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Optimizing isoconazole glycerosomes via QbD for enhanced topical antifungal therapy

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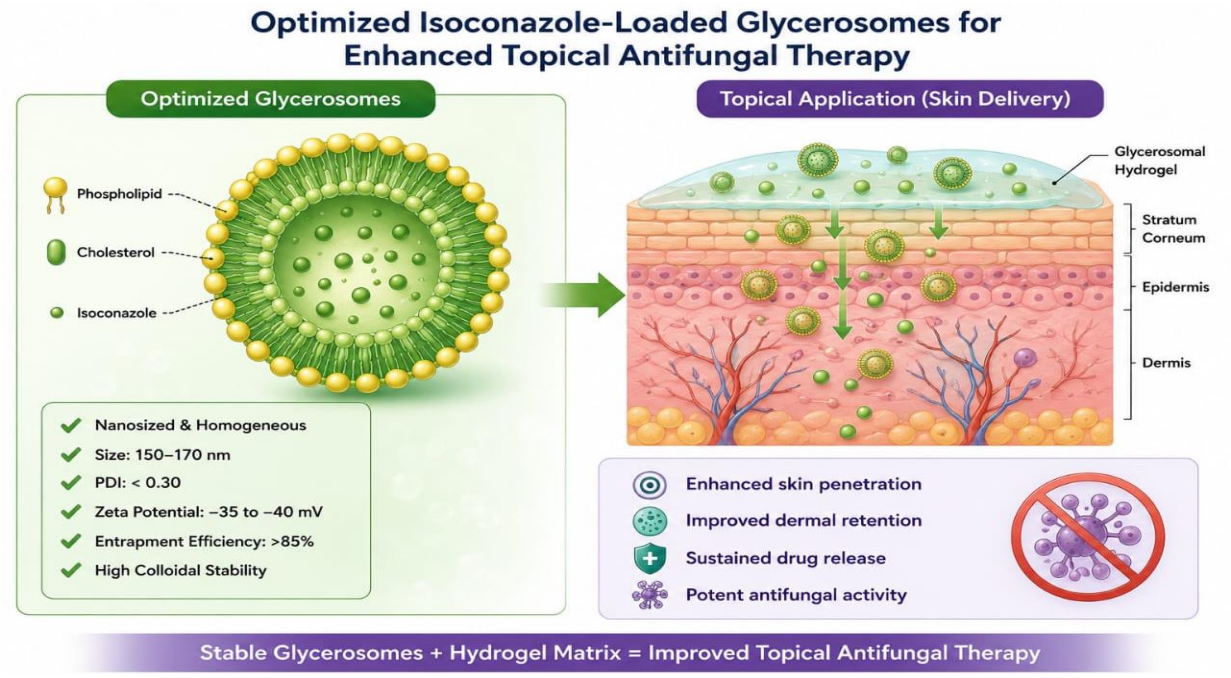
ABSTRACT

Superficial fungal infections remain a major global health challenge, while the therapeutic performance of topical antifungal agents is often limited by poor skin penetration, inadequate drug retention, and suboptimal bioavailability. Isoconazole nitrate is a potent broad-spectrum imidazole antifungal that exhibits good antimicrobial efficacy but is limited by poor aqueous solubility and low permeation across the stratum corneum. In this study, we describe the Quality-by-Design (QbD)- guided development and optimization of isoconazole-loaded glycerosomes for improved dermal drug delivery. A systematic Quality by Design (QbD) approach was employed including Quality Target Product Profile (QTPP), risk assessment and Box-Behnken experimental design to optimize the phospholipid, cholesterol and glycerol levels to achieve the desired vesicle size, polydispersity index, zeta potential and drug entrapment efficiency. The optimized glycerosomes were prepared by thin-film hydration method followed by probe sonication and loaded into Carbopol-HPMC hydrogel for topical application. The optimized composition showed nanosized and homogenous vesicle distribution with high entrapment efficiency and excellent colloidal stability. Morphological and spectroscopic studies confirmed the spherical shape of vesicles and compatibility of drug with excipients while the hydrogel showed desirable rheological properties, homogeneity, and drug content.



