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Formulation and Optimization of Film Forming System Containing Hydrocortisone Drug

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صياغة وتحسين نظام تشكيل الفيلم المحتوي على دواء هيدروكورتيزون

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Abstract:
For the topical distribution of the medication hydrocortisone, the current effort aimed to create, characterize, and optimize In-Situ Film formulations including the following polymers in varying concentrations: hydroxypropylcellulose, ethylcelullose, and eudragite E100. Hydrocortisone was synthesized in an in-situ film-forming formulation employing HPC, EC, and Eudragite E100 at two concentrations of each polymer (5% and 8%, respectively). Water, ethyl alcohol, and poropylen glycol are used as solvents and plasticizers. Formulations were evaluated using a variety of characteristics, including viscosity, drug content, in vitro release drug, drying time, pH value, physical appearance, and external sickness. All formulations are visually appealing and transparent, except for F3 and F6, which are white in color. The film-forming formulations exhibited a drying time of 2 to 3 minutes, which is deemed acceptable. The pH value of all formulations was acceptable. The viscosities of the F1, F2, and F3 formulas rose above those of F4, F5, and F6 at lower shear rates because the concentration of polymers in the first film-forming formulations was increased. The hydrocortisone content ranged from (97.22±1.3 to 105.67±1.7). The formulation that forms a film offers a good drug percentage content, rendering clinical delivery of the drug feasible. The rise in polymer concentration in film-forming formulations like F1, F2, and F3 led to lower release values compared to other formulations with lower polymer concentrations, such as F4, F5, and F6. After three months, results for F4 and F5 showed no difference in pH value or drying time. Moreover, after three months of storage, the viscosity value and drug content of the In-Situ films were successfully preserved.

Keywords: Hydrocortison, Film forming system, Hydroxypropyl cellulose. Eudragit E100, Ethylcellulose

الملخص
للتوزيع الموضعي لدواء الهيدروكورتيزون، يهدف الجهد الحالي إلى إنشاء وتوصيف وتحسين تركيبات أغشية موضعية، تتضمن البوليمرات التالية بتركيزات مختلفة: هيدروكسي بروبيل سلولوز، وإيثيل سلولوز، ويودراجيت *E100*. تم تصنيع الهيدروكورتيزون في تركيبة أغشية موضعية باستخدام *HPC* و*EC* و*Eudragite E100* بتركيزين لكل بوليمر (5% و8% على التوالي). استُخدم الماء، والكحول الإيثيلي، وبوروبيلين جليكول كمذيبات وملدنات. تم تقييم التركيبات باستخدام مجموعة متنوعة من الخصائص، بما في ذلك اللزوجة، ومحتوى الدواء، ودواء الإطلاق المختبري، ووقت التجفيف، وقيمة الرقم الهيدروجيني، والمظهر الفيزيائي، والأعراض الخارجية. جميع التركيبات جذابة بصريًا وشفافة، باستثناء *F3* و*F6*، ذات اللون الأبيض. أظهرت التركيبات المكونة للأغشية وقت تجفيف يتراوح بين دقيقتين وثلاث دقائق، وهو وقت مقبول. كانت قيمة الرقم الهيدروجيني لجميع الصيغ مقبولة. ارتفعت لزوجة تركيبات *F1* و*F2* و*F3* عن لزوجة *F4* و*F5* و*F6* عند معدلات قص منخفضة، وذلك لزيادة تركيز البوليمرات في التركيبات الأولى المكونة للأغشية. تراوح محتوى

الهيدروكورتيزون بين (97.22±1.3 و105.67±1.7). توفر التركيبة التي تشكل الغشاء نسبة جيدة من محتوى الدواء، مما يجعل توصيل الدواء سريريًا ممكنًا. أدى ارتفاع تركيز البوليمر في التركيبات المكونة للأغشية مثل *F1* و*F2* و*F3* إلى انخفاض قيم الإطلاق مقارنةً بالتركيبات الأخرى ذات تركيزات البوليمر المنخفضة، مثل *F4* و*F5* و*F6*. بعد ثلاثة أشهر، لم تُظهر نتائج *F4* و*F5* أي فرق في قيمة الرقم الهيدروجيني أو وقت التجفيف. علاوة على ذلك، بعد ثلاثة أشهر من التخزين، تم الحفاظ على قيمة اللزوجة ومحتوى الدواء في الأغشية الموضعية بنجاح.

