https://doi.org/10.15218/zjms.2024.017

Formulation and evaluation of salicylic acid hydrogel based on hydrotropic solubility enhancement technique

Received: 28/08/2022 Accepted: 27/10/2022

Sara Assif Younis [1*] Nozad Rashid Hussein [1]

Abstract

Background and objective: Salicylic acid (SA) has keratolytic activities and it is used topically to treat dandruff and seborrheic dermatitis. The hydrotropic phenomenon in pharmaceutical preparations is utilized to enhance the solubility of water-insoluble drug molecules that promoted to prepare the salicylic acid as a hair gel for local effect and it can extend its keratolytic action for a longer period compared to the salicylic acid solution.

Methods: Preformulation study was performed to exclude any unwanted chemical interaction between SA and excipients using Fourier-transform infrared spectroscopy (FTIR). The solubility of SA was determined separately in sodium acetate and sodium citrate solutions at a concentration of 1, 3, and 5 %w/v, using distilled water as a solvent. An optimum gel formulation was developed and it was used to prepare the SA gel formulation. Characterizations were performed in terms of physical appearance, viscosity, pH, and spreadability, *in-vitro* studies were performed in physiological pH, and *ex-vivo* diffusion studies were performed utilizing rats' skin.

Results: FTIR did not show any chemical interaction between the drug and sodium citrate. The hydrotropic solution of sodium citrate with a concentration of 5% w/v increased the solubility of SA by 28 folds, while the sodium acetate solutions with a concentration of 5% w/v increased the solubility of SA by 19 folds. The optimum gel formula (F1) with a drug content of 97% showed a slow dissolution rate and minimum diffusion through the skin.

Conclusion: The hydrotropic solubilization technique significantly influenced the solubilization of salicylic acid in the water and the highest solubility rate was achieved from 5% w/v sodium citrate solution. The formulated hydrogels using carbopol 971P as gelling agent decreased the diffusion rate of SA.

Keywords: Salicylic acid; Hydrotropism; Sodium citrate; Sodium acetate; Gel.

Introduction

The topical form of drug delivery has been used to treat skin disorders locally as well as to create systemic pharmacological effects.[1] Different keratolytic agents; urea, sulfur, salicylic acid (SA), and fluconazole, are commonly used in hair treatments as anti-dandruff.[2] These active ingredients are found in hair products in the form of lotions, creams, oils, emulsions, and shampoos. In comparison to creams and ointments, dermatological gels frequently give a quicker release of pharmacological material, regardless of the medication's water solubility, the main characterization of gel formulations are thixotropic, greaseless, readily spreadable, simply cleaned, emollient, non-staining, appropriate with a variety of excipients, and water-soluble or miscible.[4] SA has keratolytic activities and is used to treat hyperkeratotic and scaling skin disorders like dandruff and seborrheic dermatitis, ichthyosis, psoriasis, and acne in concentrations ranging from 2 to 6%.[5]

SA is considered as class II in the Biopharmaceutical Classification System with negligible water solubility while it is

[1] Department of Pharmaceutics, College of Pharmacy, Hawler Medical University, Erbil, Iraq.
Correspondence: sarah.younus@hmu.edu.krd

https://doi.org/10.15218/zjms.2024.017

soluble in ethanol, methanol, and isopropyl alcohol, thus it might induce formulation issues.[6] Therefore, it is crucial to increase the solubility of SA when it formulates as a topical dosage form.

Several standard techniques are employed to enhance the solubility of poorly soluble substances, including micronization, solubilization with cosolvents, pH adjustment, salt form, surfactant dispersions, the crystallization method, and oily solution.[7] Moreover, techniques like dispersion, and inclusion complexation can significantly increase the solubility of poorly water-soluble drugs.[8] Enhancing drug solubility using organic solvents may possess considerable toxicity and irritation besides the high cost of organic solvents. Using of hydrotropic enhancement technique is less costly and it is considered an alternative method if the drug is not feasible with an organic solvent.[9]

This technique provided advantages over the aforementioned techniques, combining the drug with the hydrotropic agent in water takes only a few minutes and does not need to change the chemical structure of the drug molecules, nor the use of organic solvents nor the development of an emulsion process.[10] In this study, the solubility of SA has been enhanced using various hydrotropic agents and, it is a step to develop an antidandruff hair gel containing SA.

Methods

Design, setting, and time of the study

This research was carried out at the college of pharmacy, Hawler Medical University, from the 1st of October 2021 to the 1st of June 2022.

Materials

SA and carbopol 971P were kindly gifted from Awamedica Pharmaceutical Company, Erbil, Iraq, sodium acetate was purchased from Johnson Matthey, UK, and sodium citrate was obtained from Rishi chemicals.

All other chemicals and solvents were of analytical grade.

