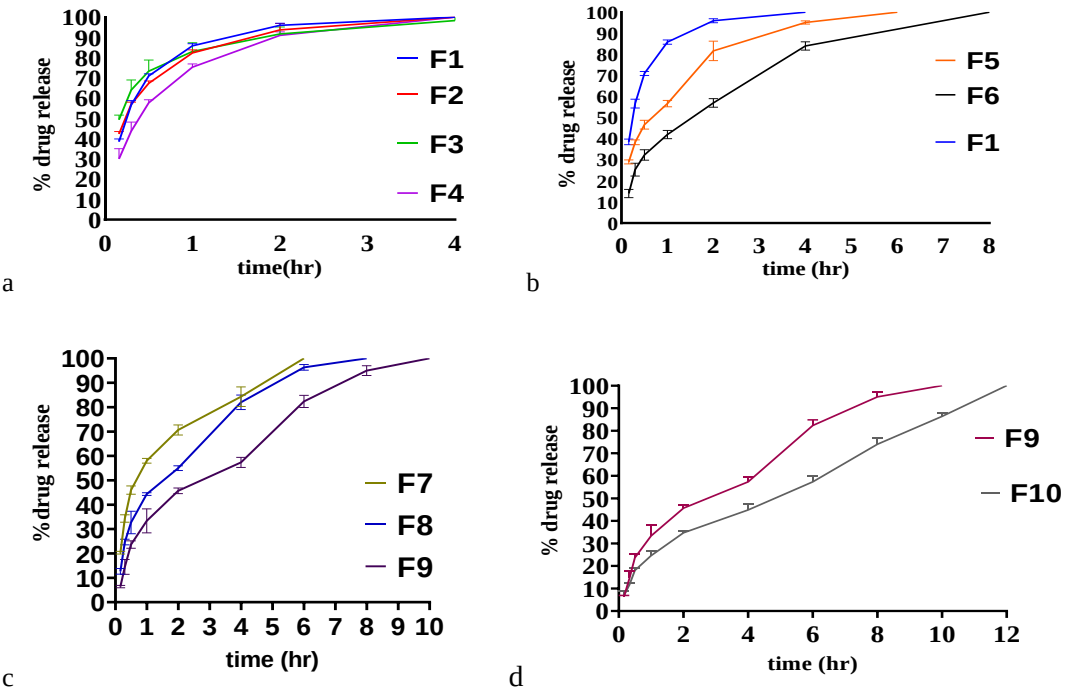

Figure 3. Variables affecting in-vitro drug release from the prepared PEC films (F1-F10) in phosphate buffer pH7.4 and 37ºC,(a) impact of AG ratio,(b) impact of both polymers concentration, (c) impact of PEC solutions pH, and (d) impact of CS molecular weight.

Results of Bioadhesion evaluation for the prepared films

One of the most crucial functional characteristics for a skin drug delivery system is skin adherence. In this study, sheep abdominal skin was used for evaluation the bioadhesion properties in term of bioadhesion force and detachment force. The results showed that the value of bioadhesion force affected by AG content in the film, as shown in the (Figure 4). Where F1 and F2 (containing more AG) had good bioadhesion force (0.095±0.015 and 0.075±0.004 N) while there was a decrease in bioadhesion force in F3 and F4 (containing low amount of AG (0.051±0.003 and 0.06±0.002), this could be explained on the basis that larger polymer ratio enhanced the degree of penetrating polymer chains into skin, improving the strength of the bioadhesion [34] . Same result observed for delivery of phycocyanin through PEC system [35].

The results also showed that increasing CS concentration from 1% (in F 1) to 2% and 3% in F5 and F6 respectively the bioadhesion forces will also increase from 0.095 ± 0.015 N (for F1) to 0.09±0.013 N (for F5), and 0.12±0.01 N (for F6). Due to a natural negative charge of the epidermis, polyelectrolyte complexes (PEC) containing excessive Cs can produce electrostatic interactions with the skin [36]. Same observation for brinzolamide delivered by PEC techniques [37].

