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Formulation and Evaluation of Drug-Loaded Tan Removal Hydrogel

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ABSTRACT

Topical gels are commonly used for topical application or to specific mucous membrane to achieve local effects, facilitate transdermal drug delivery, or provide emollient and protective properties. Incorporating drugs into gel matrices enables effective drug delivery, enhancing local action in analgesia and dermatological conditions. Nicotinamide has proven to be an effective anti-tan agent when topically applied. It reduces melanin transfer and production, thus preventing skin darkening caused by UV radiation. Additionally, nicotinamide offers other skin benefits such as improved barrier function and reduced inflammation, making it a promising component in skincare products. Kojic acid, a natural agent, inhibits tyrosinase activity and aids in reducing skin tanning.

To develop topical hydrogel formulations, Hydrophilic polymers like triethanolamine (TEA) and Carbomer at different concentrations were employed. The formulations underwent evaluation tests encompassing visual appearance, pH, viscosity, spreadability, assay, and in vitro drug release studies using a USP V dissolution apparatus. Accelerated temperature (40 ± 20°C) and humidity conditions (75 ±5%RH) were applied to assess formulation stability. Notable changes in the physicochemical properties of the formulations were not observed under these conditions. Based on in vitro evaluation studies, the gel formulation comprising 1% w/v Triethanolamine and 0.5% w/v Carbomer demonstrated suitability for topical application. These findings indicate the feasibility of formulating a topical gel containing kojic acid and nicotinamide hydrogel.

KEYWORDS: Nicotinamide, Kojic Acid, Triethanolamine, Carbomer (Carbopol-940), Hydrogel, Skin Tanning,

INTRODUCTION

Topical drug administration allows localized delivery of drugs to various parts of the body, including the eyes, rectum, vagina, and skin. The skin, being easily accessible, is a primary route for topical drug delivery[1-2]. Recent scientific and technological advancements have focused on developing hydrogel drug delivery systems to overcome challenges like first-pass metabolism and to enhance local drug action[3]. Several approaches have been explored to address skin tanning, including the use of topical formulations containing hydroquinone, kojic acid, and nicotinamide[4-5]. These ingredients inhibit melanin production, which is responsible for skin tanning. Transdermal gels have been formulated using different polymers to improve the delivery of these agents through

the skin[6].

This study aims to develop a transdermal hydrogel formulation combining kojic acid and nicotinamide using natural and semi-synthetic polymers. Gels consist of a solid network that occupies the volume of a liquid medium. This network can be formed through physical or chemical bonds, as well as other junctions or crystallites that remain intact within the surrounding fluid. The gel's three-dimensional structure is composed of physical or chemical connections, and it is immersed in a liquid medium.Gels can be extended with various fluids, such as water (hydrogels), oil, or air (aerogels). Both in terms of weight and volume, gels primarily consist of fluid components, resulting in densities similar to those of their constituent liquids[7-8].

Hydrogels are polymer networks that are insoluble in water and can exist as colloidal gels, with water serving as the dispersion medium. They are composed of natural or synthetic polymers and have a remarkable capacity for water absorption, often containing over 99% water. Hydrogels, due to their substantial water content, exhibit a flexibility that resembles natural tissue. These networks of crosslinked polymers possess the ability to absorb considerable quantities of aqueous solutions. The utilization of hydrogels has been pivotal in the progress of drug delivery technology[9].Topical formulations of niacinamide and kojic acid offer benefits compared to oral formulations by minimizing the risk of systemic side effects. These formulations are conveniently applied to the skin and effectively penetrate the skin barrier to address the root causes of skin tanning. By inhibiting melanin production and reducing skin pigmentation, a topical formulation containing niacinamide and kojic acid can enhance skin tone without causing adverse effects on other organs.[10, 11]. The objective of this research is to develop and assess hydrogel-based drug delivery systems for topical application with the goal of improving drug absorption and exposure, thus optimizing therapy. To control the drug release rate from the dosage forms, cross-linking agents, gelling agents, and thickening agents were incorporated. The primary aim was to enhance the bioavailability of the drug and improve its sustained and effective characteristics.

