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Comparison of In Vitro Ibuprofen Release Rates from HPMC and Carbopol 934® Gels

Emine Dilek Ozyilmaz[1]*, Acelya Mavideniz[1], Zahra Nobavar[1]

[1] Eastern Mediterranean University, Faculty of Pharmacy, Famagusta, North Cyprus via Mersin 10, Turkiye.

Abstract

Topical drug delivery systems have become a critical area of research because of their ability to deliver active pharmaceutical ingredients directly to the target site, thereby reducing systemic exposure and associated side effects. Non-steroidal anti-inflammatory drugs like ibuprofen are frequently used in these systems for their strong pain-relieving and anti-inflammatory properties. In the present study, an HPMC gel formulation containing the same amount of ibuprofen (5% w/w) was prepared as an alternative to the market formulation, which is prepared with Carbopol 934® as the gelling agent. The aim was to compare the two formulations in terms of the release rate of the active substance. The study results demonstrated that the HPMC gel containing ibuprofen, formulated as an alternative to the market formulation, meets pharmaceutical criteria in terms of pH, viscosity, appearance, and active ingredient content (90-105%). Furthermore, the release rate of ibuprofen from gel was statistically significantly different compared to the market formulation prepared with Carbopol 934® (p<0.05). Based on the findings, it can be concluded that the prepared gel formulation may serve as an alternative to the market formulation containing the same amount of active ingredient. This is particularly desirable for enhancing the onset of anti-inflammatory and analgesic effects by increasing the release rate.

Keywords

Carbopol 934®, HPMC, ibuprofen, release rate, physicochemical controls.

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***Corresponding author:** Emine Dilek Ozyılmaz **email:** dilek.ozyılmaz@emu.edu.tr

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INTRODUCTION

Topical drug delivery systems have emerged as a pivotal area of research due to their capability to deliver active pharmaceutical ingredients directly to the site of action, thus minimizing systemic exposure and associated side effects. Non-steroidal anti-inflammatory drugs (NSADs) like ibuprofen are widely used for their potent analgesic and anti-inflammatory effects. The formulation of ibuprofen for topical application presents unique challenges, primarily revolving around enhancing its solubility, stability, and permeation through the skin (Oba et al., 2021; Hundscheid et al., 2023; Sung et al., 2020).

In the realm of topical gels, the choice of gelling agent plays a critical role in determining the drug release rate and overall efficacy of the formulation. Hydroxypropyl methylcellulose (HPMC) and Carbopol 934® are two widely used polymers in the pharmaceutical industry. HPMC, a semi-synthetic derivative of cellulose, is renowned for its biocompatibility, mucoadhesive properties, and ability to form clear, stable gels. It provides a controlled release profile, which is advantageous for maintaining therapeutic drug levels over an extended period (Montes et al., 2022; Hundscheid et al., 2023). Additionally, rheological properties of HPMC can be fine-tuned to optimize patient compliance and ease of application (Montes et al., 2022).

Carbopol 934® is a high molecular weight, cross-linked polyacrylic acid polymer. Its ability to form highly viscous gels even at low concentrations makes it a preferred choice for many topical formulations. Carbopol 934® gels are known for their excellent bioadhesion and clarity characteristics which are desirable traits for cosmetic and pharmaceutical applications. However, the release kinetics of ibuprofen from Carbopol 934® gels can be influenced by factors such as polymer concentration, pH, and the presence of electrolytes (Mahmoud et al., 2020).

This study seeks to investigate and compare the release rate of ibuprofen from an HPMC-based gel formulation to that of a commercially available Carbopol 934®-based gel. Understanding these dynamics is crucial, as they directly impact the therapeutic efficacy, onset of action, and patient adherence. While previous studies have explored the individual characteristics of HPMC and Carbopol 934® gels, comprehensive comparative analyses focusing on ibuprofen release are limited. By systematically evaluating the release profiles, we aimed to elucidate the potential advantages and limitations of using HPMC

versus Carbopol 934® as gelling agents in topical ibuprofen formulations. This investigation could a basis for future formulation strategies, ultimately enhancing the effectiveness of topical NSAID therapies and improving patient outcomes. Our findings may also contribute to the broader field of topical drug delivery, providing insights that could be applied to other active pharmaceutical ingredients and therapeutic areas.