Methods

Determination of maximum absorbance (ƛ max) and a calibration curve of SA in phosphate buffer pH7.4 and in aqueous ethanol solution

The maximum absorbance of SA was determined at the concentration of 100 Mcg/ml using a UV-Visible double-beam spectrophotometer in a range from 200 nm to 400 nm. Calibration curve of SA in phosphate buffer solution pH 7.4 was built up by preparing serial dilutions of the SA from a secondary stock solution. Solutions with different concentrations (2,4,6,8,10,12,14,16,18 and 20) Mcg/ml were prepared and analyzed spectrophotometrically at λ max (296.13 nm). To establish a UV calibration curve model, the measured absorbance was plotted against the concentrations.[11]

Calibration curve of SA in 10% aqueous ethanol solution was established by exploiting the same steps as in the Phosphate buffer solution.

Solubility study of SA in purified water and in different concentrations of sodium acetate and sodium citrate solution

An excess amount of SA was added to each hydrotropic solution and shaken mechanically for 12 hrs., then they have been left aside for equilibration for 24 hrs. The drug/hydrotropic solution was filtered using a syringe filter size number (42). Filtrates of saturated solutions of SA were taken and diluted with distilled water up to 10 ml in a volumetric flask and then quantified using a double-beam UV-visible spectrophotometer apparatus.[12]

The amount of drug dissolved was calculated using the respective calibration curve. The solubility enhancement ratio was calculated using equation (1).[13] The optimum hydrotropic agent was chosen according to compatibility between SA with the hydrotrope and the solubility enhancement ratio to prepare the solution phase of the active ingredient.

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Preparation of gel formulations

One of the main ingredients of gel preparation is the gelling agent (polymer). Different gel formulations were prepared using 1.5, 2.0, and 2.5 %w/v of carbopol 971P. The dispersions were prepared by adding 20 ml of distilled water (D.W.) to the polymer in a beaker with slight hand-mixing, then adding the rest of D.W. up to 59 ml and mixing using a homogenizer until all the particles dissolved. After getting a complete dispersion, the dispersed solution is kept aside overnight to allow the polymer to be fully hydrated and to remove entrapped air bubbles.

After 24 hrs, 40 ml of the previously prepared solution (consisting of 2 g of the active ingredient with 3 g of sodium citrate) is added and then mix the whole mixture vigorously using a homogenizer.

Neutralization of the final gel formulations was obtained by adding 1 ml of triethanolamine. The compositions of gel formulae are illustrated in (Table 1).

Evaluation of Hydrogels

I. (Physicochemical characteristics)

Physical appearance

The prepared SA gel's transparency, appearance, and homogeneity were all visually checked.[14]

pH of formulations

The probe of the digital pH meter was directly dipped in the gel and the pH had been determined.[14]

Extrudability

After putting the gel formulations in closed collapsible aluminum tubes, the extrudability of the gel formulations was assessed. The weights of the tubes were measured after they had been filled with gel and sealed at the ends. The tubes were pinched between two glass slides, and a weight of 1000 g was put over the slides before the cap was removed.

The extruded gel was collected and weighed to ascertain its percentage, and grades (++ good; + fair) were assigned.[15]

$$\text{Solubility enhancement ratio} = \frac{\text{Solubility of SA in hydrotropic solution}}{\text{Solubility of SA in DW}} \quad \ldots\ldots \text{Equation (1)}$$

Table 1 composition of gel formulae

SA gel compositions					
Formulation code	**Drug (g)**	**hydrotropic agent (g)**	**carbopol 971P (g)**	**DW (ml)**	**Triethanolamine (ml)**
F1	2	3	1.5	99	1
F2	2	3	2	99	1
F3	2	3	2.5	99	1

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Determination of Spreadability

The spreadability test was conducted using a wooden block and glass slide apparatus. A handmade apparatus is developed according to the research which has done by Mahtab and co-workers in 2016 (Figure 1), the device is made up of a wooden block with a pulley attached to one end, two identical glass slides were utilized in this apparatus, and spreadability was measured based on the "slip" and "drag" qualities of the gel.[16] Two grams of each prepared formula were placed on the surface of a glass slide that was already fixed on the wooden block and a glass slide placed above it. 100 g weight was put on the upper slide's surface for 5 minutes to evacuate air and generate a uniformly thin coating. The upper glass layer was then pulled with a 20 g weight using a hook -attached string. The time (in seconds) required to move the upper slide 7.5 cm was recorded.[17] Spreadability (S) was calculated by equation (2).[17]

$$S = M \times \frac{L}{T} \quad \ldots\ldots \text{Equation (2)}$$

Where: S = spreadability, M = weight attached to the upper glass slide (g), L = glass slide's length (cm), T = time required for the slide to travel a certain distance (sec.)

