Topical Hydrogel Formulation of Naproxen: Design and Evaluation for Improved Therapy on Topical Administration

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Abstract: Topical gel compositions are designed to be applied topically or to specific mucosal surfaces in order to provide localised or transdermal drug penetration, as well as emollient or protective properties. Nonsteroidal anti-inflammatory drugs (NSAIDs) are non-steroidal drugs with good analgesic and anti-inflammatory properties; nevertheless, when used orally, NSAIDs can cause GIT ulcers as well as liver and renal problems. Several NSAIDs are now more often applied topically due to the negative pharmacological reaction that oral versions might cause. To prepare topical hydrogel formulations of naproxen (NAP), hydrophilic polymers such as carrageenan (CaR) and hydroxypropyl methylcellulose (HPMC-K100M) were employed at different doses. Evaluation tests were conducted for assay, viscosity, spreadability, pH, visual appearance, and in vitro drug release. Utilising the USP V dissolving equipment, in vitro drug release studies were conducted to examine the impact of polymer composition on the rate of drug release from gel formulations at 37 ± 0.5 oC. The physicochemical properties of formulation did not exhibit any significant changes during exposure to accelerated temperature and humidity settings of 40 ± 2 oC and 75 ± 5% RH, respectively. Based on in vitro assessment experiments, it was determined that the gel formulation containing 0.5% w/v CaR and 0.75% w/v HPMC ratio was appropriate for topical administration. These findings imply that the topical gel formulation of NAP produced promising results.

Keywords: Naproxen, Hydrogel, Carrageenan, In vitro drug release, Ex vivo study, Stability study, Anti-inflammatory

1. Introduction

Topical drug administration refers to the localised delivery of drug through the skin, vaginal, ophthalmic, and rectal channels to any part of the body. One of the human easiest organs to administer topically is the skin, which serves as the primary route for topical drug delivery systems [1].
By overcoming physiological challenges including first pass metabolism and for better local action, scientific and technological advancements have been made in the research and development of hydrogel drug delivery systems in recent years. Currently, a number of methods are used to treat pain, inflammation, skin conditions, disinfect skin, and function as controlled release devices for wound dressings [2].
Studies on the use of different polymers in the manufacture of transdermal gels containing anti-inflammatory drugs were conducted. In this study, polymers with natural and semi-synthetic origins are used to formulate transdermal gels of NAP. A solid three-dimensional network that fills the volume of a liquid medium is what makes up a gel. The internal network structure can be attributed to several factors such as chemical or physical linkages, crystallites, or other intact connections inside the

expanding fluid [3]. Almost any fluid, such as water (hydrogels), oil, and air (aerogel), can be utilised as an extender. Gels have densities that are comparable to the liquid components they are made of because they are primarily fluid in nature, both by weight and volume.
Aqueous-insoluble polymer chains form a network known as hydrogel, which is occasionally observed as a colloidal gel with water acting as the dispersion medium. Hydrogels are made of natural or manmade polymers that are superabsorbent—they can contain more than 99% water. Because of their high-aqueous content, hydrogels also have a degree of elasticity that is extremely close to that of genuine tissue [4-6]. Crosslinked polymer networks, or hydrogels, are able to absorb large volumes of aqueous liquids. Drug delivery technique has greatly benefited from the use of hydrogels.
Non-steroidal anti-inflammatory medicines, or NSAIDs, have good anti-inflammatory and analgesic properties. However, when taken orally, NSAIDs can cause GIT ulcers, liver, and kidney problems. Many NSAIDs are now more often applied topically due to the negative pharmacological reaction that oral versions might cause. Drugs can be delivered topically by combining them with gel matrixes for local action in treating skin conditions and managing pain [7]. This avoids first pass metabolism and allows for efficient drug administration. The main drawback of taking NSAIDs orally is not their low absorption but rather their severe adverse effects.
Poor agent specificity, which arises from the medicine binding to certain (like prostaglandins) receptors, is the primary cause of these side effects. The gastrointestinal system is the main location of such a negative effect. As a result, NSAIDs taken orally are poorly tolerated and can result in stomach ulcers [8]. Achieving the therapeutic drug concentration in the target tissue while minimising the concentrations of the gastrointestinal and systemic agents would be ideal.
It goes without saying that the only way to accomplish this is to administer NSAIDs to the body by a different route than the oral route. An attempt was made to develop and assess topical hydrogel drug delivery devices in the current work. Controlling the rate of drug release from dosage forms was one attempt to improve therapy by improving drug absorption and exposure [9]. Gelling, thickening, or cross-linking chemicals were used to alter the rate of drug release. The final goal was to increase the bioavailability of drug and enhance the formulation for the market by combining hydrophilic polymers [10].

