Preparation and Characterization of Fluocinolone Acetonide as Nanosuspension Based Hydrogel for Topical Skin Administration

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Article Info:

Received 28 May 2024
Revised 25 Jan 2024
Accepted 18 Mar 2025
Published 31 Dec 2025
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DOI: https://doi.org/10.32947/ajps.v25i5.1201

Abstract:

Fluocinolone acetonide (FA), a corticosteroid, was commonly used for treating inflammatory conditions but faced challenges due to poor water solubility, leading to low bioavailability and limited efficacy. To overcome these issues, FA was formulated as a nanosuspension (NS) within a hydrogel matrix. Nanosuspensions formulations were prepared using the precipitation method under ultra-sonication. The findings demonstrate that the prepared fluocinolone acetonide formulations' particle size values fell within the nanosized range. Carbopol at different concentrations (1%,1.5%,2%) was used as a gelling agent. The hydrogel formulations were evaluated through various characterization techniques, including skin irritation tests, spreadability, viscosity, in vitro release studies, ex vivo skin permeation studies, drug release kinetics, and compatibility studies. The results showed that Carbopol was safe, non-irritant, homogeneous, and provided high consistency with excellent spreadability. In vitro release studies demonstrated that FA release from the 1% Carbopol formula (FD1) was faster than that from 1.5% (FD2) and 2% (FD3) formulations. The Higuchi model best describes the drug release kinetics.

Ex vivo permeation studies revealed significantly higher permeation of FANS hydrogel compared to the pure drug hydrogel. FTIR spectra confirmed no significant interaction between the drug and gel base. In conclusion, FA was successfully formulated as a nanosuspension, and Carbopol effectively prolonged skin contact time, enhancing FA, s therapeutic potential for topical administration.

Keywords: Hydrogel, Fluocinolone acetonide, Nanosuspension, Carbopol

تحضير وتوصيف أسيتونيد الفلوسينولون بواسطة هيدروجيل يعتمد على المعلق النانوي للاستخدام الموضعي على الجلد.

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خلاصة

تم استخدام أسيتونيد فلوسينولون (FA)، وهو كورتيكوستيرويد، بشكل شائع لعلاج الحالات الالتهابية، ولكنه واجه تحديات بسبب ضعف قابلية الذوبان في الماء، مما أدى إلى انخفاض التوافر البيولوجي وفعاليته المحدودة. للتغلب على هذه المشكلات، تمت صياغة FA كتعليق نانوي (NS) داخل مصفوفة هيدروجيل. تم تحضير تركيبات المعلقات النانوية باستخدام طريقة الترسيب تحت الصوتنة الفائقة. أظهرت النتائج أن قيم حجم الجسيمات لتركيبات أسيتونيد الفلوسينولون المحضرة تقع ضمن نطاق النانو. تم استخدام الكاربوبول بتراكيز مختلفة (1%، 1.5%، 2%) كعامل تبلور. تم تقييم تركيبات الهيدروجيل من خلال تقنيات التوصيف المختلفة، بما في ذلك اختبارات تهيج الجلد، وقابلية الانتشار، واللزوجة، ودراسات الإطلاق في المختبر، ودراسات تخلل الجلد خارج الجسم الحي، وحركية إطلاق الدواء، ودراسات التوافق. أظهرت النتائج أن كاربوبول آمن، وغير مهيج، ومتجانس، ويوفر اتساقًا عاليًا مع قابلية انتشار ممتازة. أظهرت دراسات الإطلاق في المختبر أن إطلاق FA من تركيبة كاربوبول 1% (FD1) كان أسرع من تركيبات 1.5% (FD2) و2% (FD3). يصف نموذج هيغوتشي بشكل أفضل حركية إطلاق الدواء. كشفت دراسات التغلغل خارج الجسم الحي عن تغلغل أعلى بكثير لـ FANS هيدروجيل مقارنة بالهيدروجيل النقي. أكدت أطياف FTIR عدم وجود تفاعل كبير بين قاعدة الدواء والهلام. في الختام، تمت صياغة FA بنجاح كمعلق نانوي، وقام كاربوبول بإطالة وقت ملامسة الجلد بشكل فعال، مما يعزز الإمكانات العلاجية لـ FA للإعطاء الموضعي.