Further increase in bioadhesion force observed in F7 (with CS:AG ratio 1:1, and preparation pH 5.5) where the bioadhesion force 0.111 ± 0.019 N in comparison for F1 (which contain the same CS:AG ratio, but with preparation pH 4.5). The same was observed with F8 and F9 (containing CS:AG ratio 1:1 and pH 5.5) which had bioadhesion force of 0.129±0.00, and 0.133±0.02 N in comparison with F5 and F6 (containing CS:AG ratio 1:1,with pH 4.5). This high bioadhesion character of these PEC films may be attributed to more cationic group (NH_4^+) of CS oriented outside the PEC films which gave stronger electrostatic interaction with negative charge of the skin [38]. Same result noticed for vancomycin delivery via PEC [39].

While slightly higher bioadhesion force observed for F10 (which contain medium molecular weight CS in ratio 1:1 with acacia) in comparison to F9 (which containing low molecular weight CS in ratio 1:1 with acacia), The observed phenomenon may be attributed to the correlation between an elevation in positive charge density and the progressive increase in molecular weight of CS, this result is similar to another study for the delivery of enoxaparin by PEC techniques [40].

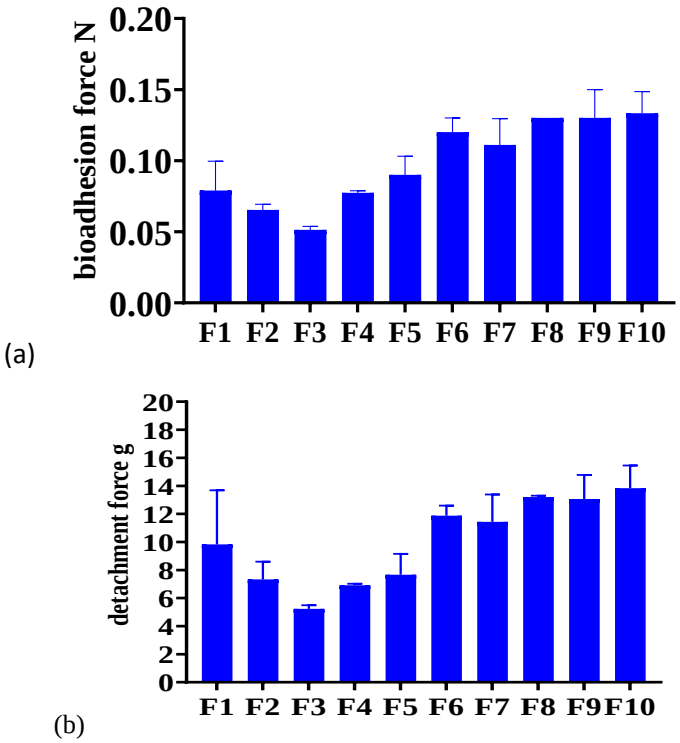

Figure 4. (a) bioadhesion force of the PEC films, (b) detachment force of the PEC film.

Selection of the best formula

Formula F10 had the highest EE%, prolonged release, and good bioadhesion property, with good film properties. This formula was further characterized for mechanical strength, surface morphology, and compatibility

Mechanical test

The optimal skin film should possess favorable mechanical qualities in order to maintain its structural integrity throughout use. Additionally, it should exhibit sufficient resistance to mechanical abrasion while being sufficiently flexible to accommodate the movements of the skin [41], it suggests that suitable skin film should have high TS and EB% [42]. The TS and EB% for formula F10 were 12.9±4.03 MPa and 55.6±4.8% respectively as shown in **(**Figure 5). These results were within the range of skin mechanical strength (TS 2.5 – 16 MPa and EB% up to 70 %) [43].