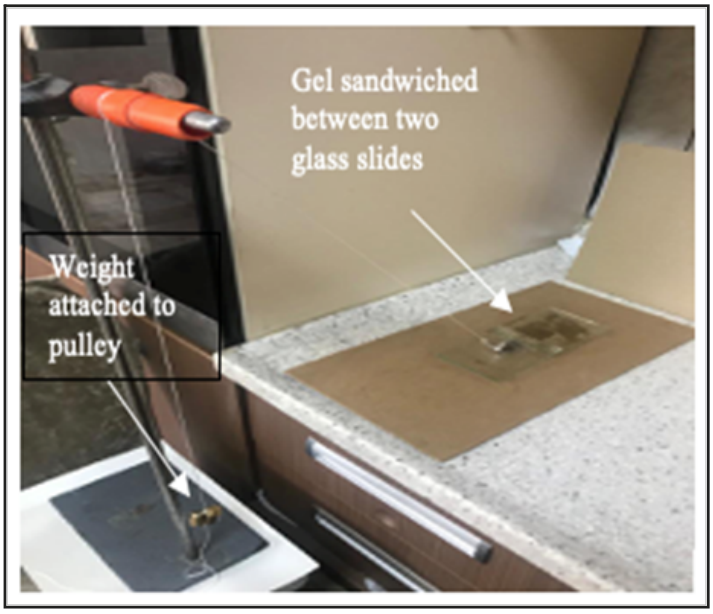

Figure 1 Spreadability measurement using handmade apparatus

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The viscosity of the formulations

The viscosity of the prepared SA formulae was measured using a Brookfield LVT viscometer with spindle number 3.[17]

Estimation of Drug Content

The drug content was determined by taking 1g of each gel formula and suitably diluting it in a phosphate buffer solution pH 7.4 to the required concentration. SA concentration was determined by measuring the absorbance using a UV-visible spectrophotometer. The drug content was calculated by equation 3.[18]

$$\text{Drug content} = \frac{\text{analyzed content}}{\text{theoretical content}} \times 100 \text{ .. Eq.(3)}$$

II. *In-vitro* drug release study using Cellophane membrane

In-vitro drug release test was performed using a USP dissolution apparatus type II (paddle apparatus) at a rotation speed of 50 rounds per minute (rpm) and temperature maintained at 37 ±0.5 °C using a dialysis bag (Molecular cut-off: 8000-14000 D). The dialysis bags were soaked in phosphate buffer solution pH 7.4 at room temperature (25±2°C) and kept overnight before use.[19] The drug release was performed for all SA gel formulae and compared to standard alcoholic solution 1%, and SA-marketed lotion (Diprosalic topical lotion). The tested samples were placed in dialysis bags and the bags were closed from both ends, then attached to the dissolution apparatus paddle using a cotton thread, and immersed completely in 500 ml phosphate buffer solution pH 7.4. Aliquots of 5 ml were withdrawn at intervals of (5, 10,15, 20, 30, 45, 60, 90) minutes, 2 hrs., 2.5hrs., 3hrs., 3.5 hrs., 4 hrs., 4.5 hrs., 5 hrs., and 6 hrs. Each withdrawn sample was compensated by an equal volume of phosphate buffer pH 7.4. The samples were quantified using a UV-visible spectrophotometer at the λ max.[20]

III. *Ex-vivo* permeability study

Ex-vivo skin permeation study protocol was approved by the ethical committee at the College of Pharmacy/ Hawler Medical University with approval number (HMU-EC 11.11.2021-411). The research was done with a modified Franz diffusion cell. Skin from Swiss albino rats weighing 200 ±10 g was used and full thickness of fresh skin was surgically removed from the abdomen and subcutaneous tissue was surgically taken. The skin was then cleansed with normal saline, and submerged in a phosphate buffer solution pH 7.4.

The *ex-vivo* drug diffusion from various gel formulations was examined using a laboratory-fabricated standard cylindrical tube.[21] The skin was firmly attached to one end of the tube, with the stratum corneum facing the donor chamber, the cell was inverted and slightly submerged in a 250 ml beaker containing 100 ml of phosphate buffer pH 7.4 as a receptor base for 2.5 hrs. at 37±0.5 ^{o}C. The medium was stirred using a magnetic stirrer, a schematic figure shows the parts of the modified Franz diffusion cell (Figures 2, a and b).[22]

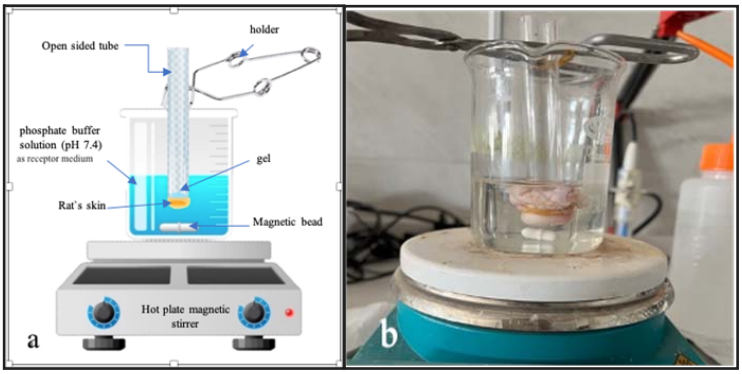

Figure 2 a: Schematic representation of modified Franz diffusion cell, b: Lab-made diffusion test

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The study was performed for the optimized (F1) and (F2) gel preparations and compared them to the marketed lotion containing SA (Diprosalic topical lotion). The tested samples were introduced directly onto the skin in the donor chamber, then samples of 5 ml were taken at (5, 10, 20, 30, 40, 60, 90, 120, and 180) minutes for up to two and half hours, and each withdrawn of the sample was replaced by an equal volume of phosphate buffer solution (pH 7.4). Samples were analyzed by a UV-visible spectrophotometer at the λ max of the drug.