الكلمات المفتاحية: هيدروجيل، فلوسينولون أسيتونيد، معلق نانوي، كاربوبول

INTRODUCTION

Fluocinolone acetonide is a corticosteroid, mostly used in dermatology to lessen itching and inflammation of the skin. It is derived from hydrocortisone, which is synthetic drug, used topically by applying a small amount of medicine to the skin [1]. FA is classified as Biopharmaceutics classification system (BCS) class II, high penetrability, and poor solubility [2] Nanosuspension is a colloidal system that consist of nanosized drug particles dispersed in a liquid medium . it is useful for improving the solubility of poorly water-soluble drugs . The drug particles are typically in the nanometer range , which increase the surface area and enhanced solubility. It is possible to administer nanosuspension orally, parenterally, pulmonary, or intraocularly [3] Stabilizer plays important role in the formation of nanosuspension. It is used to prevent aggregation , provide high physical stability , controlled release and improved bioavailability. Topical skin administration of drug has advantage for targeted treatment, localized effect, convenience and ease of use, non-invasive route, suitability for dermatological conditions [4]. The use of hydrogel has expanded both in cosmetics and pharmaceutical preparation. Hydrogels are formed from a liquid phase that has been thickened with other ingredients, Carbopol refers to a series of high molecular weight, cross linked polyacrylic acid polymers used primarily as thickening , gelling and stabilizing agents.[5] These polymers are widely used in topical formulations like gels, creams , and ointments because they can create a gel-like consistency that helps to deliver active ingredients effectively. Carbopol enhance the texture spreadability, and stability of pharmaceutical formulations , and its ability to form a gel helps to control the release rate of the drug, thereby improving the product's performance and patient compliance.[6,7] As reported by Vidlarova et al. the use of soluplus in nanosuspensions enhance the dermal delivery of curcumin , a poorly soluble drug. The researchers prepared curcumin nanocrystals stabilized with soluplus and incorporated them into a hydrogel for topical application. The study demonstrated that soluplus stabilized nanosuspension significantly improved the solubility and skin penetration of curcumin compared to

conventional formulations [8]. Also, kaur et al. explored the stabilization of ferulic acid, a poorly water – soluble antioxidant, in a topical gel formulation using a nanosuspension approach. The researchers employed combination of stabilizers, including polyvinyl alcohol (PVA) and polyethylene glycol (PEG), to prepare the nanosuspension, which was then incorporated into a hydrogel for skin application. The nanosuspension -based hydrogel demonstrated enhanced solubility and stability of ferulic acid, as well as improved antioxidant activity compared to conventional formulations [9].The aim of the study was to increase the solubility and permeability of fluocinolone acetonide by forming the drug as nanosuspension, then increase the contact time between drug and skin by formulation of fluocinolone acetonide nanosuspension based hydrogel.

MATERIAL AND METHODS

Materials

FA (fluocinolone acetonide) was bought from SDI, Carbopol 934 was bought from sigma chemicals (USA), Triethanolamine (TEA)was bought from Merck (Germany), Soluplus was bought from BASF company Germany. PVPK 90 was purchased from Germany, Tween 80 (polysorbate 80) was bought from (India), and ethanol was from Germany. Dialysis membrane:70mm Mw8000-14000D from Schuchardt Munchen- (Germany).

Method

Preparation of fluocinolone acetonide nanosuspension (FANS) hydrogel

FANS was prepared by precipitation method under Ultra-sonication technique, in which, (10 mg of fluocinolone acetonide were dissolved in (2) ml of organic solvent (ethanol) to prepare the organic phase for the liquid solvent anti-solvent precipitation method. Conversely, an aqueous phase was created by dissolving a specified weight of stabilizers in (20) milliliters of distilled water as shown in **Table (1)**. This resulted in the preparation of various concentrations of each polymer. Subsequently, the organic phase was added to the aqueous solution at a constant rate (800 rpm) , using a homogenizer with a shearing effect set at 800 rpm. Following the homogenization stage, the preparations were pulsed every five seconds and exposed to probe sonication for five to fifteen minutes using 200 W voltage [10] .

Table 1. Nanosuspension formulations are prepared by solvent-antisolvent precipitation under ultra sonication method.

Formula code	Fluocinolone acetonide	Ethanol(ml)	Water(ml)	PVPK90(mg)	Tween80 (drop)	Soluplus(mg)	Sonicator time(min)
FA	10	2	20	20	2		200W 5min
FB	10	2	20			10	400W 15 min
C	10	2	20			20	400W 15min
FD	10	2	20			30	400W 15 min
FE	10	2	20	20			200w 5min
FF	10	2	20	20			200w 10min

Evaluation of Fluocinolone acetonide nanosuspension

All nanosuspension formulations were evaluated by measuring particle size range, zeta potential, polydispersity index and entrapment efficiency (EE).