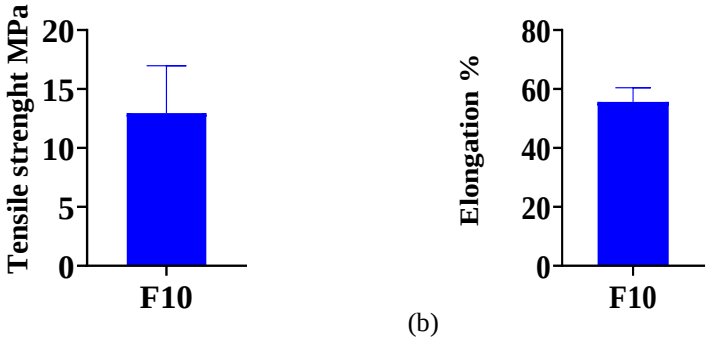

Figure 5. Mechanical characteristics of the PEC film (F10) (a)tensile strength and (b) elongation at break.

Surface morphology study

The morphological feature of CS:AG film was examined using SEM techniques as in (Figure 6). The blank film (no drug) showed smooth and compact structure, with no porous, while incorporation of the drug (PCV) showed no apparent changes expect some crystals. Same observation was found in nystatin PEC film compared to blank film [44].

(a)

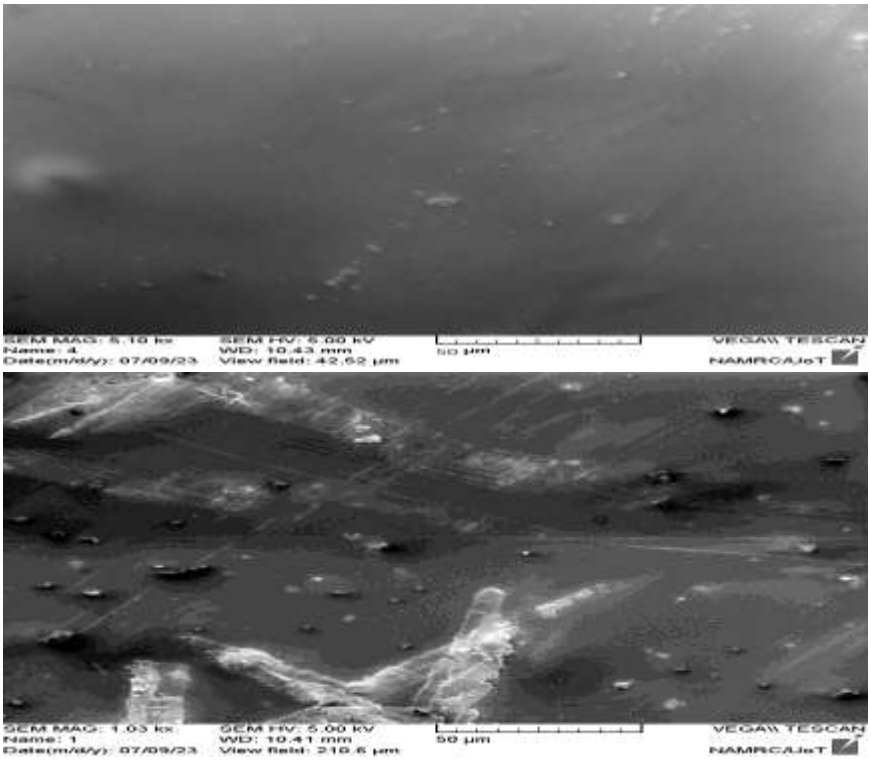

Figure 6. SEM of the PEC film ,(a) blank CS:AG film,and (b) PCV loaded film.

Result of FT- IR spectra

No drug interaction happened upon loading. Similar results observed for acyclovir fabricated in Figure 7 illustrates the FT-IR spectrum of AG, CS, PC, blank film, and drug-loaded film (F10). The spectrum of CS showed peaks at 3552, 3415 Cm^{-1} for hydroxyl and amine group stretching, 3230 cm^{-1} for CH stretch, 1635 cm^{-1} for amide group [45]. The spectra of AG showed a broad band indicative of hydroxyl group stretching vibrations at around 3300 cm^{-1}. Additionally, a peak was observed at approximately 2900 cm^{-1}, which is equivalent to CH stretching vibrations. Furthermore, peaks were seen at 1590 cm-1 and 1495 cm-1, which could be because of the acacia's C and COOH stretching vibrations [46], while The IR spectra of PCV exhibited distinct peaks at 3415 cm^{-1}, that can be attributed to the existence of an aliphatic amine group. Additionally, the observed spectral peaks at 3323 cm^{-1} and 3136 cm^{-1} are indicative of the stretching vibrations associated with the NH bonds. Furthermore, an absorption peak with a wavenumber of 2881 cm^{-1} was discovered, indicating the potential existence of a CH_2 functional group. The carbonyl group of the amide moiety appear at the absorption region 1685 cm^{-1}.