In vitro release studies showed sustained drug release with predominant control of diffusion through the vesicular bilayer and hydrogel matrix. Collectively, these data proved that QbD-facilitated glycerosomal engineering provides a robust and reproducible platform for improving the dermal delivery of isoconazole and highlights its potential as an advanced topical nanocarrier for superficial fungal infections.

Keywords: Isoconazole nitrate, Quality by design, Antifungal, Box-behnken experimental design.

INTRODUCTION

Superficial fungal infections are common, affecting around one quarter of the world's population and remaining a large clinical and socioeconomic burden. There are many topical antifungal therapies available; however, failure of treatment and recurrence of disease are common. This is due to poor drug penetration through the stratum corneum, poor drug retention in infected tissues and the poor physicochemical properties of many antifungal agents. The problems propose the need to develop new topical drug delivery methods to provide improved localised drug bioavailability and less systemic exposure [1]. Isoconazole nitrate is a broad-spectrum imidazole antifungal drug that is particularly effective against dermatophytes, yeasts, moulds, and some Gram-positive bacteria by preventing ergosterol biosynthesis [2]. However, its high lipophilicity and poor water solubility severely limit skin penetration and therapeutic efficacy when formulated as traditional topicals. Therefore, only a tiny fraction of the administered dose reaches the deeper epidermal layers where fungal infections localise, requiring repeated application and continuous therapy. Lipid-based nanovesicular systems have emerged as promising drug carriers to bypass the skin barrier by increasing drug solubilization, retention and controlled release. Among them, phospholipid vesicles containing glycerol, or glycerosomes, have attracted increased interest due to their superior membrane fluidity, deformability and ability to permeate the skin. The presence of glycerol improves bilayer fluidity and skin hydration, which leads to effective transport through the stratum corneum and persistent localisation of the medication in the skin [3]. However, successful development of nanovesicular formulations requires careful optimization of various formulation and process variables influencing vesicle properties and product performance. QbD (Quality-by-Design) provides a scientific and risk-based approach for systematic pharmaceutical development by integrating predetermined quality goals with statistical experimental design and process understanding. Identification of critical quality attributes, material attributes and process parameters based on QbD helps in developing robust formulations with better reproducibility and regulatory compliance.

In the present study, a QbD approach was adopted for formulation and optimization of isoconazole-loaded glycerosomes for enhanced dermal delivery [4]. A Box-Behnken design was used to investigate the effect of formulation variables on critical quality attributes including vesicle size, polydispersity index, zeta potential and drug entrapment efficiency [5]. The optimized glycerosomes were then formulated into a topical hydrogel and characterized in detail for their physicochemical properties, morphology, drug release profile and performance of the formulation. This work establishes a rational nanotechnology-based strategy for improving topical antifungal therapy and provides a reproducible platform for the development of advanced dermal drug delivery systems [5-7].

MATERIALS AND METHODS

Materials

Isoconazole nitrate was obtained from Sigma-Aldrich (India). Phosphatidylcholine (Lipoid S100) was purchased from Lipoid GmbH (Germany), and cholesterol was obtained from S.D. Fine Chemicals Ltd., Mumbai, India. Glycerol, chloroform, methanol, ethanol, dimethyl sulfoxide (DMSO) and phosphate-buffered saline (PBS, pH 7.4) were obtained from Merck Life Science Pvt. Ltd., India. Carbopol 934 and hydroxypropyl methylcellulose (HPMC K100M) were purchased from HiMedia Laboratories Pvt. Ltd. Propylene glycol, triethanolamine, methyl paraben and propyl paraben were of analytical grade. All reagents were used as such, and double-distilled water was used throughout the study.