Particle size/Polydispersity Index

Particle size analyzer instrument was used **(**Microtrac MRB Wave II**)** to determine the PDI and particle size distribution of the prepared FA nanosuspension. Which used helium gas to detect Brownian movement of particle and measured the variation in light source intensity of 4 micro-Watts (MW) and a 90° angle, this provides a laser width of 18 mm.[11]

Determination of Zeta Potential

The Zeta potential of the nanosuspension formulas was determined through the utilization of (Microtrac MRB Wave II) Three measurements were made at 25 ±1 °C with the sample inside the electrophoretic cell, and the average values were computed.[12]

Determination of Drug Entrapment Efficiency (EE) of nanosuspension

Using a cooling ultracentrifuge, nanosuspensions of various ratios were centrifuged for 20 minutes at 4 C at approximately 13000 rpm. Using a UV spectrophotometer the absorbance of a suitably diluted sample of supernatant was measured at λ max to determine the amount of free drug present. The trial was conducted four times for each formula, and the average was determined. (EE) could be computed using the formula below:

E.E% = (the total drug in a formula – free drug) *100 / total drug in formula (1).[13]

Preparation of fluocinolone acetonide nanosuspension (FANS) hydrogel

The best resulted FANS formula was selected based on above assessments. Then, this formula was incorporated into hydrogel base.

Different percentages of Carbopol (1%,1.5%,2%w/v) were taken then, 5 ml of distilled water was added and kept a side for 2 hours for swelling, next spread by mechanical agitation, then the FANS was added to hydrogel base and dispersed by stirring at 800 rpm. The dispersion was neutralized by adding one drop of triethanolamine [14]. The hydrogel was left to stand overnight to remove any entrapped air as shown in **Table** (2).

Table 2: Formulation of Fluocinolone acetonide nanosuspension based hydrogel

Formulas	FA NS	Carbopol 934	Distilled water
FD1	5 ml	1%	5 ml
FD2	5ml	1.5%	5ml
FD3	5ml	2%	5ml

Evaluation of Fluocinolone acetonide based hydrogel

Physical appearance

The prepared FANS based hydrogel formulation was examined visually to see color, phase separation, consistency, and homogeneity [15].

pH determination

To investigate the pH of FANS based hydrogel, the pH-meter electrode tip was submerged in 10 g of each hydrogel for one minute, and pH reading was recorded. [16]

Drug content.

One gram of hydrogel was added to volumetric flask contain 25ml of ethanol and phosphate buffer 10:100 (pH 5.5), then placed on magnetic stirrer for 2 hours. Then 4 ml sample was withdrawn and filtered in syringe filter (0.45 nm) then measured by measuring absorbance in the UV-visible spectrophotometer at λ max (240 nm). [17-19]

Spreadability studies

100 mg of each formula was placed between two glass slide, 100 g weight was placed on, then mixture was allowed to sit for approximately five minutes or until more spreading occurred. The spread circle diameters were measured and recorded in centimeter(cm) and evaluated with the spread circle's original diameter (the diameter created prior to the weight application) [20].

Viscosity determination

The viscosity of (FD1, FD2, FD3) were measured by Brookfield viscometer using at 37 °C, the viscosity was read directly after 30 seconds. The average viscosity for each formula testing was done calculated after the three times for each formula. [21]

In vitro release of drug from the prepared FANS based hydrogel.

The release of FA from hydrogel was done by using dialysis membrane (bag) (8000-14000 Da). The sealed dialysis membrane incorporated by 10 g of hydrogel contain (2.5 mg) of FA was put in dissolution Apparatus type II filled with 200ml of ethanol and phosphate buffer in ratio (10:100) as dissolution media, stirred with 400 rpm at temperature 37 ^{0}C. Five ml samples withdrawn for suitable time interval and at once replaced with five ml of same media. And estimated the absorbance for each sample at λ max (240 nm). [22]

Mathematical models of drug release kinetics

Number of kinetic models, including zero-order model, first-order model, Hixon Crowell, and Higuchi model, were fitted to the amount released to find the mechanism of FA NS release from Hydrogel. The model that best fit the data was found by taking the highest coefficient of determination (R^2). In addition, the release mechanism can be specified by using the Korsmeyer-peppas model to calculate the value of release exponent (n), which gives the release mechanism. according to reports, Fickian diffusion is shown when the n value equal to or less than 0.5 ($n \leq 0.5$) while anomalous transport (non-Fickian release) is suggested by n values larger than 0.5 and less than 1 ($0.5<n<1$). [23]