Peaks at 1396, 1305, and 1195 cm^{-1} related to the overlap of the CO and CN bond which represent the amides and amines group [47]. The Fourier-transform infrared (FT-IR) spectra of the CS-AG blank film (in the absence of any other chemicals), exhibited a distinct shift in the amino group towards a lower wave number (1543, 1639 cm^{-1}), as bending peak. The recognized shift in the spectrum implies the existence of an electrostatic connection between the amine group of CS in its protonated form and the negatively charged AG component. The observed variation in the carbonyl stretching of the amide I peak and the CH_2 bending peak of CS might potentially be related to the establishment of intermolecular hydrogen bonds between the carboxylic group in AG and CS [44]. In the drug loaded film, the main peaks of PCV still available (without shifting) indicating PEC matrix

[48].

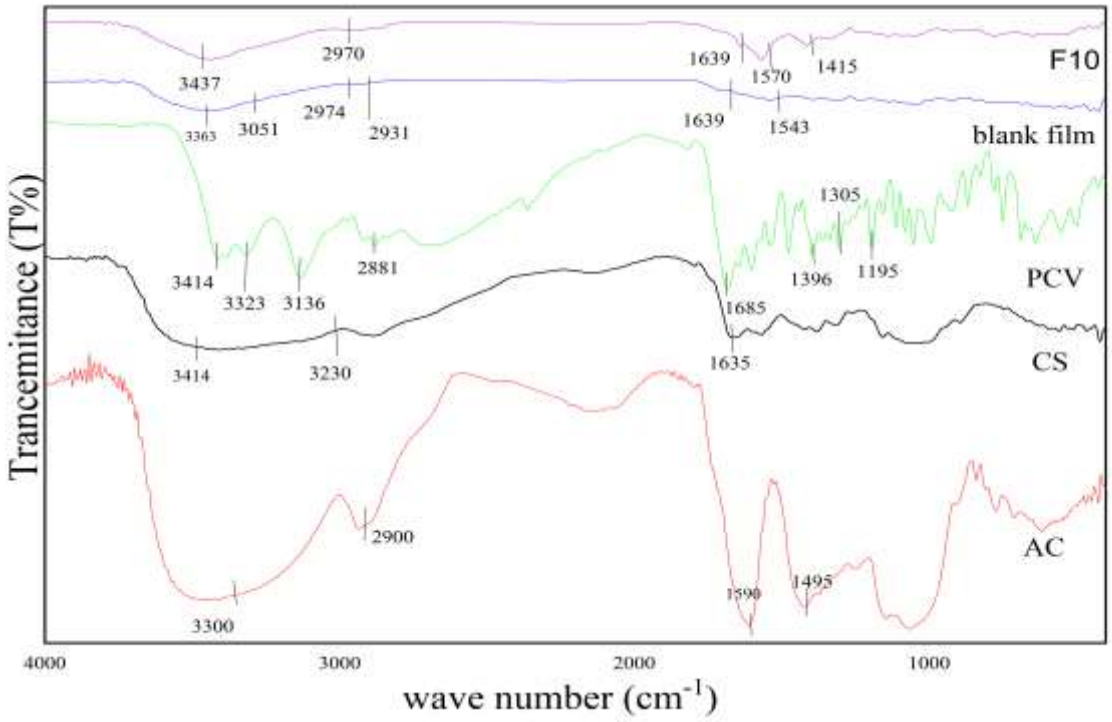

Figure 7. The FT-IR spectrum of chitosan (CS), acacia (AG), pure drug (PCV) , blank CS:AG (PEC) film, and (PCV loaded PEC film (F10).

