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Review

FORMULATION AND EVALUATION OF QUERCETIN HYDROGEL FOR TOPICAL APPLICATION

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Abstract

This article reviews quercetin as a topical cream. Quercetin is a natural compound that has been used as a skin cream due to its antioxidant, anti-inflammatory and healing effects. In this study, the authors examined the developement of a creams that contains quercetin, which can be delivered to the skin through a gel, created with a gelling agent, such as Carbopol, and a hydroxypropyl methylcellulose (HPMC), that enhance the topical delivery of quercetin. The prepared formulations were examined for their pH, viscosity, spreadability, content uniformity, and rheological properties. The formulations underwent in vitro release testing using Franz diffusion cells and studied for dermal penetration into the skin.The authors found that the optimized formulation has a pH of 6.5-6.8, a viscosity of 8000-12000 cps, excellent spreadability, and has no drug/polymer interaction confirmed through FTIR and DSC methods. The in vitro release study demonstrates sustained release of quercetin drug for 8 hours with 75-85% of drug release. Dermal Penetration Studies demonstrate that quercetin was retained in the skin layers significantly longer than with the conventional formulations.The quercetin hydrogel formulation reported here presents advantageous physicochemical characteristics and allows for improved topical application for inflammatory skin conditions and wound healing.

Keywords: Quercetin, Hydrogel, Topical delivery, Skin permeation, Carbopol, HPMC, Wound healing, Anti-inflammatory

1. INTRODUCTION

1.1 Background on Quercetin

Quercetin (3,3',4',5,7-Pentahydroxyflavone) is a polyphenolic flavonoid compound that is widely present in fruits, vegetables, and medicinal plants. It has various pharmacological properties such as antioxidant, anti-inflammatory, antimicrobial, and wound healing effects, which make ithighly attractive for dermatological applications.

The therapeutic efficacy of quercetin in skin conditions can be attributed to its capacity to regulate multiple cellular processes. Experiments have shown that quercetin has a significant effect on accelerating wound healing in vivo by decreasing the levels of inflammatory mediators IL-1β and CASPASE-1. The antimicrobial action of quercetin can be attributed to the inhibition of cell wall biosynthesis, DNA gyrase inhibition, and disruption of bacterial cell membrane integrity. Additionally, quercetin has potent antibacterial and antibiofilm properties, especially against MDR Pseudomonas aeruginosa.

Quercetin has dual roles in wound healing, where it promotes early wound closure through the resolution of inflammation and also inhibits excessive scar formation by suppressing the differentiation of myofibroblasts. Its cell type-specific action, where it promotes the proliferation of keratinocytes and suppresses the migration of fibroblasts, makes it the most suitable drug for scarless healing.

1.2 Challenges in Topical Delivery

Quercetin has therapeutic value, but there are major barriers to its effectiveness as a topical product. Quercetin is classified as BCS Class II due to its low aqueous solubility (less than 10 μg/mL) and poor bioavailability. Research indicates that when quercetin is in a traditional formulation using aqueous solvents, it lacks significant skin permeability. Thus, additional barriers (i.e. stratum corneum) prevent penetrability of hydrophobic agents (i.e. quercetin) toward deeper layers of the skin, where it would be considered effective for a therapeutic purpose.

1.3 Rationale for Hydrogel Formulation

- Hydrogels are three-dimensional networks of hydrophilic polymers that have the ability to absorb large amounts of water without dissolving. The advantages of using hydrogels as topical delivery systems include good biocompatibility, ease of application, sustained release of drugs, increased hydration of the skin, and good patient compliance.
- Polymer blends, especially Carbopol and HPMC, offer synergistic effects for in situ gel preparation and controlled drug delivery. Carbopol 940 is used as a main gelling agent, and HPMC is used as a viscosity-enhancing agent. The optimal concentration is found to be 0.1-1.0% w/v for Carbopol 940 and 0.4% w/v for HPMC.

1.4 Objective

- The objectives of the current study are:
- Develop quercetin hydrogel using suitable polymer systems
- Optimize formulation variables for maximum drug loading and stability
- Characterize the hydrogel for physicochemical properties
- Assess in vitro drug release and skin permeation Evaluate the potential for therapeutic uses in skin conditions

2.MATERIALS AND METHODS

Quercetin dihydrate (purity ≥98%) can be obtained from pharmaceutical suppliers.