Ex vivo permeation study:

In compliance with the Karbala university local ethics committee for animal experiments, the ex vivo permeation studies were conducted. To find out how much FA from the formulations permeated the skin, 385 ±10 g of healthy male albino Wistar rat skins were used, without causing any harm to the skin , the rats' abdominal regions were shaved, the rats were given a lot of anesthesia before being sacrificed. Subcutaneous fat was eliminated, and the rat's entire thickness (2.9 ± 0.9 mm) of abdominal skin was separated.[24]

A Franz cell that with diffusion area of 4.15 cm^2 and a receptor with a capacity of 50 ml was used for this investigation. Rat skin was clamped between donor and receptor compartment. The receptor compartment filled with 50 ml of phosphate buffer pH 5.5 with ethanol (100:10) ratio and was magnetically stirred at 400 rpm at 37°C. (2 g of hydrogel contain 0.5 mg FA) was placed on chamber then 2ml was taken from receptor chamber at regular time interval (1,2,3,4,5,6,7,8,9,10,10,11,12 and 13 hr.) and replaced with 2 ml of fresh medium to maintain the sink condition. And estimated the absorbance for each sample at λ max. The lag time was calculated from permeation profile. [25]

The flux of drug where calculate using the following equation.

$$J = \frac{1}{A} \cdot \frac{dC}{dt}$$

Where J is the flux diffusion, dc/dt is the concentration gradient with time and A is the surface area.

Skin irritation test

The skin irritation test was done by applying one gram of the hydrogel to the rat skin under observation for any lesions or signs of skin hypersensitivity, such as redness or irritation. [26]

Compatibility study.

Fourier- transform infrared spectroscopy (FTIR) was used to assess the drug's compatibility with another excipient (soluplus and Carbopol). The FTIR spectra of best formula (hydrogel) and the pure drug powder were compared. [27]

Statistical Analysis

The collected data were analyzed through the Statistical Package for the Social Sciences (SPSS version 26). Repeated measured ANOVA as well as post hoc analysis was used. Statistical association was considered significant when p value equal or less than 0.05 (P value ≤ 0.05).

Results and discussion

The results of particle size range, zeta potential, polydispersity index and entrapment efficiency (EE) of all nanosuspension formulations were included in **Table (3)**

Selection of FA NS best formula

The best FA NS formula (FD) was selected based on the results of low particle size (167.4nm), PDI (0.184) and high EE (98.8%) as shown in **Table** (3) . Decrease in the particle size led to an increase in the effective surface area as the nanosuspension can interact with the liquid medium and reduce the cohesive force between liquid molecules. Low value of PDI leads to uniform particle size distribution, which in turn improves the stability. High EE offers high bioavaibility because it ensures that a large portion of drug is successfully encapsulated within nanosuspension. [28]

Table (3): Physicochemical characterization of fluocinolone acetonide nanosuspension

Formula no.	Particle size(nm)	PDI	Zeta Potential
FA	140.5	0.683	24.6-
FB	88.90	0.069	22.9-
FC	135.6	0.088	6.7-
FD	167.4	0.184	-5.9
FE	2009	0.063	149.3-
FF	696	0.804	-92.2

Evaluation of Fluocinolone acetonide based hydrogel

Physical appearance

Every prepared formula had the appearance of homogeneous, transparent gel that had no grit. The findings show that the formula having Carbopol 2% were thicker than the formula having 1.5% and 1% and formula having Carbopol 1.5% were thicker than the formula1% because increase the density of polymer network formed by Carbopol 934 as its concentration rises , lead to higher viscosity and more stable gel structure as shown in **Figure** (1).[29]

Figure (1) Physical appearance of FA NS based hydrogel

pH Determination

Skin pH typically falls between 4-6. The hydrogels' pH values, as indicated by **Table** (4), were according with the average pH of skin, indicating that the formulations were suitable for topical application on skin.[30]

Spreadability studies

Spreadability may change if Carbopol concentration increased, increase the percentage of Carbopol may result in decrease in spreadability, this is because spreadability and viscosity are inversely related, that as the viscosity increases at higher concentration of Carbopol, the spreadability falls. Consequently, a higher Carbopol concentration cause the gel formulation to spread less easily as shown in **Figure** (2). [31]