MATERIALS AND METHODS:

Procurement of Drugs

The drugs Ascorbic acid, Nicotinamide was procured from Gowin Technologies Mumbai Amravati (Maharashtra) ,Glycerin, Triethanolamine, Methyl Paraben, Polyethylene Glycol, Carbomer, Distilled Water is procured from Rungta Institute of Pharmaceutical Sciences Bhilai (Chhattisgarh).

Selection of Polymers[12]:

Carbomer, a hydrophilic polymer soluble in water, was chosen, and triethanolamine solution was used as a cross-linking agent. Both components have distinct properties in water: Carbomer is soluble, while triethanolamine produces a colloidal dispersion. Polymeric dispersions were prepared separately at concentrations ranging from 0.1% to 5% w/v. Upon mixing the colloidal dispersions of triethanolamine and Carbomer in specific proportions, the resulting formulations exhibited favorable mechanical properties.

Formulation Development of Hydrogel:

Method of Preparation (Table-1)

A measured quantity of Methyl Paraben and Glycerin, along with a weighed amount of Polyethylene glycol, were dissolved in approximately 35 milliliters of water within a beaker. The mixture was vigorously stirred using a mechanical stirrer or sonicator. Carbomer, a commonly used gelling polymer in skincare products, was then gradually added to the beaker while stirring. The solution was neutralized by slowly adding triethanolamine solution with continuous stirring until a gel was formed.

In this formulation, Carbomer acts as the gelling polymer, while triethanolamine serves as a gelling agent, pH adjuster, and neutralizer. Methyl Paraben functions as a preservativeto prevent bacterial proliferation and prolong the product's stability. Distilled water, glycerin, and polyethylene glycol act as solvents, facilitating the dissolution and dispersion of the other ingredients. Together, these components create a stable gel formulation suitable for topical application and offering various skincare benefits.

Evaluation of Topical Hydrogel [13,14]:

Visual Appearance: The prepared gels were visually assessed for their physical appearance and homogeneity. A reference point was established by comparing them to a marketed formulation.

Spreadability Test: To evaluate spreadability, the gel was applied to a smooth surface and examined for any gritty texture that may be present.

pH Determination: The pH of the gel formulations was assessed by employing a pH meter. A 1% hydrogel formulation was specifically prepared in deionized water for this purpose, and its pH was subsequently measured.

Drug Content: The drug content in the gels was determined by extracting the drug from one gram of each formulation using a volume of 20 milliliters of phosphate-buffer with a pH of 7.4 for a period of 30 minutes.

After the mixture was prepared, it was filtered usinga membrane filter featuring 0.45 µm pore dimensions. The absorbance of the sample was quantified using an Elico SL150 UV-VIS spectrophotometer at a wavelength of 276 nm through spectrophotometric measurement. Prior to measurement, the sample was appropriately diluted with phosphate buffer pH 7.4. The concentration of the drug was determined by comparing it to a calibration curve.

Viscosity Determination: The viscosity of the gel formulations was evaluated employing a Brookfield viscometer equipped with spindle no. 7at a speed of 100 rpm and a temperature of 25°C.

Accelerated Stability Studies: The optimized formulation underwent stability studies in accordance with the guidelines set by ICH. The formulation, packaged in an aluminum tube underwent accelerated stability testing for a duration of 3 months, following ICH standards, at a temperature 40 ± 2°C and relative humidity of 75 ±

5%. Samples were acquired at regular time intervals of 1 month throughout the 3-month period and analyzed for changes in pH, spreadability, drug content, and in-vitro drug release using the previously described procedures. Any observed changes in the evaluation parameters were recorded. The experiments were carried out three times, and the average values, along with the corresponding standard deviation, were recorded.

RESULTS AND DISCUSSION:

The primary emphasis of this study was to develop and assess topical hydrogel drug delivery systems with the aim of enhancingdrug uptake and bioavailability.The objective was to enhance the pharmacokinetics and pharmacodynamics by precisely regulating the drug release rate from the dosage forms. This was achieved through the incorporation of cross-linkers, gel-forming agents, and viscosity modifiers, which are of great significance in controlling the rate of drug release.

The primary objective is to minimize the frequency of dosing by formulating elegant and convenient topical hydrogel dosage forms that maintain steady-state blood concentrations of the drug, thereby improving therapy compliance. Various combinations of polymers were employed to formulate topical hydrogels containing Kojic Acid with Nicotinamide, and these formulations were subjected to evaluation. The hydrogels with superior physicochemical properties were identified from the developed formulations. The specific proportions of polymers utilized in the formulation of the hydrogels are summarized in Table 1.