الكلمات المفتاحية: هيدروكورتيزون، نظام تشكيل الأغشية، هيدروكسي بروبيل سليلوز. يودراجيت E100، إيثيل سليلوز.

Introduction

Dermal products that are applied topically can be classified according to whether they are intended to create effects that are local or systemic. These systems are usually used for local skin infections when other ways of delivering medication do not work [1]. A drug that is delivered through the skin passively should possess sufficient lipophilicity and a molecular mass of less than 500 Da. Drugs that are applied dermally arrive at the target area in optimal concentration, which reduces side effects and enhances bioavailability and patient compliance [2]. The skin is one of the primary organs for topical drug delivery, as it is readily accessible in the human body. The stratum corneum acts as a primary barrier to the penetration of drugs into and through the skin. This layer, however, renders the delivery system selective. Making the skin a target organ for diagnosis and treatment is a key aspect of topical drug delivery [3].

Topical drug delivery systems are designed for the local administration of therapeutic agents through the skin to address cutaneous disorders. These systems are typically employed for local skin infection. The formulations come in various forms, ranging from solid to semisolid to liquid. When the solution's drug substance is a non-electrolyte and has a favorable lipid/water partition coefficient, skin absorption of the drug is enhanced. Various formulations and consistencies characterize dermatological products, although semisolid dosage forms are the most popular among them [4]. The films produced offer significant benefits compared to traditional topical dosage forms; they are flexible, dry quickly, are less greasy, and do not risk be wiped off the skin like semisolid formulations.

The most vital characteristic of in situ film forming solutions is, above all, that they maintain complete skin contact for the duration of application without causing fixation or irritation, unlike topical patches. This possible benefit is particularly crucial for managing chronic skin diseases, where the need for repeated application contributes to low patient compliance and satisfaction, as well as unsatisfactory treatment results. Hydrocortisone is a corticosteroid medication employed in the therapy of atopic dermatitis. Hydrocortisone (C21H30O5) is a medication belonging to the corticosteroid group, with antiallergic and anti-inflammatory properties. These medications have a low potency and are typically employed in the treatment of atopic dermatitis. The BCS (Biopharmaceutical Classification System) categorizes hydrocortisone as a class II substance, characterized by high permeability and low dissolution rate.

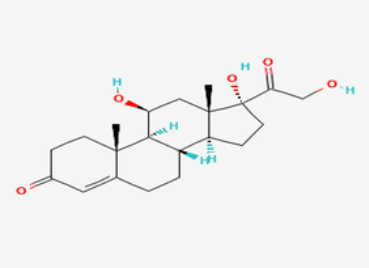

Figure (1): Structure of hydrocortisone

Hydrocortisone can be found in various forms, including a rectal cream, spray, powder for injection, ointment with concentrations of 0.5%, 1%, and 2.5%, ear solution at 1%, topical solution with concentrations of 0.1% and 2.5%, suspension solution, rectal suppositories, and tablets [5]. Hydrocortisone holds significant pharmacological importance due to its widespread use and FDA approval in 1952. It is primarily used for the therapy of different conditions as skin disorders, allergies, multiple sclerosis, lung disorders, ulcerative colitis and arthritis, lupus lung disorders [6]. Hydrocortisone serves as a steroid replacement for individuals suffering from adrenal insufficiency. Hydrocortisone has an effect on your immune system and is commonly used to address specific blood cell disorders, including anemia and thrombocytopenia. Some cancers, like leukemia, lymphoma, and multiple

myeloma, are also treated with hydrocortisone. With the rise in occurrence of these diseases, allergies and asthma have become more prevalent globally, particularly in Western and economically developed nations. This work aimed to create, characterize, and optimize Film forming formulations for the topical delivery of hydrocortisone. These formulations included varying concentrations of hydroxypropylcellulose, ethylcellulose, and eudragite E100.