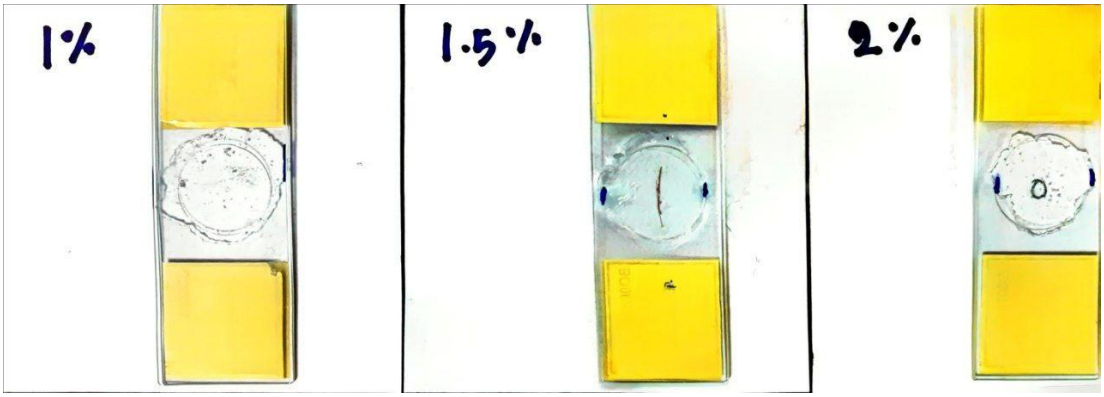

Figure (2) the Spreadability of FA NS based hydrogel

Table (4) pH, Phase separation, color, drug content, homogeneity, and spreadability and viscosity for prepared FA NS hydrogel

Formula	pH	Phase separation	Color	Drug content %	Homogeneity	Spreadability (cm)	Viscosity (rpm)	
FD1 Carbopol 1% (w/v)	5.01	NO	transparent	96.3	Good	2.3	100	5.30
							60	7.54
							30	16.51
FD2 Carbopol 1.5%(w/v)	4.84	NO	transparent	97.1	Good	2	100	High
							60	High
							30	High
FD3 Carbopol 2% (w/v)	4.82	NO	transparent	97.8	Good	1.8	100	High
							60	High
							30	High

In vitro release of drug from the prepared FA NS hydrogel

In vitro release study was done by ethanol and phosphate buffer (PH 5.5) ratio (10:100) as a dissolution media, **Figure** (1) showed the release of drug from FA NS hydrogel and compared with the release of pure drug-based hydrogel. The formula has Carbopol 1%(FD1) had the release faster than formula have Carbopol 1.5%(FD2) and 2%(FD3)

respectively, because the formation of more crosslinking within the hydrogel network as the concentration of Carbopol increases, the tighter and denser gel formation. An increase in Carbopol concentration cause increase in viscosity, which may hinder drug molecule to move through the gel matrix as shown in **Figure** (3).[32]