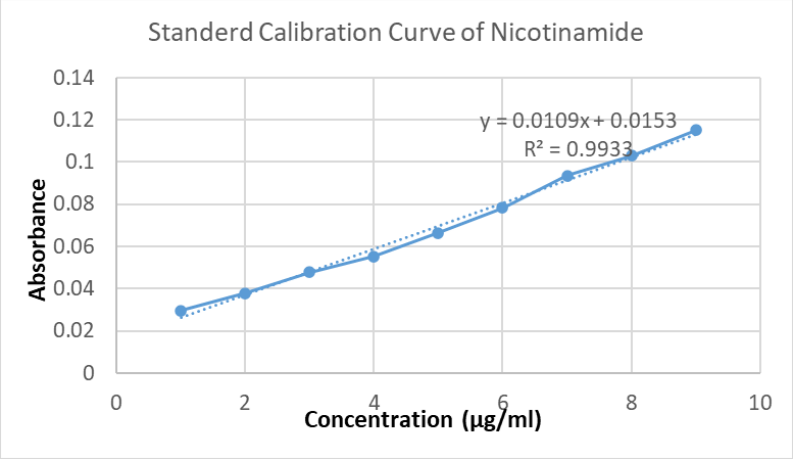

FIGURE 1: STANDARDCALIBRATION CURVE OFNICOTINAMIDE

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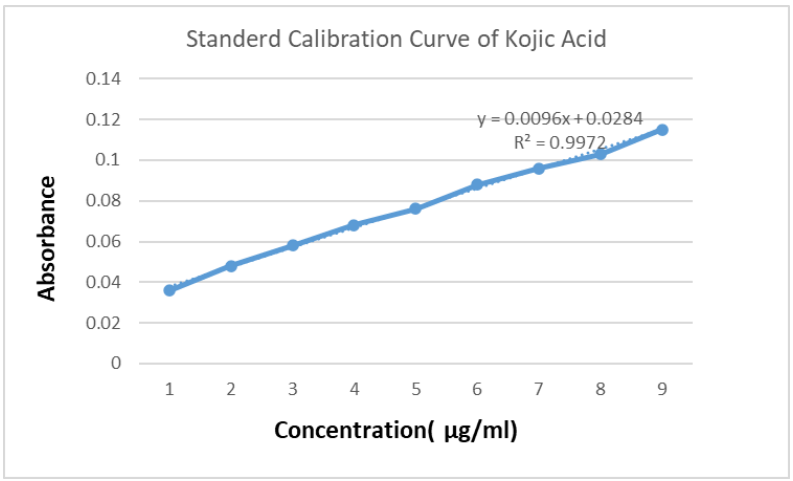

FIGURE 2: STANDARD CALIBRATION CURVE OF KOJIC ACID

Ingredients (%)	HG1	HG2	HG3	HG4	HG5	HG6
Kojic Acid	1	1	1	1	1	1
Nicotinamide	1	1	1	1	1	1
Carbomer	0.25	0.30	0.35	0.40	0.45	0.5
Polyethylene Glycol	2	2	2	2	2	2
Methyl Paraben	0.08	0.08	0.08	0.08	0.08	0.08
Triethanolamine	1.0	1.0	1.0	1.0	1.0	1.0
Distilled Water (q.s)	100	100	100	100	100	100

TABLE 1: DIFFERENT FORMULATIONS OF HYDROGEL

Formulation code	Visual appearance	Drug content	Viscosity (cps)	Spread ability
F1	Opaque, transpicuous	97.6 ± 0.3	8720 ± 2	++
F2	Opaque, transpicuous	97.8 ± 0.2	8735 ± 0.8	++
F3	Opaque, transpicuous	98.3 ± 0.1	8890 ± 0.9	++
F4	Opaque, transpicuous	98.8 ± 0.1	9042 ± 0.3	++
F5	Opaque, transpicuous	99 ± 0.5	9226 ± 1.7	++
F6	Opaque, transpicuous	99.4 ± 0.1	9345 ± 1	++