Quality-by-design (QbD) strategy

Formulation development was based on the principles of ICH Q8(R2), Q9 and Q10 guidelines using a Quality-by-Design (QbD) framework. The Quality Target Product Profile (QTPP) was set before formulation development, and Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), and Critical Process Parameters (CPPs) were identified. Risk assessment was carried out using Failure Mode and Effect Analysis (FMEA), and formulation optimization was conducted using a three-factor, three-level Box-Behnken experimental design. The optimized formulation was validated within the defined design space.

Quality target product profile

The target product profile was specified as a topical glycerosomal hydrogel for dermal delivery of isoconazole nitrate with nanosized vesicles (<200 nm), narrow size distribution (PDI <0.30), high entrapment efficiency (>80%), good colloidal stability (zeta potential >±30 mV), skin-compatible pH (5.5-6.8), sustained drug release (12-24 h), and acceptable storage stability [8].

Critical quality attributes

Particle size, polydispersity index (PDI), zeta potential and entrapment efficiency were selected as the critical quality attributes since they directly impact vesicle stability, drug loading, skin penetration and overall performance of the formulation.

Risk assessment

Formulation and process variables were initially identified using an Ishikawa (fishbone) diagram and subsequently ranked by Failure Mode and Effect Analysis (FMEA) based on Risk Priority Number (RPN). Phospholipid concentration, cholesterol concentration, glycerol concentration and sonication time were identified as the most influential variables. Accordingly, phospholipid, cholesterol, and glycerol concentrations were selected as independent formulation variables for optimization [9].

Experimental design

A three-factor, three-level Box-Behnken design was generated using Design-Expert software (Version 13, Stat-Ease Inc., USA). Phospholipid concentration, cholesterol concentration, and glycerol concentration were selected as independent variables, while particle size, polydispersity index, zeta potential, and entrapment efficiency were used as dependent responses. The design comprised 17 experimental runs, including five centre-point replicates.

Preformulation studies

Preformulation tests were carried out to examine organoleptic properties, qualitative solubility in distilled water, methanol, ethanol, chloroform, DMSO and phosphate buffer (pH 7.4) and melting point determination by capillary technique. Quadratic polynomial models were created to examine the factor impacts and predict the optimal formulation. UV-visible spectrophotometry (Shimadzu UV-1700) was performed to calculate the absorption maximum (λmax) of isoconazole nitrate and generate the calibration curve over the concentration range of 10-50 μg mL^{-1}. Drug-excipient compatibility was studied using Fourier-transform infrared (FTIR) spectroscopy with the spectrum range of 4000-400 cm^{-1} by KBr pellet analysis.

Preparation of isoconazole-loaded glycerosomes

Glycerosomes were prepared by the thin-film hydration method. Isoconazole nitrate, phosphatidylcholine, and cholesterol were dissolved in chloroform: methanol (1:1, v/v), and the solvent was evaporated under reduced pressure using a rotary evaporator (45 ± 2°C, 120 rpm) to obtain a thin lipid film. Residual solvent was removed under vacuum overnight. The dried film was hydrated with phosphate-buffered saline containing the predetermined glycerol concentration according to the experimental design and rotated for 45 min. The resulting multilamellar vesicles were reduced to nanosized glycerosomes by probe sonication (5-10 min) under ice cooling and stored at 4°C overnight before characterization [10].

Formulation optimization

All formulations generated through the Box-Behnken design were evaluated for particle size, PDI, zeta potential, and entrapment efficiency. Response surface methodology, contour plots, and perturbation plots were used to evaluate the effects of formulation variables. Numerical optimization based on the desirability function was applied to identify the formulation with minimum particle size and PDI, together with maximum zeta potential and drug entrapment efficiency.

Preparation of glycerosomal hydrogel

Carbopol® 934 (0.8%, w/w) and HPMC K100M (0.5%, w/w) were hydrated separately in distilled water and subsequently mixed under continuous stirring. Propylene glycol containing methyl paraben and propyl paraben was incorporated into the polymeric dispersion, followed by gradual addition of the optimized glycerosomal suspension equivalent to 1% (w/w) isoconazole nitrate. The formulation pH was adjusted to approximately 6.2 using triethanolamine to obtain a homogeneous gel, which was stored in airtight laminated tubes until further evaluation [11].