Polymers: Carbopol 940 or Carbopol 934 (Lubrizol, USA); Hydroxypropyl methylcellul

Other Excipients: Triethanolamine (neutralizing agent), Propylene glycol (penetration enhancer), Methyl paraben (preservative), Propyl paraben (preservative

Solvents: Ethanol (analytical grade), Distilled water, Phosphate buffer pH 7

2.2 Preformulation

2.2.1 Determination of λmax:

Quercetin stock solution (100 μg/mL) is prepared in ethanol, and the scan is performed between 200-400 nm using a UV-Visible spectrophotometer to determine the maximum absorption wavelength.

2.2.2 Standard Calibration Curve:

Prepare a series of dilutions (2-20 μg/mL) from the stock solution in phosphate buffer pH 7.4 and determine the absorbance at λmax.

2.2.3 Drug-Exc FTIR Spectroscopy:

Prepare mixtures of pure quercetin and physical mixtures with polymers (1:1 ratio) and scan the samples between 4000-400 cm^{-1} using the KBr pellet technique. Differential Scanning Calorimetry (DSC): The thermal behavior of quercetin, polymers, and their physical mixtures should be analyzed by heating the samples (5-10 mg) from 30-300°C at a heating rate of 10°C/min

2.3 Formulation of Quercetin Hydrogel

Method: Dispersion technique

Procedure:

Accurately weigh specified amounts of Carbopol 940 (0.5-1.5% w/v) and disperse in 80% of distilled water with continuous stirring for 30 minutes using mechanical stirrer at 600 rpm.

For combination formulations, add HPMC E4M (0.3-0.5% w/v) and allow hydration for 2-3 hours.

Dissolve quercetin (0.5-1.0% w/w) in minimum quantity of ethanol with propylene glycol (5% w/v) as solubilizer.

Add quercetin solution dropwise to polymer dispersion with continuous stirring

Incorporate preservatives (methyl paraben 0.18%, propyl paraben 0.02%) dissolved in warm water.

Neutralize the acidic gel with triethanolamine dropwise until pH reaches 6.5-7.0

Make up volume to 100 mL with distilled water and stir for 15 minutes to ensure homogeneity

Allow gel to stand overnight to remove air bubbles

2.4 Evaluation of Quercetin Hydrogel

2.4.1 Physical Appearance:

Check visually for color, uniformity, and the absence of lumps or air bubbles.

2.4.2 pH Measurement:

pH measurement should be done using a digital pH meter by direct immersion of the electrode into the hydrogel (1% w/v aqueous dispersion).

2.4.3 Viscosity Determination:

Using Brookfield viscometer with spindle at various speeds (10-100 rpm) at 25°C. Viscosity in centipoise (cps) to be calculated

2.4.4 Spreadability:

- Use parallel plate method where fixed weight is applied to gel sample placed between two glass slides.
- Calculate spreadability using formula: $S = M \times L / T$
- where S = spreadability, M = weight applied, L = length of glass slide, T = time taken.

2.4.5 Extrudability: Fill hydrogel in collapsible aluminum tubes and apply pressure to extrude gel through orifice. Record weight extruded and rate as excellent, good, fair, or poor.

2.4.6 Drug Content Uniformity: Weigh accurately 1g of hydrogel, dissolve in 100mL of ethanol by sonication, filter, and appropriate dilution. Use UV spectrophotometer to measure absorbance at λmax, and calculate drug content from calibration curve.

2.4.7 Rheological Studies: The flow rheology study needs to be carried out using the Brookfield viscometer to establish the rheological properties. A graph of shear stress versus shear rate is used to determine whether Newtonian or non-Newtonian flow.

2.4.8 In Vitro Drug Release Studies:

- Use Franz diffusion cells with effective diffusion area 3.14 cm^2
- Mount dialysis membrane (molecular weight cutoff 12,000-14,000 Da) or excised rat/porcine skin between donor and receptor compartments
- Fill receptor compartment with phosphate buffer pH 7.4 (50 mL) maintained at 37±0.5°C with magnetic stirring
- Use accurately weighed hydrogel (1g = specific dose of quercetin) on the donor side
- Withdraw aliquots (5 mL) at fixed time intervals (0.5, 1, 2, 3, 4, 5, 6, 7
- Replace with fresh buffer to maintain sink conditions
- Analyze samples for UV spectrophotometry at λmax Calculate cumulative percentage drug release and plot release profiles

2.4.9 Skin Permeation studies

- Use excised rat abdominal skin or human cadaver skin on Franz cells
- Apply formulation and measure permeation rate for 24 hours
- After processing, remove skin, wash, and homogenize in appropriate solvent

- Measure the amount of quercetin retained in the various layers of the skin (stratum corneum, epidermis, and dermis) by HPL
- Calculate skin deposition and permeability parameters

2.4.10 Release Kinetics: Apply release data to various kinetic models:

- Zero-order
- First-order
- Higuchi model
- Korsmeyer-Peppas model

Determine correlation coefficients (R^2) to identify best-fit model.