+Good Spreadability; ++Better Spreadability

TABLE2: EVALUATION OFTOPICALHYDROGELS

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	Cumulative % Drug Release			
Time (Min)	F1	F2	F3	F4
0	0	0	0	0
5	74.1± 0.3	74.6± 0.5	52± 0.1	45.9± 0.2
10	75.10± 0.3	80.7± 0.2	58.40± 0.4	57.20± 0.4
15	77.00± 0.1	81.4± 0.4	71.30± 0.2	65.10± 0.6
20	78.70± 0.1	81.6± 0.2	73.40± 0.3	69.40± 0.5
30	80.80± 0.3	82.4± 0.6	80.50± 0.2	75.10± 0.7

n=3± SD

TABLE3: INVITRODRUGDISSOLUTIONSTUDIESOFTOPICALHYDROGEL FORMULATIONSF1 to F4

	Cumulative % Drug Release			
Time (Min)	F5	F6	Pure Drug Kojic Acid	Pure Drug Nicotinamide
0	0	0	0	0
5	43.1± 0.2	26.6± 0.2	94.3± 0.1	95.8± 0.4
10	55.3± 0.4	34.1± 0.4	96.05± 0.2	97.4± 0.4
15	61.4± 0.6	40.2± 0.6	96.8± 0.4	97.7± 0.2
20	64.7± 0.7	49.5± 0.3	97.8± 0.5	97.9± 0.1
30	69.1± 0.3	51.7± 0.8	98.9± 0.2	98.9± 0.3

n=3± SD

TABLE 4: IN-VITRODRUGDISSOLUTIONSTUDIESOFTOPICALHYDROGEL FORMULATIONS F5, F6, PURE DRUG KOJIC ACID AND PURE DRUG NICOTINAMIDE.

In-Vitro Evaluation: The gel formulations underwent in vitro assessment, and the physicochemical properties are summarized in Table 2. It was observed that all of the gel formulations demonstrated consistent uniformity and spreadability. The gels appeared white and translucent in nature.

The drug content analysis revealed that the formulations exhibited content uniformity, with values ranging from 97.6 ± 0.3 to 99.4 ± 0.1. The pH of the gel formulations ranged from 7 ±0.07to6.9 ± 0.02, which falls withinthe usual pH spectrum of the skin and indicates that the formulations would not cause skin irritation. No significant changes in pH values were observed over time for any of the formulations. Overall, the prepared gel formulations exhibited favorable physicochemical properties.

The viscosity of the gel formulations is an indicator of their consistency. It was observed that the viscosity varied with the concentration of polymers used. Among the developed gels, formulation F6 (Carbomer 0.5% w/v: Triethanolamine 1% w/v) exhibited a higher viscosity of 9345 ± 1.5 cps compared to the other formulations.

To determine the ideal polymer composition for the gel formulation, in vitro studies were performed to assess drug release characteristics, ensuring an appropriate texture for topical use. The drug release profile was evaluated using in vitro dissolution studies conducted with the USP V apparatus (Paddle over Disc). The cumulative data on in vitro drug release can be found in Table 3 and Table 4.Among them, Hydrogel F6 demonstrated a drug release of 51.7 ± 0.8%, while the pure drug exhibited a release of 98.9 ± 0.2% within 30 minutes. Notably, F6 formulation exhibited superior controlled drug release in comparison to the pure drugs, as depicted in Figure 3 and 4. Considering after evaluating the physicochemical attributes and in vitro drug release behavior, it was concluded that formulation F6 is suitable for extended topical use.

Table 2 provides an overview of the physicochemical properties of the gel formulations, indicating consistent homogeneity and spreadability for all samples. The gels exhibited a translucent and white appearance, while maintaining a uniform texture and overall appearance.