Fourier Transform Infrared Spectroscopy (FTIR)

Samples of pure SA powder, the excipients, and the final gel formula were analyzed by FTIR spectroscopy in the wavelength range of 400-4000 cm^{-1}.[23]

Statistical Analysis

Every experiment was carried out and repeated three times (n=3). Data were analyzed and expressed using Microsoft Office Excel 2016.

Numeric data were expressed as (Mean ±SD). One-way ANOVA and unpaired t-test were used to compare values of the mean in the various groups when the values were within the normal distribution. The statistical significance was ascertained at ($P \leq 0.05$).

Results

Determination of maximum absorbance (λ max) and a calibration curve of SA in both phosphate buffer pH 7.4 and aqueous ethanol solution.

Spectra for the drug in aqueous ethanol solution and in buffer solution pH 7.4 were observed in the range of 200 nm to 400 nm, which showed absorption maxima at 296.99 nm and 269.13 nm respectively. The calibration curve was created and a straight line was obtained with a high r^2 (Figure 3 a & b).

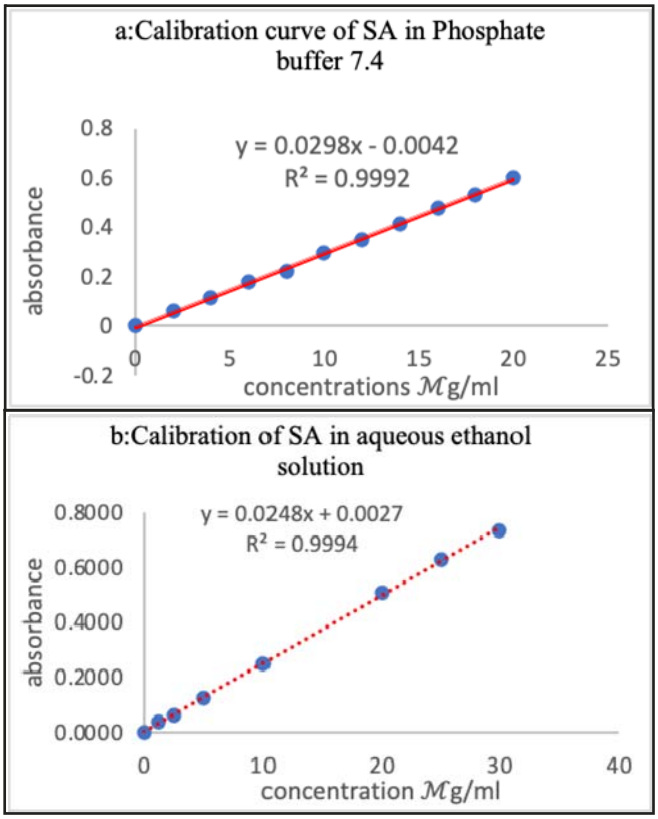

Figure 3 The scatter plots show the results of the linear correlation analysis of SA in buffer pH7.4 (a) and in an aqueous ethanol solution (b).

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Solubility study of SA in water, in different concentrations of sodium acetate, and sodium citrate solution

SA is a slightly water-soluble drug with a solubility of 2.37 mg/ml.

The solubility of SA in different hydrotropes was determined, and the results are summarized in (Table 2).

Evaluation of Hydrogels (Physicochemical characteristics)

1. Physical appearance

The physical parameters of the gel formulations are demonstrated in (Table 3).

2. Evaluation of the Hydrogels (Physiochemical characteristics)

The physicochemical characteristics of the formulations using various polymer concentrations are explained in Table 4.

3. Estimation of Drug Content

The formulations were evaluated for the active content. The results were found in the acceptable range and % of drug content is shown in (Table 4).

Table 2 Solubility study of SA in water, sodium citrate & sodium acetate.

Solvent	Solubility mg/ml	Solubility enhancement ratio
water	2.37± 0.21	0
1% Na citrate	21.75± 0.92	9.2
3% Na citrate	51.88± 0.74	21.9
5% Na citrate	66.67± 0.23	28.1
1% Na acetate	14.15± 0.26	6.0
3% Na acetate	25.92± 0.92	10.9
5% Na acetate	45.01± 0.54	19.0

Table 3 Physical characteristics of Hydrogel formulations

Characteristics	F1	F2	F3	Market product
Transparency	Transparent	Transparent	Cloudy	Transparent
Gel appearance	Very good	good	Thick	Thin
Odor	No	No	No	offensive
Removal	Easy	Easy	Not easy	Easy
Homogeneity	+++	++	-	+++

+++ excellent, ++ good, – not good (non-homogenous)

Table 4 Physicochemical characteristics and percentage of drug content in gel formulations.