Characterization of glycerosomes

Particle size, polydispersity index, and zeta potential were determined by dynamic light scattering using a Malvern Zetasizer Nano ZS (Malvern Instruments, UK) at 25°C following appropriate sample dilution. All measurements were performed in triplicate. Entrapment efficiency was determined by ultracentrifugation (15,000 rpm, 45 min, 4°C). The free drug in the supernatant was quantified spectrophotometrically, and entrapment efficiency was calculated as [12].

Entrapment efficiency

The entrapment efficiency (EE%) of the isoconazole-loaded glycerosomes was determined using an indirect centrifugation method. Briefly, the glycerosomal dispersion was centrifuged at 15,000 rpm for 30 min at 4°C to separate free drug from the vesicular fraction. The supernatant containing unentrapped isoconazole was collected, diluted with methanol, and quantified by UV-Visible spectrophotometry at the predetermined λmax. Entrapment efficiency was calculated using the following equation [13].

$$(\%) = [(Wt - Wf)/Wt] \times 100$$

where Wt is the total amount of drug added, and *Wf* is the amount of unentrapped drug.

Scanning electron microscopy

The optimized formulation was freeze-dried. A small quantity of dried sample was mounted onto aluminium stubs using double-sided adhesive tape. Samples were coated with a thin gold layer using a sputter coater and observed under scanning electron microscopy to evaluate vesicle morphology.

Evaluation of the Optimized Glycerosomal Gel

Physical Appearance

The optimized glycerosomal gel was visually examined for colour, homogeneity, consistency, transparency, phase separation, and the presence of visible particulate matter. Observations were recorded immediately after preparation and during stability studies.

pH determination

The pH of the gel was determined using a calibrated digital pH meter. Briefly, 1 g of gel was dispersed in 25 mL of distilled

water and equilibrated for 2 h at room temperature before measurement. All measurements were carried out in triplicate and reported as mean ± SD.

Drug content

For drug content determination, 1 g of gel was dissolved in 100 mL ethanol under magnetic stirring and then sonicated for 15 min. Then this solution was filtered through a 0.45 µm membrane filter and was properly diluted and analyzed at 249 nm in a UV-Visible spectrophotometer. The drug content was determined from the calibration curve using the following equation;

Drug content (%) = (Practical drug content/Theoretical drug content) ×100

Spreadability

Spreadability was determined by the parallel glass slide method. A regular weight was applied on top of the gel (about. 0.5 g) placed between two glass slides to produce a homogeneous film. The time taken for the upper slide to move a given distance under a load applied was recorded. Spreadability was determined as

$$S = (M \times L) / T$$

where S is spreadability ($g \cdot cm\ s^{-1}$), *M* is the applied weight (g), *L* is the distance travelled (cm), and *T* is the time required (s).

Viscosity

The rheological behaviour of the gel was studied using a Brookfield digital viscometer with spindle No 64 at 25 ± 1°C throughout a range of rotational speeds of 5-100 rpm. Measurements were done to determine the flow behaviour of the formulation after recording equilibrium and viscosity values.

Homogeneity

Homogeneity was judged by visual inspection, after mild pressing of the gel between two fingers, for uniformity and lack of coarse particles or phase separation.

Extrudability

The extrudability was determined by filling of the optimized gel in aluminium collapsible tubes. Ease of application was assessed by measuring the quantity of gel extruded in 10s under constant weight applied to the tube.

***In vitro* drug release study**

The in vitro release profile of the improved glycerosomal gel and the traditional gel was studied using Franz diffusion cells with a hydrated cellulose acetate membrane. The receptor compartment was filled with phosphate-buffered saline (pH 7.4, 20% (v/v) ethanol) and kept at 37 ± 0.5°C with continuous stirring (600 rpm) to maintain sink conditions. Approximately 1 g of gel was loaded in the donor chamber. Samples were collected (2 mL) at predetermined time points (0.5-24 h) and replaced with an equal volume of fresh medium. The concentration of medication was determined spectrophotometrically at 249 nm, and the cumulative drug release after correction for dilution was estimated.