MATERIALS AND METHODS

Materials

Ibuprofen, HPMC, and Carbopol 934® were obtained from Sigma-Aldrich (USA). Carbopol 934® ibuprofen (Carbopol-IBU) that was used as a reference was commercially available. All other chemicals and reagents used in this study were of analytical grade.

The equipments used in the study include: Electric balance: Mettler Toledo (USA), viscometer: Thermo Scientific Viscotester (USA), pH meter: Ohaus (USA), water bath: N-Biotech (Korea), magnetic stirrer: Velp Scientifca (USA) and UV/Visible spectrophotometer: Shimadzu UV-1800 (Japan).

Methods

Spectrophotometric analysis of ibuprofen

The stock solution was prepared by dissolving 50 mg of ibuprofen in 100 mL of 0.1 N NaOH solution. Using the prepared stock solution, the wavelength at which ibuprofen exhibits maximum absorbance was determined. The stock solution was then diluted to various concentrations, and the absorbance values of these dilutions were measured at the determined wavelength. The calibration equation was subsequently established based on these absorbance values (Kashyap et al., 2020; USP 32, 2009).

Preparation of HPMC-ibuprofen (HPMC-IBU) gel

The HPMC gel was prepared by dispersing the required amount of HPMC in distilled water under continuous stirring. The mixture was heated to 70°C and stirred until a homogeneous solution was obtained. After cooling to room temperature, ibuprofen was added and dispersed completely. The gel contained 5% (w/w) ibuprofen (Hasnain et al., 2020).

In vitro evaluation of ibuprofen gels

In vitro evaluation and characterization of ibuprofen gels were carried out via organoleptic controls, pH determination, viscosity measurement, and analysis of the percent ibuprofen content in the prepared gel formulations. For the analysis of

ibuprofen content in the gel formulations, 1 gr of the gel was mixed with 50 mL of pH 6.8 phosphate buffer. The mixture was stirred continuously using a magnetic stirrer for 12 hours, followed by ultrasonic bath treatment. The solution obtained was passed through a 0.45 µm membrane filter, and suitable dilutions were prepared to quantify the active ingredient using a UV spectrophotometric technique in triplicate (Pradal, 2020).

Organoleptic evaluations

The visual appearance and texture of the ibuprofen gel formulations were examined to determine their uniformity.

pH measurement

Ibuprofen gel formulations were dispersed in distilled water. A digital pH meter (Ohaus, USA) was utilized to measure their pH levels. The measurement was done in triplicate.

Viscosity

The viscosity of the gel formulations was assessed using a Thermo Scientific Viscotester (USA). The measurements were conducted in triplicate at room temperature, utilizing spindle No. 94 at a speed of 15.0 rpm (Boshrouyeh et al., 2023; Hasnain et al., 2020).

Assay

The concentration of ibuprofen in the gels was quantified using a UV spectrophotometric method. Initially, a standard solution of ibuprofen was prepared by thoroughly mixing 100 mg of ibuprofen in 1000 mL of a 6.8 pH buffer solution in a volumetric flask. The standard solution was then serially diluted to create a range of solutions with different concentrations of ibuprofen. The absorbance of these solutions was measured at 272 nm using UV spectrophotometry. Analytical parameters were determined using ANOVA (Mancini et al., 2021; USP 32, 2009).