Conclusion

This work succeeded in preparing polyelectrolyte complex film using chitosan and acacia for penciclovir by solvent casting method that had high %EE , good bioadhesion properties with drug release continued for 12 hr. , that could be easily applied to the skin as alternative to the marketed topical cream to improve patient compliance where the topical cream usually applied every 2 hr.

Acknowledgment

The authors would like to thank Mustansiriyah University (www. uomustansiriyha .edu.iq) for supporting this work.

Funding

This research did not receive any financial support from any institution.

Conflict of interest

The authors would like to confirm that there are no conflict of interest with this work .

Author contribution

The authors contributed to the manuscript equally.

Reference

1. Alsaide NH, Maraie NK. Insights into medicated films as attractive dosage forms. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2023;23(1):1-13.
2. Potaś J, Szymańska E, Winnicka K. Challenges in developing of chitosan–based polyelectrolyte complexes as a platform for mucosal and skin drug delivery. European Polymer Journal. 2020;140:110020.
3. Hamzah ZO. Utilization of Natural Polyelectrolytes in the Preparation of Naproxen as Sustained Release Matrix Tablet. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2019;19(2):17-29.
4. Lefnaoui S, Moulai-Mostefa N, Yahoum MM, Gasmi SN. Design of antihistaminic transdermal films based on alginate–chitosan polyelectrolyte complexes: characterization and permeation studies. Drug development and industrial pharmacy. 2018;44(3):432-43.
5. Paşcalău V, Bogdan C, Pall E, Matroş L, Pandrea S-L, Suciu M, et al. Development of BSA gel/Pectin/Chitosan polyelectrolyte complex microcapsules for Berberine delivery and evaluation of their inhibitory effect on Cutibacterium acnes. Reactive and Functional Polymers. 2020;147:104457.
6. Dehghan MHG, Marzuka M. Lyophilized chitosan/xanthan polyelectrolyte complex based mucoadhesive inserts for nasal delivery of promethazine hydrochloride. Iranian journal of pharmaceutical research: IJPR. 2014;13(3):769.
7. Sharma S, Swetha KL, Roy A. Chitosan-Chondroitin sulfate based polyelectrolyte complex for effective management of chronic wounds. International journal of biological macromolecules. 2019;132:97-108.
8. Alkahtani S, Hasnain MS, Nayak AK, Aminabhavi TM. Polysaccharide-based

polyelectrolyte complex systems for biomedical uses. Tailor-Made Polysaccharides in Biomedical Applications: Elsevier; 2020. p. 151-74.