Drug release kinetics

The mechanism of drug release was explained by fitting the release data to zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas kinetic models. The best model to represent the release behaviour was considered the one with the highest coefficient of determination (R 2). The drug-release mechanism underneath was described by the release exponent (n) determined from the Korsmeyer-Peppas model.

Stability study

The optimized formulation was subjected to stability studies according to ICH Q1A(R2) recommendations for three months at chilled (4 ± 2°C), room temperature (25 ± 2°C/60 ± 5% RH) and accelerated settings (40 ± 2°C/75 ± 5% RH). The samples were analyzed for particle size, polydispersity index, zeta potential, entrapment efficiency, drug content, pH and visual appearance at predefined time intervals.

Statistical analysis

All experiments were performed in triplicate. Results are expressed as mean ± standard deviation (SD). Statistical analyzes were carried out using Design-Expert® software (Version 13, Stat-Ease Inc., USA) and GraphPad Prism. Statistical significance was assessed by analysis of variance (ANOVA), with $P < 0.05$ being statistically significant. Adequacy of the Box-Behnken models was tested by regression analysis, adjusted and anticipated R2 values, lack-of-fit tests and desirability functions [14].

RESULT AND DISCUSSION

Preformulation studies

Preformulation studies were performed to establish the physicochemical characteristics of isoconazole nitrate and support rational formulation development. The drug appeared as a white crystalline, odourless powder and exhibited poor aqueous solubility but high solubility in ethanol, methanol, chloroform, and dimethyl sulfoxide, consistent with its lipophilic nature. The selection of a lipid-based glycerosomal carrier for improved dermal delivery was facilitated by these properties. Purity and crystallinity of the drug were indicated by the experimental melting point (185.78 ± 0.42 °C), which was in agreement with the reported data in the literature. UV-visible spectroscopic analysis showed a maximum absorption wavelength (λmax) at 249 nm and a calibration curve in the concentration range of 10-50 µg mL−1, which was highly linear (R2 > 0.999), validating the suitability of the analytical method for quantitative determination. FTIR spectroscopy confirmed the presence of characteristic functional groups of isoconazole nitrate. The absence of significant shifts or disappearance of peaks in the spectra of the optimized formulation indicated the absence of chemical interactions between the drug and formulation excipients, confirming their compatibility during the development of the formulation.

Optimization of isoconazole-loaded glycerosomes using box-behnken design

A Box-Behnken design based on the Quality-by-Design (QbD) approach was applied to optimize the glycerosomal formulation by investigating the effect of phosphatidylcholine (A), cholesterol (B), and glycerol (C) on particle size (Y 1), polydispersity index (Y 2), zeta potential (Y 3), and entrapment efficiency (Y 4). Seventeen experimental runs were carried out, and the responses were fitted to quadratic polynomial models. The models were statistically significant as ANOVA tests showed high coefficients of determination (R 2) and non-significant lack-of-fit values indicating good predictive ability. The response surface analysis showed significant interaction between the formulation variables. Vesicle size increased with increasing phosphatidylcholine and cholesterol concentrations due to increased bilayer formation and membrane rigidity, while moderate levels of glycerol increased membrane flexibility and decreased particle size. The numerical optimization resulted in an optimum composition that exhibited minimum particle size and PDI and maximum zeta potential and drug entrapment. The good agreement between predicted and experimental responses validated the robustness and the reliability of the optimized formulation.

Particle size analysis

Dynamic light scattering revealed that the optimized glycerosomes had an average particle size of about 150-170 nm, which is considered favourable for dermal drug delivery. Probe sonication reduced multilamellar vesicles to uniformly distributed nanosized vesicles, while glycerol enhanced bilayer flexibility and reduced vesicle aggregation. Statistical analysis showed phosphatidylcholine concentration as a main factor affecting vesicle size, while cholesterol further increased vesicle diameter by bilayer stabilisation. However, glycerol was used as a membrane fluidizer and resulted in smaller vesicles. The optimized nanoscale sizes are expected to penetrate the stratum corneum and improve localized drug deposition.