2. Materials and Methods

Naproxen (NAP) was procured from SRL Labs, Mumbai, India. Hydroxypropyl Methylcellulose (HPMC-K100M), Guar gum, Isopropyl myristate and Benzalkonium chloride, (Loba Chemie Pvt. Ltd., Mumbai, India), potassium dihydrogen phosphate and sodium hydroxide (Merk, Bangalore, India) was obtained and used in this study. All other chemicals and regents were of analytical grades.
Construction of calibration curve
The UV spectrophotometric method was used to measure the content of NPR. To make a stock solution of 1 mg/mL, NPR was dissolved in Milli-Q water to reach a concentration of 10 $\mu g.mL^{-1}$. Using Milli-Q water as a blank, aliquots of these solutions were put into a quartz cell and exposed to a UV spectrophotometer (SECOMAM UviLine 9400, Selangor, Malaysia) to measure λmax in the 200–800 nm range. The standard calibration curve was prepared by plotting concentration against absorbance, and several concentrations of NPRsolution were built in the range of 1–10 $\mu g.mL^{-1}$ [11].
Preparation of NAP hydrogel
Hydrophilic polymers, such as CaR (0.05 to 0.5 g) and HPMC (0.25 to 0.75 g), were chosen, and the cross-linking agent was 0.1N NaOH solution. Distilled water dissolved in HPMC, although it causes colloidal dispersion in CaR. The concentrations of polymeric dispersions, which were prepared independently, had good mechanical qualities. The topical hydrogels were made in the following ways as shown in Table 1, utilising various ratios of different polymeric dispersion concentrations were used to prepare hydrogels. Milli-Q water was used to prepare CaR and HPMC colloidal dispersions at the similar concentrations. Following thorough dispersion, the two polymer solutions were left in the dark for a full day to allow for swelling. Polymer dispersions were prepared using magnetic stirrer (REMI 2) with a 720 rpm. HPMC was dissolved in Milli-Q water, and then CaR colloidal dispersion was added while being stirred magnetically. 0.25% w/v benzalkonium chloride and 0.75 % v/v isopropyl myristate were added. Following the addition of sodium hydroxide solution, aqueous drug solution was added to the polymeric dispersion [12]. Ultimately, the residual Milli-Q water was included to achieve a uniform gel dispersion while magnetic stirring.

Table1. Various composition of NPR-Gels

Ingredients (in mg)	F1	F2	F3	F4	F5
NPR (mg)	100	100	100	100	100
HPMC-K100M (g)	0.25	0.35	0.45	0.55	0.75
CaR (g)	0.05	0.25	0.35	0.35	0.5
Isopropyl myristate (%)	0.75	0.75	0.75	0.75	0.75
Benzalkonium chloride (%)	0.25	0.25	0.25	0.25	0.25
Purified water (mL)	50	50	50	50	50

Evaluation of hydrogel

Physical structure

The commercial formulation served as the standard (Naprox; Eskayef Pharmaceuticals Ltd.). Visual observations were used to assess the manufactured gels physical appearance and uniformity [13].

pH determination

A pH metre was used to measure the gel compositions pH. In order to calculate pH, 1% of the hydrogel formulation was produced in deionized water.

Assay

To assess the material in the gels, NAP was extracted from 1 g of each gel formulation using 20 mL of phosphate buffer pH 7.4 for 30 min. The resultant mixture was filtered using a membrane filter with a pore size of 0.45 µm membrane filter. The samples absorbance was measured spectrophotometrically at 230.1 nm using an Agilent Cary 60 UV-Vis Spectrophotometer, USA spectrophotometer after it had been suitably diluted with phosphate buffer pH 7.4 [14]. The NAP concentration was estimated using the calibration curve.

Spreadability

Applying the gel to a level surface and checking for any present grit in the hydrogel will reveal the spread ability.

Viscosity of hydrogel

Using a Brookfield viscometer with spindle no. 7 at 100 rpm and 25 ^{o}C, the viscosity of the gel compositions was measured [15-17].