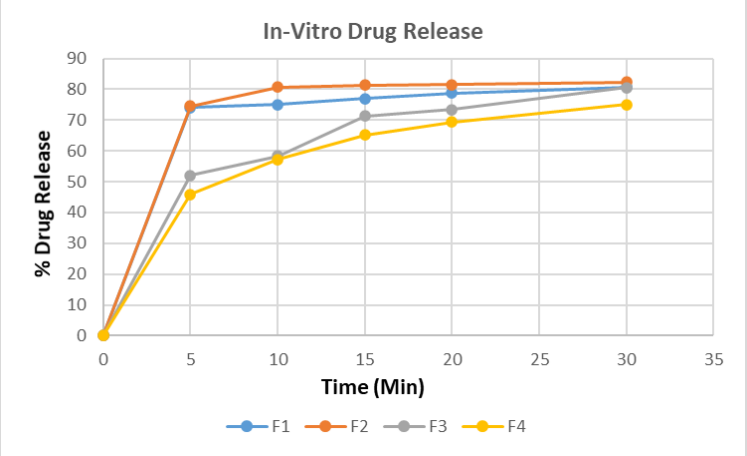

FIGURE 3: IN-VITRO RELEASE OF DEVELOPED HYDROGEL FORMULATIONS

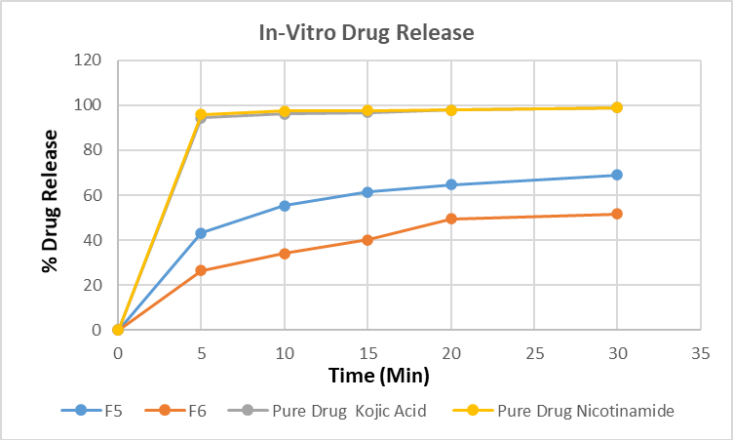

FIGURE 4: IN- VITRO RELEASE OF DEVELOPED HYDROGEL FORMULATIONS

Stability Studies: No noteworthy alterations were observed. Following a 3-month exposure to accelerated temperature and humidity conditions, formulation F6 demonstrated stability. Physical evaluation parameters listed in Table 5 did not exhibit significant changes. The in-vitro drug release data for formulation F6 after the accelerated stability study can be found in Table 6.

Physical Parameter	Temperature: 40º ±2ºC ;Relative humidity (RH): 75 ± 5%RH			
	Initial	After 1 month	After 2 months	After 3 months
pH	7 ±0.07	6.9 ± 0.07	6.9 ± 0.04	6.9 ± 0.02
Assay	99.4 ± 0.2	99.3 ± 0.1	99.2 ± 0.1	99.1 ± 0.1
Viscosity (cps)	9345 ± 1.5	9346 ± 1.2	9348 ± 1.5	9350 ± 2

n= 3 ±S

TABLE5: PHYSICAL PARAMETERS AFTER ACCELERATED STABILITY STUDY OF FORMULATION F6

Time (min)	Cumulative % of drug release (mean)			
	Initial	After 1 month	After 2 months	After 3 months
5	26.6	26.4	26.2	25.9
10	34.1	33.8	33.4	32.9
15	40.2	39.8	39.2	38.9
20	49.5	48.6	48.4	47.2
30	51.7	51.2	50.9	50.4

TABLE 6: IN-VITRO DRUG RELEASE OF FORMULATION F6 AFTER ACCELERATED STABILITY

Table 5 and 6 shows no significant changes in the physicochemical properties and *in-vitro* drug release profile of the optimized formulation even after its exposure to accelerated conditions of temperature (40ºC) and humidity conditions (75 ±5%RH).Consequently ,the developed formulation was found to be stable after exposing to, accelerated stability conditions.

CONCLUSION: In conclusion, this study aimed to develop and evaluate topical hydrogel drug delivery systems for improved drug uptake and bioavailability. The incorporation of cross-linkers, gel-forming agents, and viscosity modifiers played a significant role in controlling the drug release rate. Various formulations were tested, and formulation F6, with a composition of Carbomer 0.5% w/v and Triethanolamine 1% w/v, exhibited favorable physicochemical properties and demonstrated controlled drug release. The gel formulations maintained uniformity, spreadability, and translucent appearance. Stability studies showed no significant changes in physical parameters or drug release profile for formulation F6 after exposure to accelerated temperature and humidity conditions. Overall, formulation F6 is deemed suitable for extended topical application, offering potential benefits in terms of therapy compliance and steady-state drug concentrations.

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