Material and methods

Materials

A standard of hydrocortisone HCL was acquired from Sigma-Aldrich (USA). Hydroxypropyl cellulose (HPC), Ethylcellulose, and Eudragite E100 were sourced from El Pharaonia Pharmaceutical Co. in Alexandria, Egypt. Ethanol (96%) was acquired from Al-Zahra ALbyda company in Al-byda, Libya. Propylene glycol (PG) was obtained from the faculty of pharmacy at Omar AL-Mukhtar University in Albyda, Libya. All chemicals employed were of analytical grade.

Methods

UV Spectrophotometry of Hydrocortisone

Hydrocortisone with the equally concentration (50 mg in 100 mL) in ethanol was analyzed using a UV spectrophotometer, and the wavelength of maximum absorbance (λ max) was identified. Hydrocortisone was diluted serially to concentrations of 20, 30, 40, 50, 60, and 90 µg/mL. Using a spectrophotometer, the absorbance of the serial dilutions that were prepared was measured at 288 nm, which is the maximum wavelength. To create a calibration curve, absorbance values were plotted against the corresponding concentrations

In-situ film preparation

The polymer was dissolved in the solvent to prepare the polymeric solution formulations and mixed with a magnetic stirrer until a clear solution formed. The plasticizer (5% v/v) was incorporated into the clear polymeric solution formula obtained and stirred. (1% w/v) was incorporated and dissolved through continuous stirring until the drug was fully integrated into the polymeric solution [7]. Using three different polymers, six formulations were prepared by adjusting the polymer concentration to two levels, as shown in Table 1.

Table 1: Composition of hydrocortisone loaded In-Situ Film of formulations

Ingredients	Formulations					
	F1	F2	F3	F4	F5	F6
HC (%w/v)	1%	1%	1%	1%	1%	1%
HPC (%w/v)	8%	-	-	5%	-	-
Ethocel (%w/v)	-	8%	-	-	5%	-
Eudragite E100 (%w/v)	-	-	8%	-	-	5%
PG (%v/v)	5%	5%	5%	5%	5%	5%
Ethanol (mL)	80%	80%	80%	80%	80%	80%
Distilled water (mL)	5%	5%	5%	5%	5%	5%

Characterization of hydrocortisone in-situ film:

Physical assessment

The physical properties such as appearance, transparency and consistency of the film forming system were evaluated based on visual examination [8].

pH measurement

A digital pH meter was used to measure the pH of gel formulations that had been developed. The pH of each formulation was measured three times, and the average values were calculated [7].

Time for drying

The drying time was evaluated by applying the formulations to the inner sides of a volunteer's forearm. This individual took part in the research on the basis of informed consent. After 2 minutes, a glass slide was positioned on the film without exerting pressure. If, following the removal, there were no visible traces of liquid on the glass slide, the film was considered dry. If any liquid residue was visible on the glass slide, the experiment was repeated until the film was found to be completely dry. [8].

Integrity formulation on skin

As described for assessing the drying time, the formula was applied to a volunteer's forearm. The person being tested used the dry film overnight. A visual inspection was conducted of the test area. after 24 hours for film completeness and any signs of cracking or flaking [8].

External stickiness

To evaluate the characteristics of the film, 1 gram of the preparations was poured into a stainless steel mold to produce films using a solvent evaporation method. The films were allowed to dry for 48 hours at ambient temperature. The outer surface's stickiness was evaluated by applying low pressure

to a dry film with cotton wool. The stickiness was evaluated as high (when there was a dense accumulation of fibers on the film), medium (when there was a thin fiber layer on the film), or low (when fibers adhered occasionally or not at all), based on the amount of cotton fibers retained by the film [8].

Viscosity

The viscosity of gels was assessed with a Brookfield Digital viscometer equipped with a cone and plate measuring system using spindle 4. The sample was positioned in the space between the cone and plate, and this space was slowly closed. The sample underwent dynamic shear rates of 5, 10, 20, 50, and 100 rpm, and its viscosity was assessed. All measurements were conducted under isothermal conditions at room temperature (25 ˚C ± 2) [9].