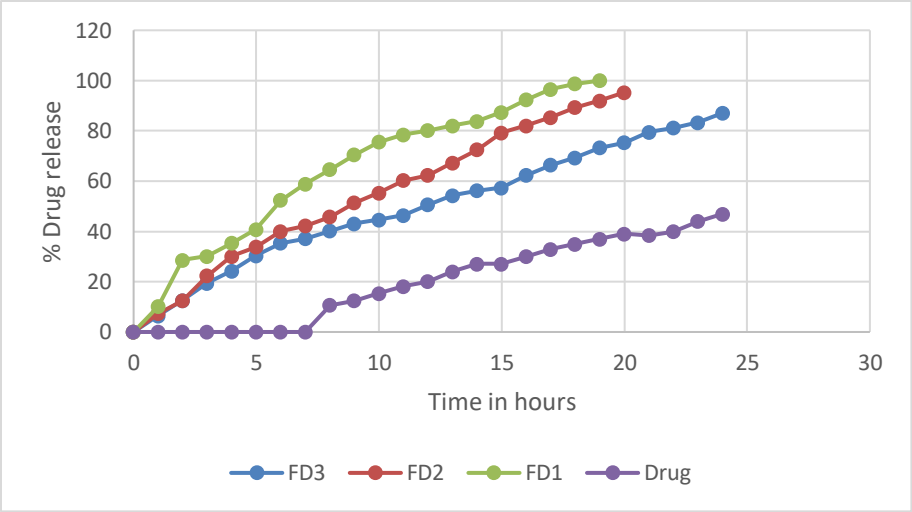

Figure (3) In vitro release of Drug from the prepared FA NS hydrogel

Mechanical model of drug release kinetics

Five mathematical models were applied to the release data to find the release kinetics of FA NS from hydrogel to elucidate the mechanism of drug release from the prepared hydrogel. The model with the best fit was found based on the R^2 value. Since the Higuchi model R^2 values are higher than those of zero order and first order models, it said to be the best fit model for explaining the FA NS release kinetics from hydrogel, furthermore, based on the n value, the Korsmeyer-peppas equation was used to determine the release mechanism Fickian or non-Fiackian nature. The (n) of FA NS hydrogel had values greater than 0.5, saying that they followed an anomalous (non-Fickian) release mechanism, such as the diffusion of water into hydrogel followed by dissolution (erosion) to release the drug as shown in **Table** (5). [33]

Table (5) Kietic models for FA NS hydrogel penetration through synthetic membranes

Formula	R^2(Higuchi)	R^2(first)	R2(zero)	R2(Hixon-Crowell)	Korsmeyer-peppas	n-value	Type of release
FD1	0.987	0.858	0.946	0.917	0.758	0.711	Non-Fickian diffusion
FD2	0.990	0.9111	0.989	0.972	0.858	0.556	Non-Fickian diffusion
FD3	0.988	0.954	0.986	0.981	0.848	0.592	Non-Fickian diffusion

Ex-vivo permeation study

The ex-vivo skin permeation study of FA NS based hydrogel was conducted with Franz cell using rat skin. The cumulative percentage of FA (from FD1) permeated through the skin was 10 %, 55.4% ,63.3%, 70.2 %, 85% respectively after 1, 8 ,10, 13,19 hr. compared with the permeation rate of pure drug-based hydrogel was 0%, 0%, 10.2%, 18.3%, 26.1% respectively after 1,8,10,13,19 hr. as shown in **Table** (6) and **Figure** (4). The lag time of pure drug was 9 hours whereas the lag time of FD1 was less than one hour. The J flux for this formula was 0.1028, Papp was 0.0002 and this is acceptable since the Papp more than $1x10^{-6}$. The permeation of FA NS hydrogel compared to pure drug hydrogel was significantly high with p value less than 0.01, this shows the reduction in particle size caused increase in surface area then increase in permeation and eventually increased absorption. [34]

Table (6) Ex-vivo permeation study

Dosage form	Drug permeated % at 1 hr.	Drug permeated % at 8 hr.	Drug Permeated % at 10 hr.	Drug permeated % at 13 hr.	Drug permeated % at 19 hr.
FANS hydrogel	10	55.4	63.3	70.2	85
Pure drug hydrogel	0	0	10.2	18.3	26.1