Evaluation of Hair Hydrogels (Physio-Chemical Characteristics)					
Formulation code	pH	extrudability	viscosity (cps)	spreadability g.cm/s	% Drug content
F1	5.9±0.25	+++	24400±0.17	21.5±1.25	97±1.50
F2	5.6±0.16	++	42800±0.29	16±1.16	88±1.05
F3	5.4±0.31	+	68000±1.04	1.5±2.23	106±2.41

https://doi.org/10.15218/zjms.2024.017

***(In-vitro* drug release using the Prehydrated Cellophane membrane)**

The percentages of cumulative drug release profiles of F1, F2, F3, standard aqueous ethanolic solution, and marketed products (Diprosalic lotion) were calculated as shown in Figure 4.

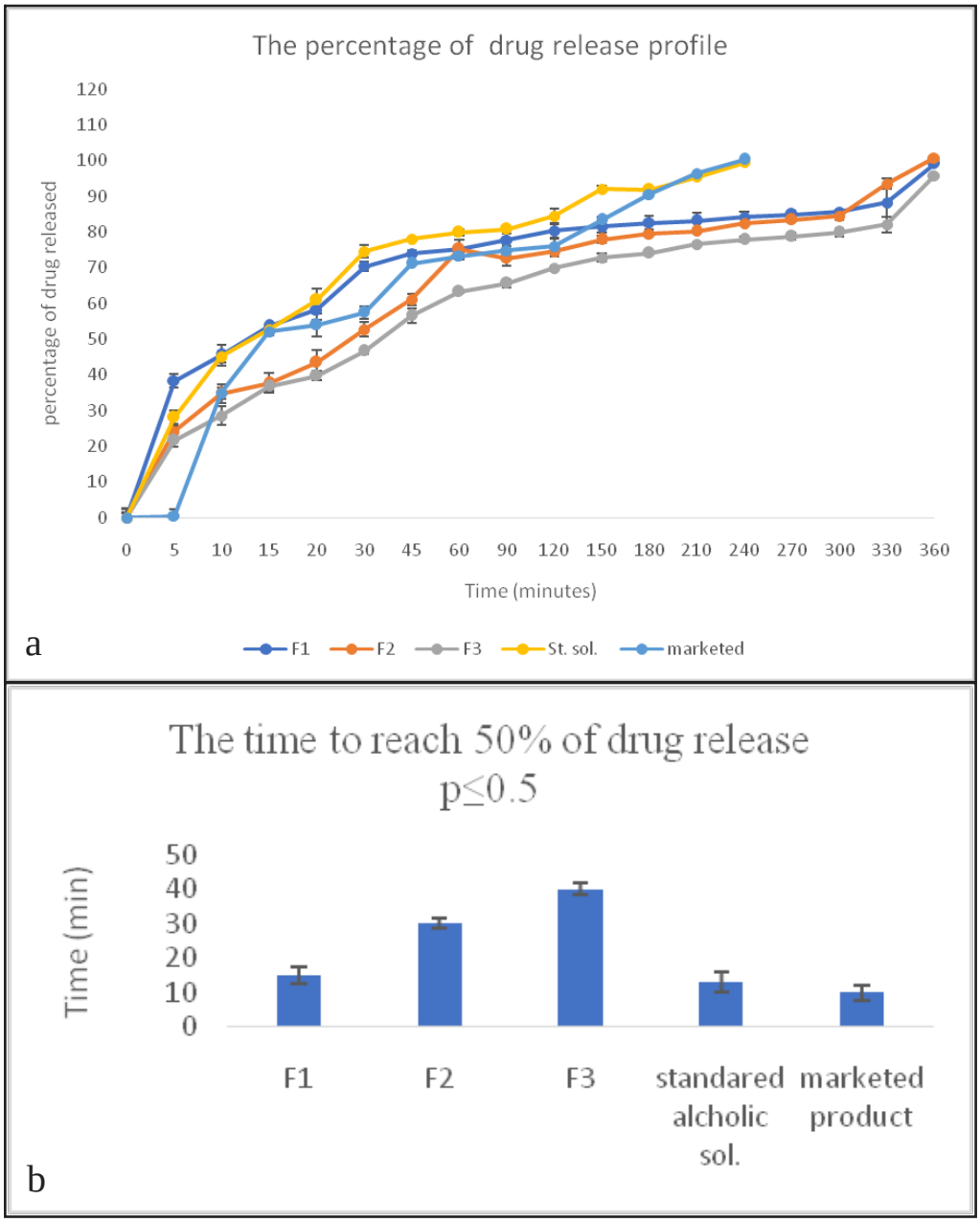

Figure 4 a: In vitro drug release for all gel formulations F1, F2, F3, marketed solution, and standard aqueous ethanol solution, b: The time required for each formula to achieve 50% of cumulative drug release

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(Ex-vivo permeability study)

Ex-vivo permeationability was conducted for optimized formula F1, and F2, and compared with the marketed product (Diprosalic topical lotion) as shown in (Figure 5).