Drug content

In order to assess the amount of drug present A 50 mL volumetric flask was filled with 10 mL of phosphate buffer solution (pH 6.5) and 1 g of gel was added. The volume was adjusted to the calibration mark with additional phosphate buffer solution (pH 6.5), after which the mixture was filtered and appropriately diluted. The absorbance of the solution prepared was measured at the λ max of 288 nm using a UV-visible spectrophotometer [7].

In-vitro drug release study (Diffusion study)

The dissolution studies of the HC from gel formulations were performed using a USP dissolution Apparatus II with drug diffusion cells across dialysis bags. Approximately 1.0 g of each gel formulation (corresponding to 10 mg of HC) was inserted into the diffusion cell, covered with a dialysis bag, and immersed in a vessel containing 500 mL of phosphate buffer at pH 6.5. The temperature was maintained at 37 ± 0.5 ◦C, with a stirring rate of 75 rpm. At the specified time intervals (1h, 2h, 3h, and 4h), a volume of 5 mL was taken from the acceptor medium and examined with UV spectrophotometry at a λ max of 288 nm.

Storage stability study

The formulations were assessed primarily based on their physical characteristics at the scheduled intervals of one month and three months. The pH value, drug content, viscosity and drying time were assessed.

Results and discussion

Hydrocortisone UV spectrophotometry

The hydrocortisone concentration calibration curve in the ethanol organic solvent was represented by the equation Y = 0.0072x - 0.0174. Hydrocortisone levels of (20–90 µg/mL). The plot shows a strong linear correlation (R^2 = 0.9975) between HC concentrations and absorbance at the maximum wavelength of 288 nm as shown Figure 2.

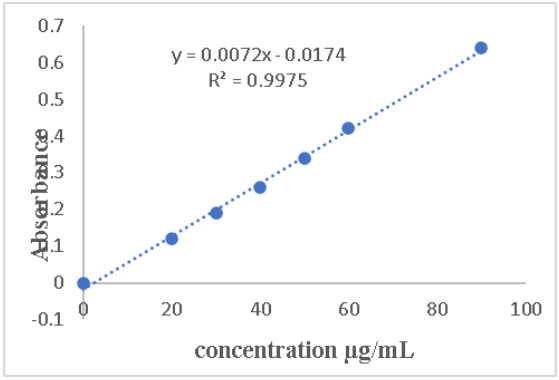

Figure 2: Calibration curve of hydrocortisone at 288 nm.

Screening of polymers and evaluation in vitro of preparation of polymeric In-Situ film:

It was crucial to pinpoint a volatile solvent that offers the drug its highest solubility as a first measure for the formulation. The literature survey revealed that the drug exhibits the highest solubility in ethanol compared to other volatile solvents. Furthermore, during the creation of the drug-loaded film, it was observed that ethanol evaporated rapidly, resulting in a drug-loaded film devoid of any precipitation. PG was chosen as a plasticizer because it provides the film with good flexibility and a smooth texture. A choice of three polymers from various chemical classes, all characterized as film formers by their suppliers or in literature, was assessed. Each polymer underwent testing at two distinct concentrations: 5% and 8% w/w. the properties of the resulting films are significantly influenced by both the polymer's nature and its content. It is crucial to select the right polymer, as it must be soluble in a volatile solvent that is compatible with skin. Polymers that have inadequate solubility in volatile solvents face issues such as extended drying times or an inability to produce clear solutions and, consequently,

homogeneous clear films. As demonstrated in the subsequent characterization. The evaluation criteria used were founded on essential characteristics for practical, precise, and patient-friendly use of this dosage form. As demonstrated in the subsequent characterization [10].

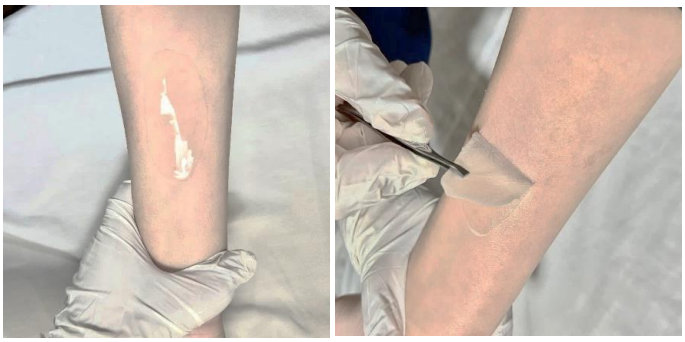

Figure (3): Application of a film-forming formulation.