9. Li D, Zhang Q, Deng B, Chen Y, Ye L. Rapid, sensitive detection of ganciclovir, penciclovir and valacyclovir-hydrochloride by artificial neural network and partial least squares combined with surface enhanced Raman spectroscopy. Applied Surface Science. 2021;539:148224.
10. Hosny KM, Sindi AM, Alkhalidi HM, Kurakula M, Alruwaili NK, Alhakamy NA, et al. Oral gel loaded with penciclovir–lavender oil nanoemulsion to enhance bioavailability and alleviate pain associated with herpes labialis. Drug Delivery. 2021;28(1):1043-54.
11. Yaşayan G. Chitosan films and chitosan/pectin polyelectrolyte complexes encapsulating silver sulfadiazine for wound healing. İstanbul Journal of Pharmacy. 2020;50(3):238-44.
12. Anirudhan T, Nair SS. Deposition of gold-cellulose hybrid nanofiller on a polyelectrolyte membrane constructed using guar gum and poly (vinyl alcohol) for transdermal drug delivery. Journal of Membrane Science. 2017;539:344-57.
13. Rahman L, Lembang RS, Lallo S, Handayani SR, Permana AD. Bioadhesive dermal patch as promising approach for improved antibacterial activity of bioactive compound of Zingiber cassumunar Roxb in ex vivo Staphylococcus aureus skin infection model. Journal of Drug Delivery Science and Technology. 2021;63:102522.
14. Hamedi H, Moradi S, Tonelli AE, Hudson SM. Preparation and characterization of chitosan–alginate polyelectrolyte complexes loaded with antibacterial thyme oil nanoemulsions. Applied Sciences. 2019;9(18):3933.
15. Sharma A, Puri V, Kumar P, Singh I. Rifampicin-loaded alginate-gelatin fibers incorporated within transdermal films as a fiber-in-film system for wound healing applications. Membranes. 2020;11(1):7.
16. Sadeq ZA, Rajab NA, Abd Alhammid SN, Zaki H. Preparation, in-vitro evaluation, mechanical characterization, and release of nebivelol hydrochloride as a transdermal film using combined eudragite-polyvinyl alcohol as adhesive film forming polymer. Journal of pharmaceutical sciences and research. 2019;11(3):1052-5.
17. Yousif NZ, Maraie NK. Optimization and evaluation of metoclopramide HCl as mucoadhesive buccal patch. World J Pharm Res. 2015;4(2):79-99.
18. Pansara C, Mishra R, Mehta T, Parikh A, Garg S. Formulation of chitosan stabilized silver nanoparticle-containing wound healing film: in vitro and in vivo characterization. Journal of pharmaceutical sciences. 2020;109(7):2196-205.
19. Soud SA. Affect the Cross Linking Degree and Polymer Composition on the Mechanical Properties of Poly (vinyl alcohol)/Pullu-lan Films. Al-Mustansiriyah J Sci. 2017;28:86-92.
20. Sakloetsakun D, Preechagoon D, Bernkop-Schnürch A, Pongjanyakul T. Chitosan–gum arabic polyelectrolyte complex films: Physicochemical, mechanical and mucoadhesive properties. Pharmaceutical Development and Technology. 2016;21(5):590-9.
21. Ćirić A, Medarević Đ, Čalija B, Dobričić V, Rmandić M, Barudžija T, et al. Effect of ibuprofen entrapment procedure on physicochemical and controlled drug release performances of chitosan/xanthan gum polyelectrolyte complexes. International Journal of Biological Macromolecules. 2021;167:547-58.
22. Wang L, Yang S, Cao J, Zhao S, Wang W. Microencapsulation of ginger volatile oil based on gelatin/sodium alginate polyelectrolyte complex. Chemical and Pharmaceutical Bulletin. 2016;64(1):21-6.
23. Wu D, Delair T. Stabilization of chitosan/hyaluronan colloidal polyelectrolyte complexes in physiological conditions. Carbohydrate polymers. 2015;119:149-58.
24. Anirudhan T, Shainy F, Thomas JP. Effect of dual stimuli responsive dextran/nanocellulose polyelectrolyte complexes for chemophotothermal synergistic cancer therapy. International journal of biological macromolecules. 2019;135:776-89.
25. Mishra B, Mishra M, Yadav SK. Antibacterial loaded spray dried chitosan polyelectrolyte complexes as dry powder aerosol for the treatment of lung infections. Iranian Journal of Pharmaceutical Research: IJPR. 2017;16(1):74.
26. Lopes SA, Veiga IG, Bierhalz ACK, Pires ALR, Moraes ÂM. Physicochemical properties and release behavior of indomethacin-loaded polysaccharide membranes. International Journal of Polymeric Materials and Polymeric Biomaterials. 2019;68(16):956-64.
27. Putri FR, Adjeng ANT, Yuniar N, Handoyo M, Sahumena MA. Formulation and physical characterization of curcumin nanoparticle transdermal patch. Int J Appl Pharm. 2019;11:217-21.
28. Lal N, Dubey J, Gaur P, Verma N, Verma A. Chitosan based in situ forming polyelectrolyte complexes: A potential sustained drug delivery polymeric carrier for high dose drugs. Materials Science and Engineering: C. 2017;79:491-8.
29. Yan J-K, Qiu W-Y, Wang Y-Y, Wu L-X, Cheung PC. Formation and characterization of

polyelectrolyte complex synthesized by chitosan and carboxylic curdlan for 5-fluorouracil delivery. International journal of biological macromolecules. 2018;107:397-405.