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of pure SA, SA with the hydrotropic agents (sodium citrate) and the final gel formula, are shown in (Figures 6, A, B, C, and D).

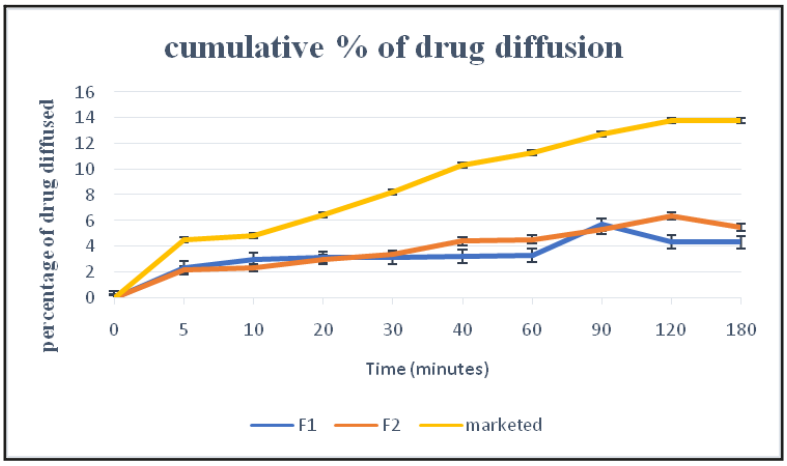

Figure 5 Ex-vivo permeation ability of F1, F2, marketed product, and standard alcoholic solution

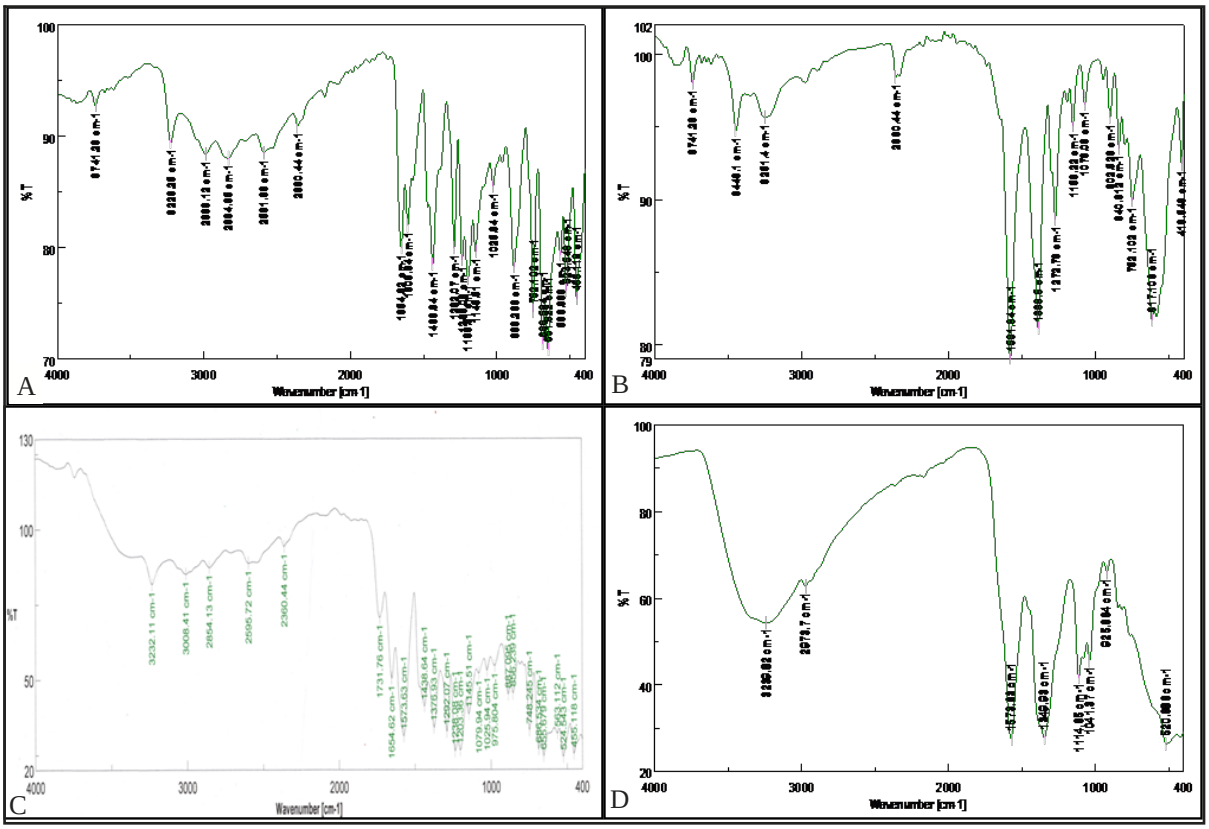

Figure 6 FTIR spectrum of (A) pure SA, (B) sodium citrate, (C) blend of SA and hydrotropic agents (sodium citrate, and (D) final gel formula.