In vitro release studies

For the dissolution studies, a precisely weighted amount of the hydrogel was extracted. Aliquots of the substance were removed at prearranged intervals, and the absorbance at 230.1 nm in a dissolving medium of double-distilled water was used to measure the drug release. At each time interval, the volume withdrawn was replaced with the same volume of new medium as described by our earlier research Li et al. (2025) [18].

Ex vivo drug permeation studies

After being sacrificed by spinal dislocation, Wistar male albino rats weighing 180–200 g had their belly hair removed with a razor. Adhesive subcutaneous fat was meticulously cleansed after the abdomen skin was surgically removed. The entire thickness of skin was then soaked in a 2 M sodium bromide solution in water for 6–8 hours in order to separate the epidermis from the dermis. After being completely cleaned with water, the epidermis was put in the freezer to be used later. Skins were put on the Franz diffusion cell with the stratum corneum (SC) facing the donor compartment after being given a one-hour hydration period for ex vivo permeation investigations [19]. Phosphate buffer pH 7.4 was used to fill the receptor compartment, and the temperature of the receptor phase was kept at 32 ± 0.5 ^{o}C. In the donor compartment, 1 g of the gel was put on the SC side. By passing a 1 mL aliquot through a hypodermic syringe equipped with a 0.22 mm membrane filter at predetermined intervals for 30 min, the amount of medication that permeated was measured spectrophotometrically at 230.1 nm. To preserve sink conditions, the same amount of pre-warmed receiver solution was added to the volume.

Statistical analysis

The data derived from three measurements taken in triplicate are reported as mean values and standard deviations. Statistical analysis was conducted using Student's t-test after performing a one-way analysis of variance (ANOVA), with the analyses carried out using SPSS software.

3. Results and Discussion

First, λmax of NPR was determined by scanning solution of NPR in a UV spectrophotometer. Calibration curve of CuR was also plotted as observed from Figure 1, and λmax was determined to be 230.1 nm [20].

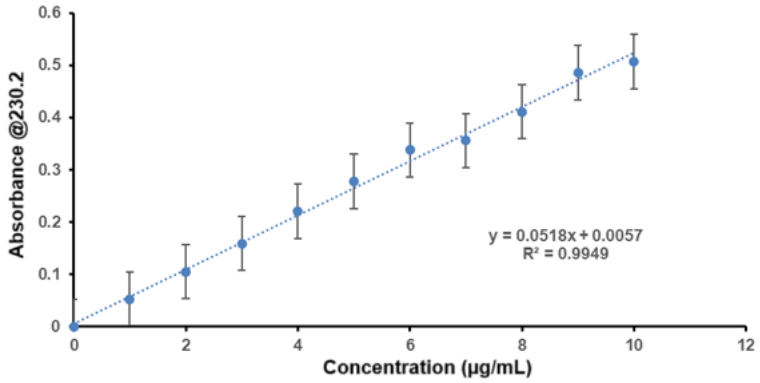

Figure 1. Standard calibration curve of NPR. Each value signifies mean ± SD, n = 3.

Physicochemical parameters

The topical hydrogels of NAP were prepared with varying polymer ratios. Better physicochemical gels were chosen from among the developed gels. Table 1 tabulates the various proportions of polymers employed in gel preparation. The table compares comparative analysis of five naproxen sodium gel formulations (F1–F5) with a product in the market. All the five formulations are thick and translucent, while the product in the market is thick but opaque [21]. Viscosity was highly different among the formulations, with F3 having the highest value (89764.11 ± 278.41 cps), which reflects much thicker consistency than the others. The other formulations are 7822.12 to 9274.71 cps, comparable to that of the commercial product (9191.43 ± 323.18 cps). Drug content in all the formulations is within good range from 96.38% to 98.55%, with F2 having the highest uniformity (98.55 ± 7.11). Spreadability is indicated by plus signs (++ to +++), with F2, F4, F5, and commercial gel displaying superior spreadability (+++), implying ease of use. pH values of all gels are in a skin-compatible range of 5.36 to 5.52, minimizing irritation potential. In general, F5 and marketed gel exhibit the desired properties—high drug loading, good spreadability, and suitable viscosity and pH—like the commercial product [22].

Table 2. Various evaluation of NPR-Gels, mean ± SD, n = 3.