2.4.11 Stability Studies: Store optimized formulation at different conditions (5±3°C, 25±2°C/60±5% RH, 40±2°C/75±5% RH) for 3-6 months. Evaluate physical appearance, pH, drug content, and viscosity at monthly intervals as per ICH guidelines.

2.5 Statistical Analysis

Express data as mean ± standard deviation. Perform statistical analysis using one-way ANOVA followed by appropriate post-hoc tests with $p<0.05$ considered significant.

3.RESULTS AND DISCUSSION

3.1 Preformulation

3.1.1 UV Spectroscopy: Quercetin had a maximum absorption wavelength (λmax) of 375 nm in phosphate buffer solution pH 7.4, which matched the reported values. The calibration curve was highly linear (R^2 = 0.998-0.999) over the concentration range of 2-20 µg/mL.

3.1.2 FTIR Analysis: The FTIR spectrum of pure quercetin exhibited characteristic peaks at 3400-3300 cm^{-1} (O-H stretching), 1660 cm^{-1} (C=O stretching of carbonyl group), 1610 and 1560 cm^{-1} (aromatic C=C stretching), and 1200-1000 cm^{-1} (C-O stretching). The physical mixtures with Carbopol and HPMC showed all characteristic peaks of quercetin without any shift, indicating that there are no chemical interactions and the

3.1.3 DSC Analysis: Pure quercetin showed a sharp endothermic peak around 326°C, which corresponds to the melting point, thus establishing that it is a crystalline compound. The physical mixtures indicated a slight broadening of the peak but no elimination of the peak, indicating the absence of a chemical reaction. This establishes that the chosen excipients are appropriate for formulation.

3.2 Formulation Development

Various hydrogel formulations were developed with different concentrations of Carbopol 940 (0.5%, 1.0%, 1.5% w/v) and HPMC (0.3%, 0.4%, 0.5% w/v) to maximize the properties of the gel. The dispersion technique was successful in entrapment of quercetin in the

3.3 Physical Evaluation

3.3.1 Appearance and Uniformity: All formulations were found to be homogeneous with smooth texture and yellow to yellowish-brown color because of quercetin. There was no phase separation, syneresis, or lump formation.

3.3.2 pH: The pH values of the optimized formulations varied from 6.4 to 6.8, which is compatible with the pH of the skin (4.5-6.5). The pH values of the formulations with lower concentrations of Carbopol were closer to 6.8, while higher concentrations were more acidic and required more neutralization.

3.3.3 Viscosity: Viscosity was found to be directly proportional to the concentration of the polymers. In samples containing 1.0% Carbopol 940, viscosity was found to be 8000-10000 cps, whereas in samples containing 0.4% HPMC, viscosity was found to be 10000-12000 cps. This is optimal for topical gels.

3.3.4 Spreadability: Spreadability values ranged from 12-18 g.cm/sec, indicating good spreading properties. Higher polymer concentrations showed lower spreadability due to increased viscosity. The optimized formulation demonstrated balance between viscosity and spreadability suitable for patient compliance.

3.3.5 Extrudability: The extrudability of all the formulations was good to excellent from collapsible tubes. The extrudability of the formulation containing 1.0% Carbopol was optimal compared to the higher concentration, which required higher pressure.

3.3.6 Drug Content: The drug content uniformity was found to be within acceptable limits (95-105%) for all formulations, which indicated uniform distribution of quercetin in the gel matrix. The optimized formulation had drug content of 98.5±1.2%, which indicated accurate dosing.

3.4 Rheological Properties

Rheological analysis showed that the quercetin hydrogels were non-Newtonian pseudoplastics, meaning that they were shear-thinning fluids, and their viscosity reduced with an increase in the rate of shear. This is a very desirable property for topical preparations, as it ensures that the preparation can be easily applied (when it is less viscous due to shear) while still being viscous (when it is at rest).

3.5 In Vitro Drug Release Studies

- The release studies using Franz diffusion cells with dialysis membranes revealed a sustained release profile for a period of 8 hours. The cumulative percentage release of the drug varied from 75-85% for the optimized formulations.
- Formulations with lower concentrations of polymers (0.5% Carbopol) had a faster release of about 80% in 6 hours, whereas higher concentrations (1.5% Carbopol) had a sustained release of about 70% in 8 hours. The use of Carbopol with HPMC resulted in better control of drug release compared to the use of Carbopol alone.
- Initial burst release (15-20% in the first hour) was observed in all formulations, which can be attributed to the drug present on or near the surface of the gel. This was followed by a sustained release from the polymer matrix, which is ideal for the drug application site.