In vitro ibuprofen release studies

The amount of ibuprofen in the hydrogel formulations was determined by accurately weighing and placing 2 gr hydrogel samples into dialysis bags made of xylene cellulose acetate. These bags were then immersed in a pH 6.8 phosphate buffer and maintained in a beaker with a water bath at 37 °C ± 0.5 °C, equipped with a heater and stirrer. The ibuprofen content of the samples was measured at 15, 30, 60, 90, 120, and 150 minutes using a UV spectrophotometric method. Each measurement was performed in triplicate (Theochari et al., 2021).

Statistical analysis

To optimize the ibuprofen gel formulations, ANOVA was employed. A p-value of less than 0.05 was considered as an indicative of a statistically significant difference. The results were presented as mean ± standard deviation**.**

RESULTS AND DISCUSSION

Spectrophotometric analyses of ibuprofen

The results show that the absorbance value of ibuprofen at 272 nm was consistent with prior studies. The method validation parameters are shown in Table 1, and the calibration curve and equation are presented in Figure 1.

Table 1: Analytical method validation parameters for the assay of ibuprofen.

Parameters	Results
Linearity range (mM)	0.2-2.0
Slope (m)	0.3796
RSD (%)[1]	0.42
Determination of coefficient	0.03
LOD (µg/mL)[2]	0.0207
LOQ (µg/mL)[3]	0.09
RSD for accuracy	0.29

[1]RSD: Relative standard deviation
[2]LOD: Limit of detection
[3]LOQ: Limit of quantification

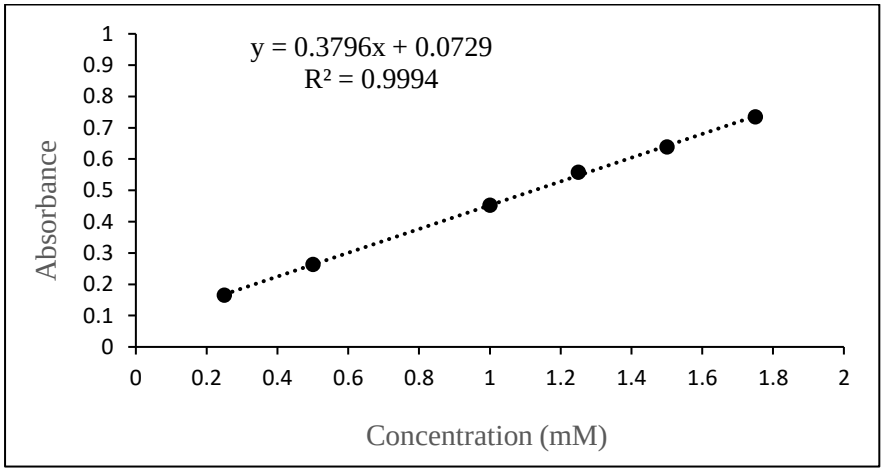

Figure 1: Calibration curve of ibuprofen.

In vitro evaluation of ibuprofen gels

Table 2 illustrates the physicochemical characteristics of the gels including pH, uniformity, viscosity, and percentage of ibuprofen content in the gel formulations.

According to the studies involving gels formulated with HPMC, the pH range of the gels is between 6.0 and 7.0 at room temperature. This range is associated with the neutral nature of HPMC and its compatibility with the pH values of other components in the gel. This characteristic suggests that the formulation is compatible with the skin and provides a suitable environment for the stability of active ingredients such as ibuprofen (Ardana et al., 2015; Nogami et al., 2021; Rahmani and Zulkarnain, 2023).

Due to the use of a medium molecular weight HPMC gel agent in the formulation, the viscosity of the prepared HPMC-IBU gel, considering its concentration, was as

expected within the medium-high range (1015±5.58 cPs). This viscosity value is suitable for a pharmaceutical gel, indicating that the formulation will form a thicker layer on the skin and will spread more slowly compared to water.

The ibuprofen content in the hydrogels was therapeutically adequate, with percentages ranging from 96.00 to 98.66% ± 1.32–2.77.

Table 2: The physicochemical characteristics of the formulated gel.