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The FTIR spectra of SA with the other hydrotropic agent (sodium acetate) is shown in (Figures 7, A, and B).

Discussion

The peak values obtained from the FTIR spectrum for the functional groups of both salicylic acid and sodium citrate (Figure 6C) showed no shift, indicating compatibility between salicylic acid and sodium citrate. The FTIR spectrum of SA gel (Figure 6D) showed the IR absorption peaks at 3239 and 2973cm^{-1} that were assigned to carboxylic (O-H) and (C-H) stretching, respectively. Some minor changes in the peaks were observed, indicating there is a physical interaction that may be related to the formation of hydrogen bonding between the functional groups of the polymer and SA. However, this interaction did not affect the carboxyl group of SA which is important to demonstrate the acidic behavior.[24] While (Figure 7B) showed an interaction between sodium acetate and SA, it also caused SA to lose its acidic character, as the peak at 3008cm^{-1} corresponds to hydroxyl (O-H) of the phenolic group, despite the absence of a broad peak of carboxylic (O-H).[25]

Increasing the solubility of salicylic acid using hydrotropic agents is aimed to enhance the stability of gel formulations containing SA. The solubility of SA increased using hydrotropic agents compared with parent SA (Table 1), and it has been shown the solubility enhancement of SA proportionally increased with increasing the concentration of the hydrotropic agent.[26] Sodium citrate has the highest solubilization capacity of SA without consuming any organic solvent, which ought to increase the

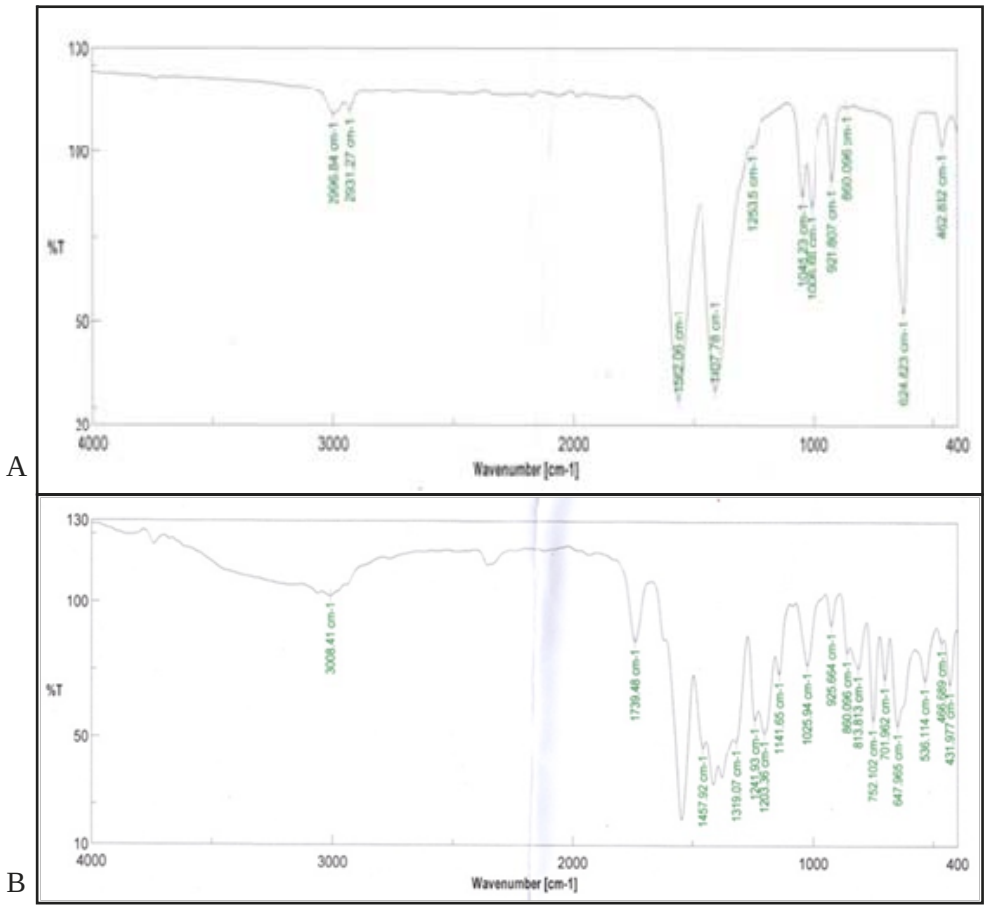

Figure 7 FTIR of (A) Sodium acetate and (B) Blend of sodium acetate with SA.