Polydispersity index

The optimized formula showed a polydispersity index of less than 0.30, indicating a narrow particle size distribution and a good colloidal homogeneity. Response surface analysis indicated that over-concentration of phospholipids slightly increased the polydispersity index because of multilamellar vesicle formation, while an appropriate level of glycerol improved hydration efficiency and decreased aggregation during vesicle formation. The low PDI indicates the reproducibility of the preparation method and predicts good physical stability during storage.

Zeta potential

The optimized glycerosomes demonstrated negative zeta potential in the range of −35 to −40 mV suggesting good colloidal stability. The negative surface charge was mainly attributed to the phosphate groups of phosphatidylcholines that provided adequate electrostatic repulsion to prevent vesicle aggregation. The membrane flexibility was retained at moderate glycerol concentrations without influencing the surface charge, thus contributing to the long-term stability of the vesicular dispersion.

Entrapment efficiency

The optimized formulation exhibited an entrapment efficiency of more than 85%, indicating efficient loading of lipophilic isoconazole nitrate within the phospholipid bilayer. Increasing the concentration of phosphatidylcholine led to increased drug loading due to the presence of more hydrophobic regions for encapsulation, while moderate cholesterol concentrations stabilised the lipid membrane and minimised drug leakage. However, a slight increase in the amount of cholesterol reduced the encapsulation efficiency, possibly due to competition for the occupation within the lipid bilayer. These results suggest balanced lipid composition is important for loading maximum drug and keeping vesicle integrity.

Scanning electron microscopy

Spherical glycerosomes with smooth surfaces and uniform size distribution were confirmed by scanning electron microscopy. No aggregation, fusion or structural collapse of vesicles were observed, which verified the successful vesicle formation by the thin-film hydration method. The SEM particle size was in agreement with the dynamic light scattering results, which further confirmed the structural integrity and nanoscale properties of the optimized formulation.

Fourier transform infrared spectroscopy

The FTIR spectra of optimized formulation showed the characteristic absorption bands of isoconazole nitrate without significant shifting or disappearance of bands, which indicates no chemical interaction between drug and formulation components. Slight differences in the intensity of bands were due to intermolecular hydrogen bonding between glycerol and the phospholipid head groups rather than structural modification of the drug. These results confirm the physicochemical compatibility of isoconazole with selected excipients and also suggest that the process of formulation did not affect the drug integrity.

Evaluation of the optimized glycerosomal gel

The optimized glycerosomal dispersion was incorporated into a Carbopol-HPMC hydrogel to enhance its topical applicability and increase skin residence time. Physicochemical Properties of the Optimized Gel. Physicochemical properties of the optimized gel were evaluated, including appearance, pH, drug content, spreadability, viscosity, homogeneity, and extrudability.

Physical appearance

The optimized gel was observed to be translucent, homogeneous, smooth in consistency and free from phase separation,

syneresis, grittiness or drug crystallisation throughout the study period. The uniform distribution of glycerosomes within the polymeric matrix confirmed the successful incorporation of the gel without affecting the vesicular integrity.

pH

The pH of the gel was 6.1 ± 0.08, which is within the physiological range of skin pH and hence suitable for topical application. The pH was stable during the storage period, showing good chemical stability and low risk of skin irritation.

Drug content

The analysis of drug content showed homogeneous distribution of isoconazole in the gel with a drug content of 98.64 ± 0.91 %. The high recovery indicated that the loss of drug during formulation was low and the glycerosomal dispersion was efficiently incorporated in the hydrogel.

Spreadability

The spreadability of the optimized gel was 18.74 ± 0.56 g•cm s-1, which indicates good application properties. The presence of glycerol enhanced the flexibility of the polymeric network, resulting in uniform spreading of the gel on the surface of the skin.