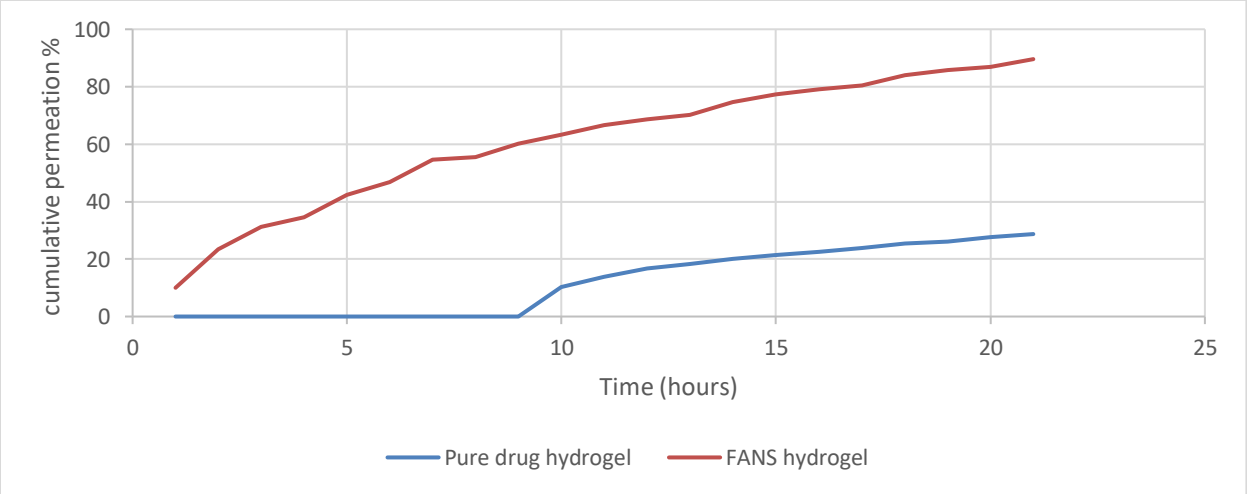

Figure (4) permeation of pure drug and FA NS hydrogel

Skin irritation test

Skin irritation testing for the chosen formulation was done to ensure the safety of the prepared nanosuspension based hydrogel after topical gel formulation, as a result safe and proper use of FA NS hydrogel part on the skin since non redness, non-irritating topical application as shown in **Figure** (5) . [35]

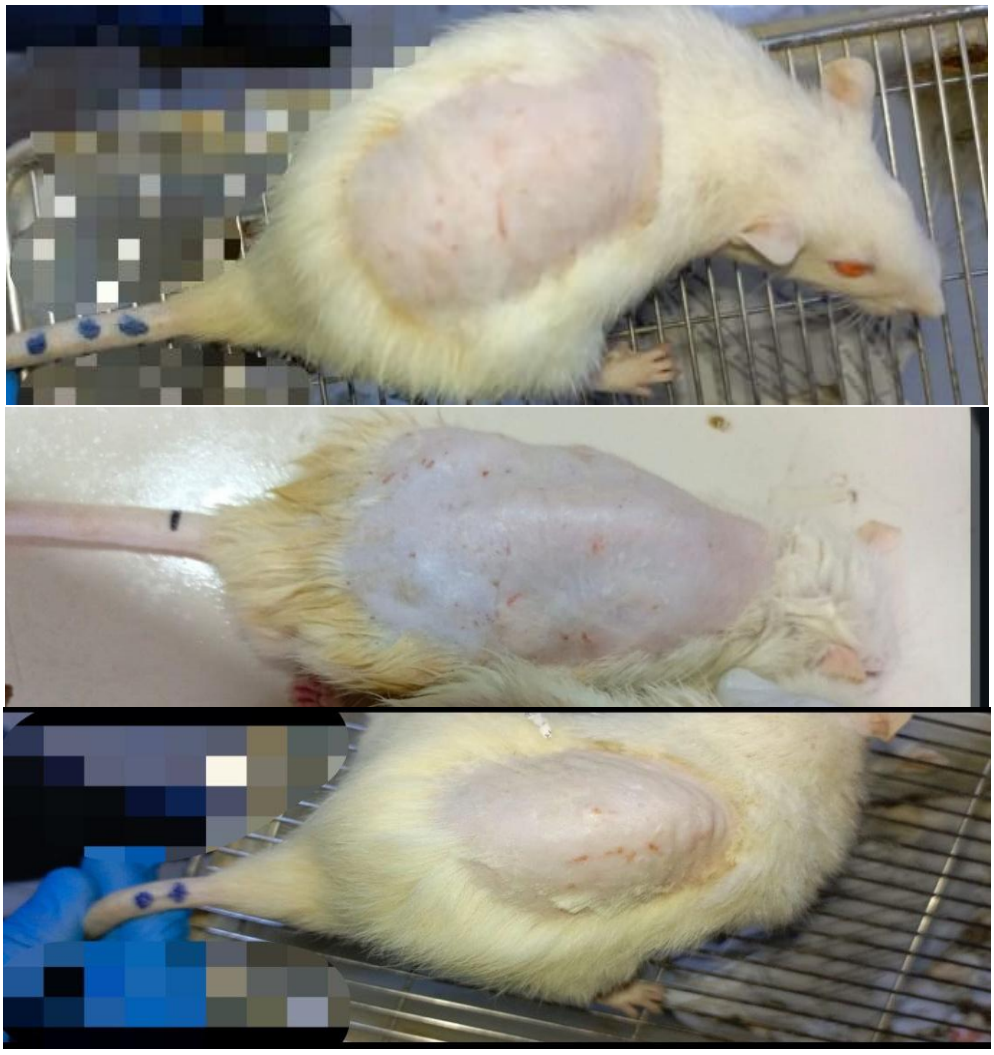

Figure (5) Skin irritation test for FD3,FD2 and FD1

Compatibility study

The gel mixture and the pure FA peaks did not significantly alter, according to the FTIR spectra **Figure** (6). Which indicated the drug and the gel base had no interaction as shown in **Table** (7)[36-38].