Preparation Code	Visual Appearance	Viscosity (cps)	Drug content	Spread ability	pH
F1	Translucent & Thick	7822.12 ± 243.28	96.38 ± 6.21	++	5.36 ± 0.71
F2	Translucent & Thick	8178.53 ± 257.76	98.55 ± 7.11	+++	5.44 ± 0.68
F3	Translucent & Thick	89764.11 ± 278.41	97.56 ± 0.09	++	5.45 ± 0.65
F4	Translucent & Thick	8976.45 ± 302.28	97.92 ± 0.46	+++	5.48 ± 0.66
F5	Translucent & Thick	9274.71 ± 341.81	98.34 ± 6.77	+++	5.51 ± 0.43
Marketed Gel	Thick, opaque	9191.43 ± 323.18	96.81± 8.65	+++	5.52 ± 0.47

An attempt was made to develop and assess topical hydrogel drug delivery devices in the current work. Controlling the rate of drug release from dosage forms has been tried as a way to alter drug in vitro characters. The use of thickening, gelling, or cross-linking agents will regulate the rate of drug release. The ultimate goal is to decrease the number of doses administered in order to provide patients with acute and elegant dosage forms that are convenient and meet the requirements for a steady state blood concentration of the drug, which will improve therapy compliance [23]. Different polymer ratios were used to prepare topical hydrogels, which were then assessed.

In vitro evaluation

To choose the right polymer composition for a gel formulation with the right consistency for topical administration, in vitro drug release tests were conducted. Using the USP V apparatus (Paddle over Disc), in vitro drug dissolving investigations were conducted to measure in vitro drug release. Figure 2 represents the cumulative in vitro drug release data, which indicates that F5 releases 87.22 ± 4.76% while the marketed product releases 43.35 ± 2.91%. When compared to the commercial formulation, the F5 formulation exhibits superior in vitro drug release, according to the data. The physicochemical

characteristics and in vitro drug release of formulation F5 indicated that it was appropriate for topical use [24].

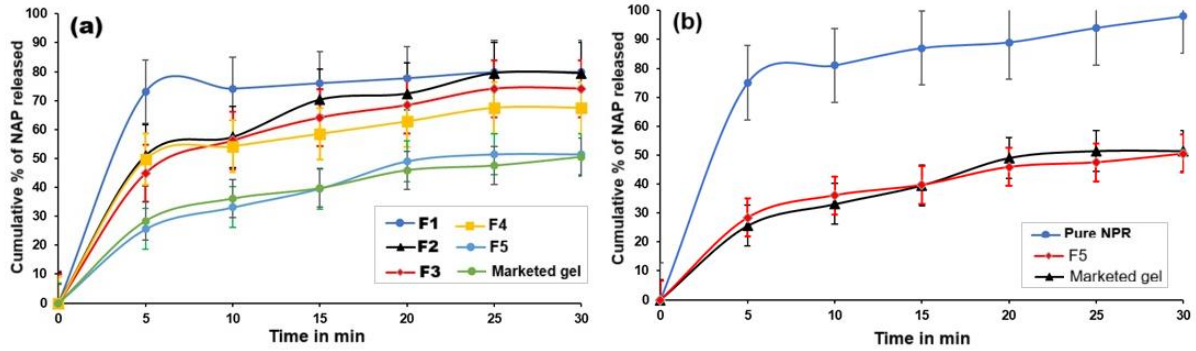

Figure 2. In vitro cumulative percentage of NPR released from NPR-gel. (a) F1-F5 and marketed gel and (b) pure NPR, F5, and marketed gel, mean ± SD, n = 3.

Ex vivo drug release

The ex vivo skin penetration profile of diclofenac sodium gels across rat abdomen skin is shown in Figure 3. The in vitro drug release profile and the skin penetration profile displayed the same pattern. At the conclusion of 30 min, formulation F5 percentage ex vivo cumulative drug release was 78.26 ± 8.12%, which was superior than that of the marketed formulation, which had a percentage ex vivo cumulative drug release of 40.43 ± 4.78%.

The physicochemical properties of optimised formulation and in vitro drug release profile remain unchanged even after being exposed to accelerated temperature (40 ± 1°C) and humidity conditions (75 ± 5% RH), as indicated by Tables 8 and 9. Therefore, after being exposed to accelerated stability conditions, the new formulation was determined to be stable [25].