Viscosity

Rheological study confirmed pseudoplastic (shear-thinning) behaviour with viscosity decreasing with an increase in shear rate. Flow behaviour: This flow behaviour is advantageous for topical formulations, providing adequate consistency during storage and easy spreadability during application

Homogeneity

The gel was homogeneous without apparent aggregates or phase separation, indicating an even distribution of glycerosomes in the polymeric matrix.

Extrudability

The formulation exhibited good extrudability from the aluminium collapsible tubes with a low extrusion force, which provided ease of use to the patients.

***In vitro* drug release**

The improved glycerosomal gel exhibited a biphasic release pattern with an initial burst release and sustained drug release over 24 h. The surface-associated drug was attributed to the first release (initial release, and the following sustained phase to the diffusion of isoconazole through the phospholipid bilayer and hydrogel matrix. Whereas the normal gel demonstrated quick drug release and an early plateau. The sustained release of the glycerosomal formulation showed improved drug retention and maintained drug availability at the site of application, which may result in decreased dose frequency and improved therapeutic efficacy.

Drug release kinetics

The drug release data were fitted to zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models. The Higuchi model was the best fit with the highest coefficient of determination (R2), indicating a diffusion-controlled drug release. The release exponent (n) obtained from the Korsmeyer-Peppas model indicated an anomalous non-Fickian transport mechanism, meaning that both diffusion and polymer relaxation contributed to the overall release behaviour.

Stability studies

The optimized formulation was found to be physically and chemically stable for three months of storage under ICH-recommended conditions. No significant changes were observed in appearance, pH, drug content, particle size, polydispersity index, zeta potential and entrapment efficiency when stored under refrigerated and room temperature conditions. Although some minor variations were observed under accelerated storage conditions, all quality attributes were within acceptable limits, confirming the robustness and stability of the glycerosomal formulation.

Overall discussion

In this work, we report the successful implementation of Quality-by-Design technique for rational development of isoconazole-loaded glycerosomes for cutaneous drug delivery. Through systematic optimization, nanosized vesicles with limited size distribution, high entrapment efficiency, and outstanding colloidal stability were obtained, which are likely to enhance skin penetration and prolong local drug retention. The improved vesicles, when included in a Carbopol-HPMC hydrogel, resulted in a formulation with desirable rheological properties, physiological pH, high drug content and outstanding spreadability. Collectively, the prolonged drug release profile, diffusion-controlled release mechanism and good stability imply that the proposed glycerosomal hydrogel is a potential nanocarrier platform for topical antifungal therapy. Furthermore, the QbD framework provides a robust and scalable approach for the development and future translation of lipid-based dermal delivery systems.

CONCLUSION

In this work, we successfully prepared an isoconazole-loaded glycerosomal hydrogel by adopting a Quality-by-Design (QbD)-guided formulation strategy. Critical formulation variables for nanosized glycerosomes with narrow size distribution, good drug entrapment and superior colloidal stability were identified through systematic optimisation utilising a Box-Behnken design. The inclusion of glycerol increased vesicle flexibility, and FTIR analysis confirmed physicochemical compatibility of isoconazole with the specified excipients.

The tailored glycerosomal dispersion was successfully included in the Carbopol-HPMC hydrogel with suitable physicochemical features such as physiological pH, homogeneous drug content, excellent rheology and high spreadability. The proposed formulation displayed sustained release of the medication

over 24 h, and kinetic studies indicated a major diffusion-controlled release mechanism. The formulation showed steady behaviour under ICH-prescribed storage settings, which demonstrates its robustness and pharmacological acceptability. To summarise, these results indicate that QbD-assisted glycerosomes are a promising lipid-based nanocarrier for topical delivery of isoconazole, which could enhance skin drug retention and provide sustained local therapy over the standard formulations. Future studies should focus on ex vivo skin penetration, in vivo pharmacokinetic and pharmacodynamic evaluation and clinical validation to further verify the translational potential of this delivery technology.

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