Formulations	pH±SD	Viscosity (cPs) ±SD (25°C)	Homogenity	Ibuprofen assay (%)±SD
HPMC-IBU gel	6.91±0.1	1015±5.58	+	96.14±1.32
Carbopol-IBU gel	6.87±0.5	1114±6.44	+	98.66±2.77

In vitro ibuprofen release studies

The therapeutic efficacy of gel formulations is closely linked to the release of ibuprofen. The release occurs through the three-dimensional network structure of the gels, either by passive diffusion or by erosion of the gel matrix due to degradation over time. Because ibuprofen is a small molecule, it can penetrate the stratum corneum, the outermost layer of the skin, primarily through passive diffusion. Additionally, the type and amount of gel agent used may affect the release of ibuprofen. As a result, the cumulative release profiles of ibuprofen were measured from the HPMC-IBU gels and the commercial Carbopol-IBU gel formulation. The release rate of ibuprofen from the new formulation prepared using HPMC was statistically significantly faster than that of Carbopol available on the market ($p = 0.004$). Release profiles from these gels that were tested in triplicate are shown in Figure 2.

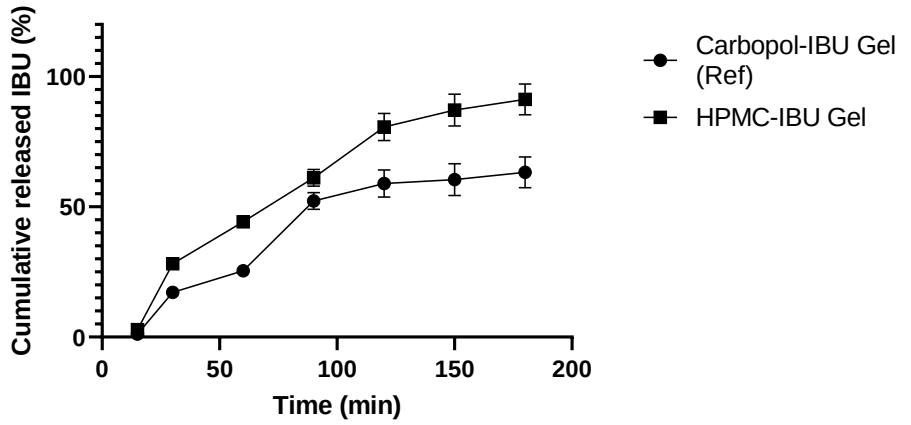

Figure 2: Release profiles of ibuprofen from gels.

CONCLUSION

In the present study, the aim was to prepare an ibuprofen gel formulation, frequently preferred for topical application in the pharmaceutical market due to its analgesic and anti-inflammatory properties, using HPMC as the gelling agent. The prepared gel formulation was compared with gels prepared with Carbopol, both in terms of physicochemical properties and the release rate of the active substance.

When the results were evaluated, it was determined that the physicochemical properties of the prepared HPMC gels were compatible with the references. The HPMC-IBU gel and the Carbopol 934®-IBU gel had comparable physicochemical properties, such as characteristic pH, viscosity, and appearance. The release rate of ibuprofen from the new formulation prepared using HPMC was statistically significantly faster than that from the Carbopol 934®. The reason for this difference is that the gel matrix formed with Carbopol 934® tends to have a higher viscosity, which can further slow the release rate of ibuprofen.

A gel containing HPMC can generally provide a more controlled and consistent release but does not form as viscous structure as Carbopol 934®. Therefore, the release rate of ibuprofen may be higher in the gel containing HPMC. HPMC forms a less viscous matrix that dissolves more rapidly, increasing the release rate of ibuprofen. On the other hand, Carbopol 934® may slow down the release of ibuprofen further by creating a more viscous structure. As a result, the prepared HPMC-IBU gel may be preferred over the market formulation, as it is desirable for the pain-relieving and anti-inflammatory effects to be observed in a short time after application.

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