Characterization of hydrocortisone in-situ film:

Physical characteristic

The formulation's appearance was assessed visually and characterized as clear or opaque, with or without polymer precipitation. The films were evaluated for their cosmetic appearance[5], films that are complete, uniform, and transparent were considered very cosmetically attractive. Although they were incomplete, non-uniform and/or visible films were deemed less appealing. As shown in Figure (4) and Table (2), all formulations F1, F2, F3, F4, F5, and F6 were deemed successful when appearances were clear.

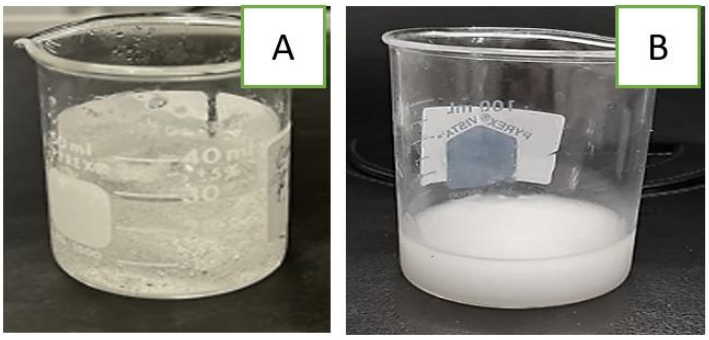

Figure (4): A. Placebo film forming formulation (F4), B. HC film forming formulation (F4).

Table (2): Physical characteristic of blank and HC film forming formulations:

		Blank film forming formulations			HC film forming formulations		
No.	**Code**	**Appearance**	**Transparency**	**consistency**	**Appearance**	**Transparency**	**consistency**
1	F1	Thick	Transparent	Smooth	Thick	Opaque	Smooth
2	F2	Medium	Transparent	Smooth	Medium	Opaque	Smooth
3	F3	Thin	White color	Smooth	Thin	Opaque	Smooth
4	F4	Thin	Transparent	Smooth	Thin	Opaque	Smooth
5	F5	Thin	Transparent	Smooth	Thin	Opaque	Smooth
6	F6	Thin	White color	Smooth	Thin	Opaque	Smooth

pH measurement:

A glass electrode from the pH meter was used to measure the pH in triplicate. The results of the pH test indicated that all hydrocortisone In-situ film formulations conform to the skin-tolerable pH criteria. pH fluctuated from 6.6 to 6.7 as showed in Table 3.

Time for drying

The formed films have drying time as a highly significant attribute. To avoid long waiting times for the patient, it is convenient that the films have a drying time of 5 minutes or less [11]. The drying time

of in-situ film formulations, as indicated in table (4), ranged from 1 minute to 3 minutes. All formulations demonstrated a short drying time.

Table (3): pH value of HC film forming formulations

Formulation code	pH value
F1	6.58±0.1
F2	6.71±0.08
F3	6.72±0.1
F4	6.52±0.2
F5	6. 32±0.08
F6	6.64±0.1

Table (4): Drying time of HC film forming formulations

NO.	Formulation code	Drying time
1	F1	3 min.±0.06
2	F2	2 min.±0.08
3	F3	1 min.±0.08
4	F4	3 min.±0.09
5	F5	2 min.±0.06
6	F6	1min. ±0.07

Integrity formulation on skin

The integrity of the formulations on the skin, appearing as a thin, almost film-like layer, was assessed for formulations F1 to F6. Below is a table of the test results.

Table (5): Integrity of film after 24 hours.

NO.	Formulation code	Integrity of film after 24 hours
1	F1	Good
2	F2	Good
3	F3	Good
4	F4	Good
5	F5	Good
6	F6	flake

The film-forming formulations F1, F2, F3, F4, and F5 produced films that were flexible, soft to the touch, and fully intact after 24 hours. Films created by F6 formulation were flaky and had ruptures in certain areas. Figure (5) demonstrates the integrity of the film created with formulation F2.