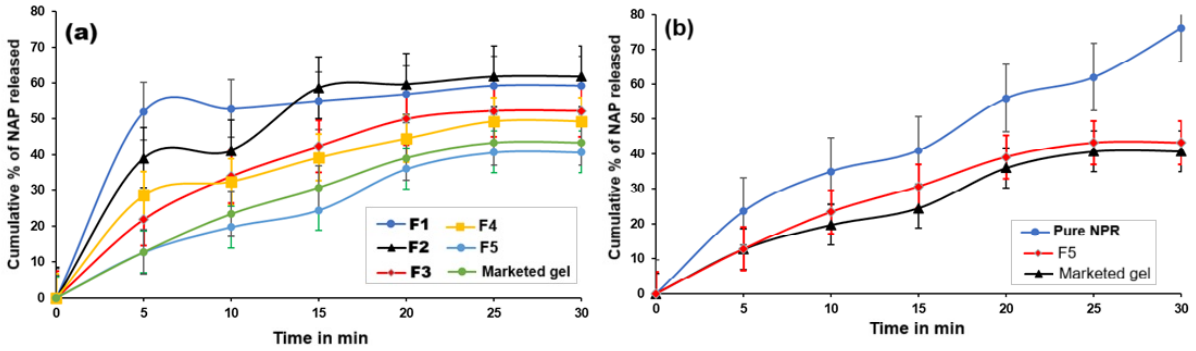

Figure 3. Ex vivo cumulative percentage of NPR released from NPR-gel. (a) F1-F5 and marketed gel and (b) pure NPR, F5, and marketed gel, mean ± SD, n = 3.

Stability of NPR-gel

30-day stability of NPR-gel below Table 3 represents the stability profile of a naproxen sodium gel system over storage for 30 days, with variation in visual appearance, viscosity, drug content, spread, pH, and in vitro drug release. Visual appearance did not change (translucent and thick) up to day 14. On day 30, the gel was translucent and thin, which may be an indication of the degradation of the gel matrix over time. Viscosity indicated a progressive fall from 9274.71 ± 341.81 cps (initial) to 9075.71 ± 366.23 cps on day 30. Although this is insignificant, it justifies the recorded change in appearance, implying partial structural deterioration or water gain/loss impacting gel consistency [26]. Drug content reduced from 98.34% to 96.25% within 30 days. This reduction is minor but still falls within acceptable pharmaceutical criteria and demonstrates satisfactory stability regarding retention of drug. Spreadability was still very good (+++) on day 14 and dropped to ++ on day 30 slightly because of lower viscosity and change in gel composition. pH was increased marginally from 5.51 ± 0.43 to 5.71 ± 0.22 but again within a suitable range to be used on the skin, reducing irritation risk to zero. In vitro drug release decreased slightly from 87.22% to 84.01% over the 30 min test period, indicating a slight loss of release efficiency, perhaps as a result of gel consistency or drug distribution changes in the matrix [27].

Table 3. various stability studies of optimised preparation of NPR-gel (F5), mean ± SD, n = 3.

Preparation Code	Initial	7 days	14 days	30 days
Visual Appearance	Translucent & Thick	Translucent & Thick	Translucent & Thick	Translucent & thin
Viscosity (cps)	9274.71 ± 341.81	9177.49 ± 355.55	9143.22 ± 354.17	9075.71 ± 366.23
Drug content	98.34 ± 6.77	97.75 ± 7.22	97.22 ± 7.14	96.25 ± 7.89
Spread ability	+++	+++	+++	++
pH	5.51 ± 0.43	5.55 ± 0.51	5.61 ± 0.65	5.71 ± 0.22
In vitro drug release (after 30 min)	87.22 ± 4.76	86.56 ± 5.12	84.56 ± 7.88	84.01 ± 6.57

Based on the result, we concluded that the NPR-gel (F5) was found to have acceptable physical, chemical, and release properties after 30 days but with some slight effects on viscosity, spreadability, and drug release such that longer-term studies will need to be conducted to guarantee shelf life and storage.

4. Conclusion

Using carrageenan and HPMC, the NAP hydrogel for topical application was prepared, and assessment experiments were run. Based on in vitro permeation investigations, it was discovered that the topical distribution of NAP from the prepared gel formulations over rat abdomen skin was superior to that of the commercial formulation. Choosing the right polymers and figuring out how much of them to use is a must when preparing a transdermal drug delivery system. In comparison to the marketed formulation, the developed gels demonstrated superior drug release rates, good homogeneity, and good stability. Based on its evaluation criteria, the optimised formulation F5, which consists of 0.75 %w/v carrageenan 0.5 %w/v HPMC, was determined to be appropriate for topical application.

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