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concentration of alkali metal salts of various acids.[10] Although sodium acetate participated in improving SAs` solubility but the FTIR spectra (Figure 7B) of SA with sodium acetate demonstrated that the mixture lost its acidity and turned into a salt form which is indeed an undesirable effect in this experiment because of the acidity of SA is the key role for keratolytic activity. According to the official Europe cosmetic ingredient database, many manufacturers assert that sodium salicylate act as a preservative and has antibacterial activity, knowing that the salt of an exfoliant is a neutralized form; thus, if exfoliation is desired then it is better to be in pure acidic form.[27]

Gel formulations containing SA were prepared with different concentrations of the polymer (carbopol 971P) and a fixed concentration of the active ingredient. The concentration of carbopol 971P as a gelling agent directly has an effect on the viscosity and other physical properties of the prepared gel formulations.[28] An optimum percentage of the polymer being used to prepare gel formulations was optimized, and using 1.5% w/v, and 2 % w/v of carbopol 971P were explored to be compatible with the requirements of gel formulations. Sugan Chouhan *et al* formulated ketoconazole hair gel utilizing different concentrations of carbopol, they found using a high concentration of carbopol 940 more than 2% affects the psych-rheological characteristic, introducing the presence of clogging and decreasing homogeneity.[21]

The physical appearance of the formulations F1 and F2 were transparent, homogenous, slightly glossy in nature, and smooth on application to the skin to avoid irritation (Table 4). The pH of the prepared gels was in the range of 5.4-5.9 and was found to be suitable for application to the scalp.[29]

The drug content in the formulated gels was presented in acceptable limit ranges (Table 4). These results align with those of Kashyap *et al*, who formulated a transdermal topical gel of the non steroidal anti-inflammatory drug Ibuprofen.[19]

The viscosity of the formulated gel preparations was determined and the results showed that F3 had the highest viscosity, while that of formulation F1 was found to be lowest at 1.5 RPM.(Table 4). Higher gel formula viscosity is related to an increase in the concentration of the gelling agents in the formulation. Increasing viscosity has an effect on spreadability.[30] The spreadability values indicate that the gel formulae are eminently spreadable with the application of a small amount of shear, with the exception of the thick F3 formula. A good gel is easy to distribute, requiring little time, though as the concentration of the gelling ingredient increased, the spreadability of the gel decreased,[31] therefore, the F3 formulation was neglected. Rheological measurements are utilized to characterize the ease pouring of the formulations from a bottle, or squeezing from a tube or container. Semi-solid formulations with optimum extrudability should keep their rheological properties or viscosity constant during applications and storage. Gel formulations F1 and F2 containing SA were easily extrudable from the tubes (Table 4), indicating less force was required to easily extrude the gel. The higher the value of firmness, the thicker the consistency of the F3 sample which has the highest viscosity due to the high concentration of carbopol 971P gelling agent.[32]

The drug should first be released from the vehicles before being partitioned into or absorbed by the skin during the permeation process. *In vitro* drug release testing is an important quality and performance parameter for evaluation of the topical semisolid formulations. The *in-vitro* drug release profile was conducted to evaluate the release rate of SA from optimum gel formulae in comparison to the aqueous ethanol solution and market lotion (diprosalic) in phosphate buffer solution pH 7.4. The SA gel formula showed around

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99% drug release within 360 min while the aqueous ethanol solution showed around 99% cumulative drug release within 270 minutes (Figure 4a) indicating that SA-loaded formulae have a slower release rate compared to alcoholic standard solution and marketed lotion under the same testing circumstances, this is due to the fact of viscosity of gel formulations. The time required for each formula to achieve 50% of cumulative drug release was measured and the interpolation analysis was calculated and compared (Figure 4b). It was observed that 50% cumulative drug release was achieved at different times and was ranked according to the following order, from fastest to slowest formulae: marketed lotion > standard solution > F1 > F2, and F3). The results shown in (Figure 4b) indicate that the release from the gel formulae was significantly ($P \leq 0.05$) slower than the aqueous ethanol standard solution under the same experimental conditions. The formulas F1 and F2 achieved 100% and 99% of drug release respectively at 360 minutes and were selected for further permeation study.

The optimized gel formula F1, F2, and marketed lotion were subjected to an *ex-vivo* skin permeation study to validate and compare their penetration capabilities. The amounts of SA that permeated through the excised rat skin for the optimized SA-loaded gel for F1, F2, and the marketed lotion in phosphate buffer solution pH 7.4 were evaluated, and the permeation profiles of all formulations were shown in (Figure 5). The cumulative amount of SA that permeated through the skin over 2.5 hours from the F1 and F2 formula was significantly less than the marketed lotion ($P \leq 0.05$). This provides advantages to gel formulations containing SA as it remains at the site of application for a longer period. *In vitro* mucoadhesion test is required to prove the availability of SA at the site of application for a longer period compared to the ethanol solution of SA.

Conclusion

The hydrotropic solubilization technique significantly enhanced the solubility of SA. Increasing concentrations of hydrotropic agents lead to an increase in the solubility of SA. The highest solubility rate was achieved for 5% sodium citrate solution.

Acceptable physical properties concerning pH, drug content, viscosity, spreadability, and extrudability were obtained with F1 formula. The gel formulae F1 and F2 revealed controlled release of the active ingredient and modest diffusion through the rats` skin. It is possible to prepare SA as a topical hydrogel for the treatment of some skin diseases, and a clinical study is required to validate the efficiency of SA hydrogel formulation as a keratolytic agent over traditional formulations containing SA.

Funding

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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