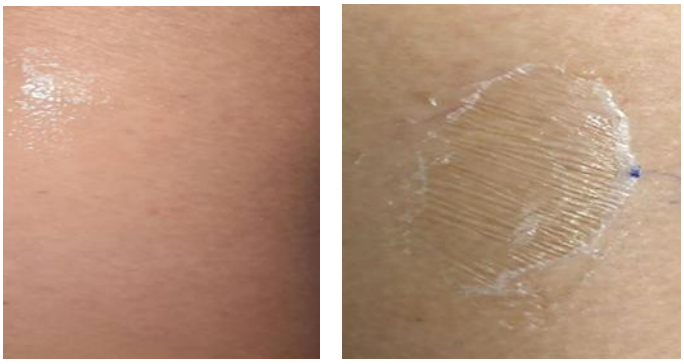

Figure (5): Integrity of Film forming formulation of F2 before (A) and after 24 hours (B)

External stickiness

The outward stickiness of the films was assessed by applying minimal pressure with cotton wool on the dry film [12]. Except for F6, all film-forming formulations that demonstrated low outward stickiness exhibited medium levels of outward stickiness. Table (6) presents the results for outward stickiness of the formulations.

Table (6): External stickiness of preparations that form a film

NO.	Formulation code	Observation
1	F1	Low
2	F2	Low
3	F3	low
4	F4	low
5	F5	low
6	F6	medium

Viscosity

Viscosity measurements were obtained by applying shear rate values that increased progressively. In the continuous shear rheology study, all formulations demonstrated shear-thinning behavior (pseudoplastic flow) at room temperature (25˚C ± 2), which is advantageous for the diffusion of the active ingredient. In the context of Figure 6, which depicts viscosity in relation to shear rate, it was observed that the viscosities of formulas F1, F2, and F3 were greater than those of F4, F5, and F6 at lower shear rates. However, as the concentration of polymers in the initial film-forming formulations rose, the viscosity decreased with an increase in shear rate [9]. The rheogram of film-forming formulations demonstrate that the system exhibits shear-thinning behavior, which is desirable for topical formulation.

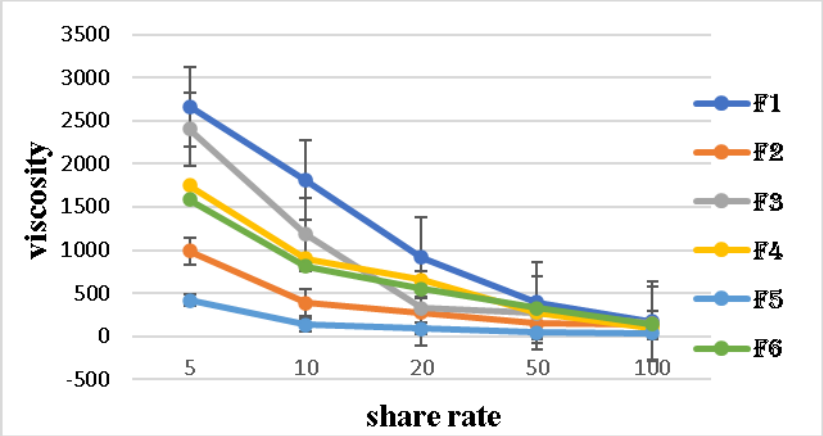

Figure (6): Apparent viscosity of film forming formulations. at room temperature.

Drug content:

Hydrocortisone levels in the film-forming formulations made with various polymers (HPC, EC, EUD) and at differing concentrations (8% and 5%) were measured using UV spectrophotometry at a wavelength of 288 nm. The results ranged from (96.34±1.7 to 105.67±1.7). The formulation that forms a film offers a good drug percentage content, rendering clinical delivery of the drug feasible [7].