30. Espinosa-Andrews H, Báez-González JG, Cruz-Sosa F, Vernon-Carter EJ. Gum arabic−chitosan complex coacervation. Biomacromolecules. 2007;8(4):1313-8.

31. Lee M-H, Chun M-K, Choi H-K. Preparation of Carbopol/chitosan interpolymer complex as a controlled release tablet matrix; Effect of complex formation medium on drug release characteristics. Archives of pharmacal research. 2008;31:932-7.

32. Yegappan R, Selvaprithiviraj V, Amirthalingam S, Jayakumar R. Carrageenan based hydrogels for drug delivery, tissue engineering and wound healing. Carbohydrate polymers. 2018;198:385-400.

33. Shao Y, Li L, Gu X, Wang L, Mao S. Evaluation of chitosan–anionic polymers based tablets for extended-release of highly water-soluble drugs. Asian journal of pharmaceutical sciences. 2015;10(1):24-30.

34. Sosnik A, das Neves J, Sarmento B. Mucoadhesive polymers in the design of nano-drug delivery systems for administration by non-parenteral routes: A review. Progress in Polymer Science. 2014;39(12):2030-75.

35. Manconi M, Mura S, Manca ML, Fadda A, Dolz M, Hernandez M, et al. Chitosomes as drug delivery systems for C-phycocyanin: Preparation and characterization. International Journal of Pharmaceutics. 2010;392(1-2):92-100.

36. Hong H-J, Jin S-E, Park J-S, Ahn WS, Kim C-K. Accelerated wound healing by smad3 antisense oligonucleotides-impregnated chitosan/alginate polyelectrolyte complex. Biomaterials. 2008;29(36):4831-7.

37. Dubey V, Mohan P, Dangi JS, Kesavan K. Brinzolamide loaded chitosan-pectin mucoadhesive nanocapsules for management of glaucoma: Formulation, characterization and pharmacodynamic study. International journal of biological macromolecules. 2020;152:1224-32.

38. Kulkarni AD, Vanjari YH, Sancheti KH, Patel HM, Belgamwar VS, Surana SJ, et al. New nasal nanocomplex self-assembled from charged biomacromolecules: N, N, N-Trimethyl chitosan and dextran sulfate. International journal of biological macromolecules. 2016;88:476-90.

39. Bigucci F, Luppi B, Cerchiara T, Sorrenti M, Bettinetti G, Rodriguez L, et al. Chitosan/pectin polyelectrolyte complexes: Selection of suitable preparative conditions for colon-specific delivery of vancomycin. European journal of pharmaceutical sciences. 2008;35(5):435-41.

40. Sun W, Mao S, Wang Y, Junyaprasert VB, Zhang T, Na L, et al. Bioadhesion and oral absorption of enoxaparin nanocomplexes. International journal of pharmaceutics. 2010;386(1-2):275-81.

41. Pereira R, Carvalho A, Vaz DC, Gil M, Mendes A, Bártolo P. Development of novel alginate based hydrogel films for wound healing applications. International journal of biological macromolecules. 2013;52:221-30.

42. Schroeder IZ, Franke P, Schaefer UF, Lehr C-M. Development and characterization of film forming polymeric solutions for skin drug delivery. European Journal of Pharmaceutics and Biopharmaceutics. 2007;65(1):111-21.

43. Rezvanian M, Amin MCIM, Ng S-F. Development and physicochemical characterization of alginate composite film loaded with simvastatin as a potential wound dressing. Carbohydrate polymers. 2016;137:295-304.

44. Armenta-Rojas E, Cornejo-Bravo JM, Serrano-Medina A, López-Maldonado EA, Olivas-Sarabia A, Castillo-Martínez NA, et al. Nystatin-loaded polyelectrolyte complex films as a mucoadhesive drug delivery system for potential buccal application. Biointerface Res Appl Chem. 2022;12:4384-98.