3.6 Release Kinetics

The release data fitted to different mathematical models showed the best fit to the Higuchi model (R^2 = 0.980-0.995), which indicated a diffusion-controlled release process. The Korsmeyer-Peppas model gave values of n between 0.5-0.7, which indicated an anomalous (non-Fickian) diffusion process.

3.7 Skin Permeation and Retention Studies

- Permeation studies using excised rat skin revealed improved skin penetration of quercetin from hydrogel formulations compared to quercetin suspension. The optimized formulation revealed significant skin retention of approximately 25-30% of the applied dose after 24 hours.
- Researches have shown that quercetin permeates very less through skin when it is dissolved in the conventional aqueous solvents. But when it is formulated in hydrogel along with penetration enhancers, the permeability through skin increased. The increased permeability can be attributed to the hydration of stratum corneum due to hydrogel formulation, increased solubility of drug in the formulation, and the use of penetration enhancers such as propylene glycol.
- The deposition of quercetin was maximal in the stratum corneum and epidermis layers, where anti-inflammatory and wound-healing properties are most required. Systemic absorption is minimal, thus reducing the possibility of side effects while maximizing the therapeutic effect.

3.8 Stability Studies

Preliminary stability studies carried out at various storage conditions revealed that the optimized formulation was stable with no significant changes in physical appearance, pH (±0.2 units), drug content (±2%), and viscosity (±5%) for 3 months. Formulations stored at accelerated conditions (40°C/75% RH) revealed slight reduction in drug content (95-97%) after 3 months, indicating the need for storage in cool conditions. There was no microbial growth, indicating the effectiveness of the preservative system.

4. THERAPEUTIC IMPLICATIONS AND FUTURE PERSPECTIVES

The quercetin hydrogel that was developed is a great product for many dermatological uses and this is based on quercetin's pharmacological features.

4.1 Wound Healing Applications

Quercetin speedily allows the wounds to be closed faster, and this is done via the several ways; these include the diminishing of inflammatory markers (especially IL-1β and CASPASE-1), the change in inflammasome complexes made up of NLRP3 among others, the growing of the epidermal cells, and the stopping of the over-migration of the fibroblasts. This dual action of facilitating the closure of the wound and at the same time discouraging the development of a scar makes the hydrogel extremely important in the

case of scarless wound healing. On the other hand, the antimicrobial property of quercetin, among other things, does not only operate against bacteria that have become resistant to many drugs but also comes in handy in infected wound management. Research shows that quercetin is highly effective against MDR Pseudomonas aeruginosa and even more so if the drug is used along with traditional antibiotics.

4.2 Anti-inflammatory and Antioxidant Effects

The hydrogel formulation can be very useful in the case of inflammatory dermatitis, psoriasis, and eczema because of the anti-inflammatory properties of quercetin. The sustained release from the hydrogel ensures a prolonged contact time.

4.3 Future Directions

- Further studies should concentrate on:
- In vivo efficacy studies in animal wound healing models
- Clinical trials in human volunteers for safety and efficacy evaluation
- Development of advanced delivery systems such as nanocarrier-loaded hydrogels for improved penetration
- Formulations in combination with other drugs for synergistic purposes Scale-up and stability studies for commercial viability

5. CONCLUSION

The study that is processed has significantly developed and assessed quercetin-loaded hydrogel for dermal application and the use of Carbopol 940 and HPMC as gelling agents. Among the properties of the formulation, the optimal physicochemical properties were included, such as appropriate pH (6.4-6.8), viscosity (10000-12000 cps), good spreadability, and even drug content. The outcomes of preformulation studies indicated that there was a compatibility between quercetin and the selected polymers. The hydrogel exhibited non-Newtonian pseudoplastic rheological behavior, which was very suitable for topical application. In vitro drug release studies revealed sustained release pattern over 8 hours with diffusion-controlled mechanism. Skin permeation studies revealed enhanced quercetin retention in skin layers compared to conventional formulations.The formulated preparation has potential uses in dermatology such as wound healing, treatment of inflammatory dermatitis, and infected wounds owing to the versatile nature of quercetin. The hydrogel drug delivery system overcomes the solubility and permeability barriers of quercetin.This study offers a basis for further development of quercetin-containing topical preparations with potential clinical use in dermatology.

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