Table (7): Drug content of hydrocortisone film forming formulations

No.	Formulation code	Drug content (%) (±SD)
1	F1	97.52±2.5
2	F2	96.34±1.7
3	F3	97.22±1.3
4	F4	98.97±1.5
5	F5	101.36±2.3
6	F6	105.67±1.7

In-vitro release study

The hydrocortisone in-vitro release study from various formulations was conducted three times with the dialysis membrane diffusion method. The release study demonstrated that the type of polymer used, and its concentration influenced the drug's release from the formulation. The investigation revealed that the hydrophilic polymer, such as HPC, exhibited a superior sustained release property in comparison to the hydrophobic polymers like EC and Eudragit E 100. Furthermore, as illustrated in figure (7 a), the release values decreased with the rise in polymer concentration in film-forming formulations. The hydrocortisone-free solution demonstrated a quicker release of hydrocortisone across all time intervals in comparison to various film-forming formulations, as illustrated in figure (7a). As illustrated in figure (7b), the film-forming formulations F4, F5, and F6 respectively enhanced drug

release after 4 hours compared to F1, F2, and F3. This was due to an increase in polymer concentration, which resulted in a reduction of the in vitro release. Among the four polymers utilized, those with a concentration of 5% exhibited the highest drug release. As shown in Figure (7c), after 4 hours, almost 70% of the drug was released from the formulation containing 5% HPC and 5% EC. Considering the low viscosity, rapid drying time, and relatively sustained drug release, formulations made with HPC were chosen for further development. Furthermore, the HPC film was observed to be non-sticky and to remain well adhered to the skin for an extended duration without dispersing from the application site [13].

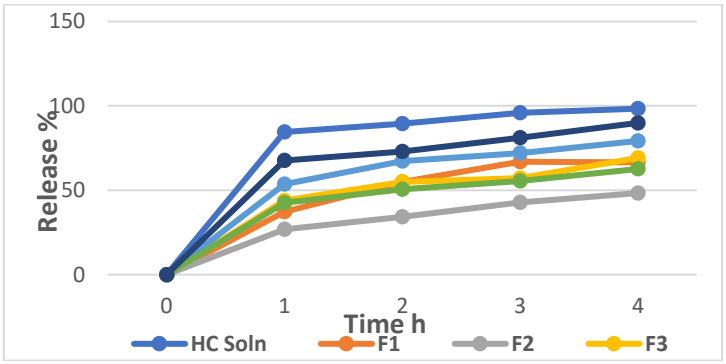

Figure 7 (a): Invitro release of HC soln, F1 (HPC 8%), F2 (EC8%), F3 (EUD 8%), F4 (HPC 5%), F5 (EC 5%), F6 (EUD 5%).

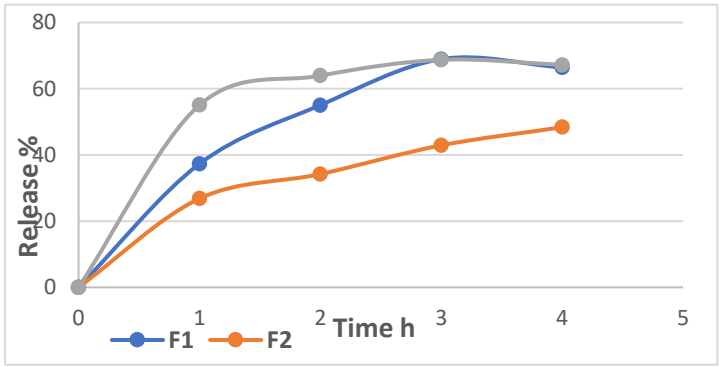

Figure 7 (b): Invitro release of F1 (HPC 8%), F2 (EC8%), F3 (EUD 8%).

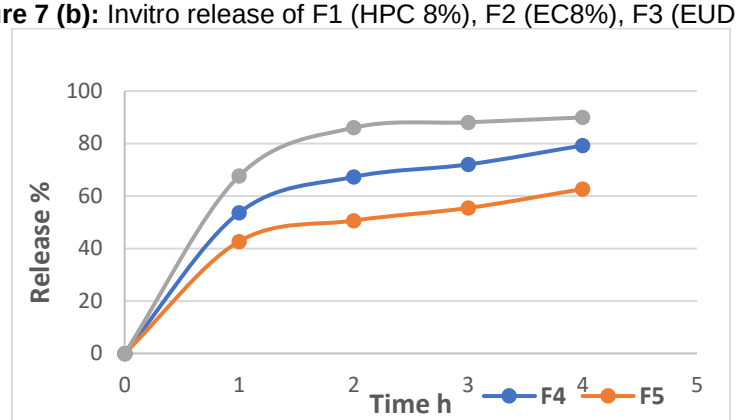

Figure 7 (c): Invitro release of F4 (HPC 5%), F5 (EC 5%), F6 (EUD 5%).