Table (7) Characteristics FTIR peaks of drug, soluplus , carbopol and formula

peaks	FA	Soluplus	Carbopol 934	FD1
O-H stretching (hydroxyl group)	3468.42	3566.45	3391.67	3346.98
C-H stretching(aliphatic and aromatic)	2887.98 2975.78			2340.93
C=O stretching (carbonyl groups)	1728.77			1635.42
C=C stretching (alkene groups)	1614.26 1673.91			1541.13 1635.42

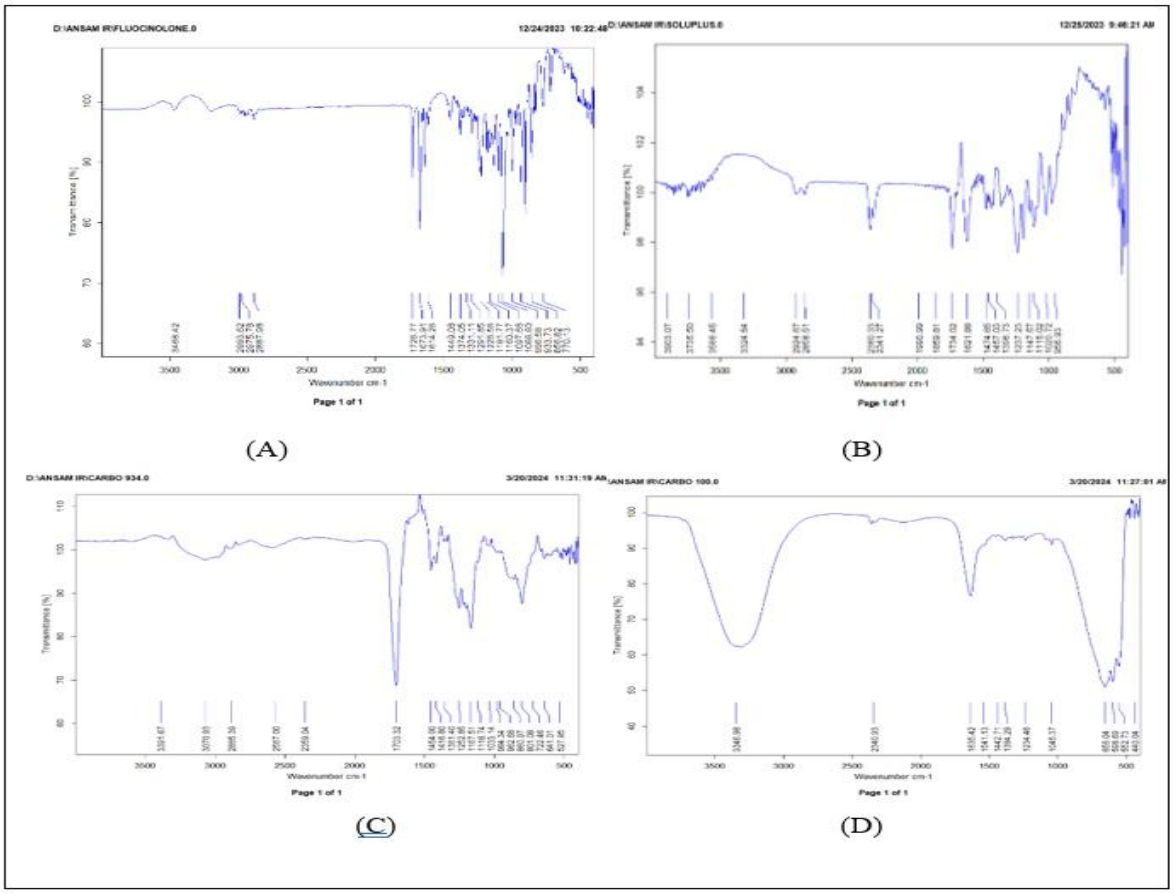

Figure (6) Compatibility study of Drug from the prepared FA NS hydrogel where (A) Fluocinolone acetonide, (B) Soluplus, (C) Carbopol 934, (D) The gel mixture of A, B and C

Conclusion:

Fluocinolone acetonide nanosuspension based hydrogel was prepared and evaluated successfully for in vitro release and skin permeation. Using Carbopol 943 as gelling agent in different ratio (1%,1.5%,2% w/v) was led to increase the time of contact of the drug with the skin, no interaction between the drug and the excipients was found and no skin irritation was demonstrated.

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