45. Amini-Fazl MS, Mohammadi R, Kheiri K. 5-Fluorouracil loaded chitosan/polyacrylic acid/Fe3O4 magnetic nanocomposite hydrogel as a potential anticancer drug delivery system. International journal of biological macromolecules. 2019;132:506-13.

46. Güldiken ÇG, Karaosmanoğlu O, Sivas H, Gerçel HF. ZnO microparticle-loaded chitosan/poly (vinyl alcohol)/acacia gum nanosphere-based nanocomposite thin film wound dressings for accelerated wound healing. Journal of Applied Polymer Science. 2020;137(10):48445.

47. Meira RZ, Biscaia IF, Nogueira C, Murakami FS, Bernardi LS, Oliveira PR. Solid-state characterization and compatibility studies of penciclovir, lysine hydrochloride, and pharmaceutical excipients. Materials. 2019;12(19):3154.

48. Malik NS, Ahmad M, Minhas MU, Tulain R, Barkat K, Khalid I, et al. Chitosan/xanthan gum based hydrogels as potential carrier for an antiviral drug: Fabrication, characterization, and safety evaluation. Frontiers in chemistry. 2020;8:50.

تصميم غشاء رقيق بتقنية المعقد المتعدد الشحنات كنظام توصيل دوائي عبر الجلد لدواء البنسكلوفير

مينا عماد طه[١] و نضال خزعل مرعي*[٢]

[١]فرع الصيدلانيات، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق.

[٢]فرع الصيدلانيات، كلية الصيدلة، جامعة الفراهيدي، بغداد، العراق.

الخلاصة

الاغشية الرقيقة عبارة عن طبقات بوليمرية مرنة الى حد ما نتيجة احتوائها على مادة ملدنة في اغلب الاحيان. في هذه الدراسة تم استخدام عقار البنسكلوفير من المجموعة الثالثة حسب تصنيف علم الصيدلانيات, و هو دواء ذائب في الماء لكن ذو نفاذية ضعيفة, و توافر حيوي محدود (٥- ١٠٪) , بالإضافة الى قصر عمر النصف (ساعتين). تهدف هذه الدراسة الى تحضير وتقيم غشاء رقيق لاصق حيويا بتقنية المعقد المتعدد الشحنات محمل بدواء البنسكلوفير لمعالجة العدوى الفيروسية للجلد. حضرت هذه الاغشية بطريقة صب المذيبات باستخدام الكيتوسان (كبوليمر ذو شحنة موجبة) مع الصمغ العربي (كبوليمر ذو شحنة سالبة) كمكونات رئيسية للغشاء البوليمري. حضرت هذه الاغشية بتراكيز مختلفة لكل من الكيتوسان والصمغ العربي , وتغير الاسي الهيدروجين لمزيج البوليمرات , وايضا تمت المقارنة استخدام نوعين مختلفين من الكيتوسان (حسب الوزن الجزيئي). تم تقييم الاغشية بالنسبة لقدرة تحميل الدواء, معدل انطوائية الغشاء, ونسبة الانتفاخ, خاصية الالتصاق الحيوي , ومعدل اطلاق الدواء عبر الغشاء. اظهرت النتائج ان افضل غشاء كان له قدرة تحميل دوائية عالية تصل الى ٩٠٪ و معدل انتفاخ جيد و قوة التصاق حيوي جيدة تصل الى ٠,١٣٣ نيوتن. اما عملية اطلاق الدواء فكانت بطيئة حيث تم اطلاق ٥٧,٣ % من الدواء خلال ٦ ساعات فقط و استغرت العملية حوالي ١٢ ساعة لاطلاق الجرعة الدوائية بالكامل. اما بالنسبة لفحص الاشعة تحت الحمراء حيث اثبتت النتائج تكوين المعقد بين الكيتوسان والصمغ العربي . واخيرا يمكن اعتبار هذا الغشاء (F10) بديل مناسب للشكل الدوائي المتوفر بالصيدليات لزيادة التزام المريض بالعلاج.

الكلمات المفتاحية :الصمغ العربي,الكيتوسان , دواء البنسكلوفير , معقد متعدد الالكتروليت , مستحضر جلدي