Storage stability study

Formulations F4 and F5, which are film-forming and contain 5% HPC and EC respectively, were stored in a refrigerator for three months to characterize their pH value, drying time, viscosity, and drug content. Results shown in Table (8) indicate that after 3 months, F4 and F5 exhibited no differences in pH value or drying time. Furthermore, after 3 months of storage, the FFF successfully preserved their viscosity profile (Figure 8) and drug content.

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in pH value or drying time. Furthermore, after 3 months of storage, the FFF successfully preserved their viscosity profile as illustrates Figure 8 and drug content.

Table (8): Stability after 3 months storage.

Time (month)	F4			F5		
	pH value	Drying time	Drug content	pH value	Drying time	Drug content
Zero	6.72±0.1	3 min.±0.09	98.97±1.5	6.52±0.2	2 min.±0.06	101.36±2.3
One	6.70±0.1	3 min.±0.14	98.12±1.9	6.52±0.1	2 min.±0.4	100.47±3.6
Three	6.59±0.2	3 min.±0.11	97.93±2.1	6.48±0.2	2 min.±0.2	100.03±2.9

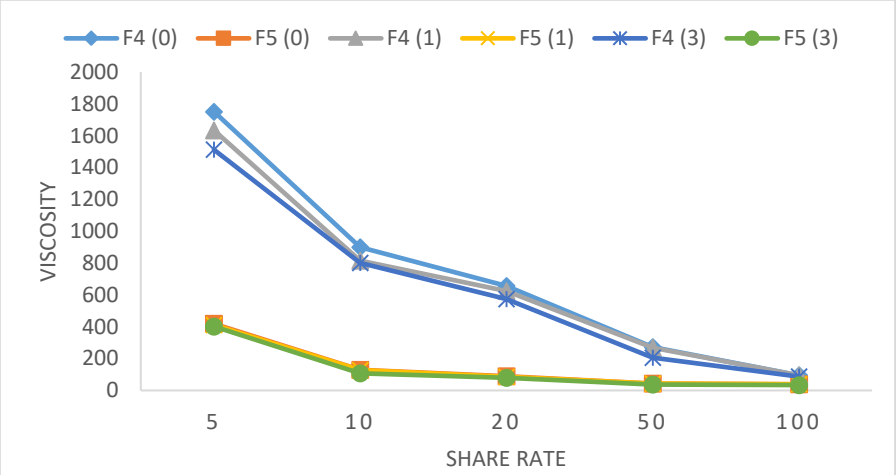

Figure (8): Viscosity of F4 and F5 after storage for three months.

Conclusion

Hydrocortisone was formulated as an in-situ film-forming preparation using hydroxypropyl cellulose, ethyllulose, and Eudragit E100 at two concentrations (5% and 8%) for each polymer. Propylen glycol is used as a plasticizer, while ethyl alcohol and water serve as solvents. The evaluation of the formulations was based on several characterizations, including physical appearance, pH value, drying time, outward sickness, viscosity, drug content, and in vitro release. All formulations are visually appealing and transparent, except for F3 and F6, which are white in color. The film-forming formulations exhibited a drying time of 2 to 3 minutes, which is deemed acceptable. The viscosities of the F1, F2, and F3 formulas rose above those of F4, F5, and F6 at lower shear rates because the concentration of polymers in the first film-forming formulations was increased. The hydrocortisone content ranged from (97.22±1.3 to 105.67±1.7). The formulation that forms a film offers a good drug percentage content, rendering clinical delivery of the drug feasible. The rise in polymer concentration in film-forming formulations like F1, F2, and F3 led to lower release values compared to other formulations with lower polymer concentrations, such as F4, F5, and F6. After three months, results for F4 and F5 showed no difference in pH value or drying time. Furthermore, after three months of storage, the FFF successfully retained their viscosity value and drug content.

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