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Research Article

Formulation and Evaluation of Butenafine hydrochloride loaded Niosomes for the Treatment of Superficial Dermatophytosis

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ABSTRACT

The present study aims to prepare and optimize Butenafine hydrochloride niosomes utilizing varying concentrations of surfactant and cholesterol as a lipid for topical application. Thin film hydration method was employed to optimize the niosomes using cholesterol as a lipid and span series as surfactant. The optimized niosomes was assessed for particle size, poly dispersity index, entrapment efficacy, and the invitro drug release study. The particle size of prepared niosomes was found within the range of 236.2 to 486.4. Zeta potential was found in range between -20.2 to -39.0 mV with entrapment efficacy ranging from 80.558±0.448 to 88.492±0.206%. The in vitro studies demonstrated that optimized niosomes showed sustained drug release for 6 hours (92.77%), and follows Higuchi Model which is much improved than the marketed formulation of BT HCl which releases 92% of drug in 4 hours. From the above results it was concluded that optimized niosomes demonstrate slow and prolonged release profile to maintain the concentration of drug with the skin for a longer duration hence gives patient compliance.

Keywords: Butenafine hydrochloride; Cholesterol; Niosomes; Entrapment efficacy; Prolonged release

INTRODUCTION

Niosomes are a class of lipid-based vesicles that exhibit structural similarities to liposomes. The vesicles are comprised of nonionic surfactants, specifically Span and Tween, in addition to cholesterol, which contribute to the stabilization of the vesicles [1]. Niosomes are frequently employed as pharmaceutical carriers owing to their capacity to encase drugs with both hydrophilic and hydrophobic properties. The process of niosome formation entails the spontaneous organization of surfactant molecules within a water-based medium [2]. The arrangement of surfactant molecules occurs in bilayers, resulting in the formation of enclosed vesicles or compartments. The vesicles possess the capability to encapsulate drug molecules either within their aqueous core or within the lipid bilayers, contingent upon the physicochemical characteristics of the drug. Niosomes present numerous benefits as carriers for pharmaceutical agents [3]. Lipid-based formulations have the potential to enhance the stability and bioavailability of pharmaceutical compounds, safeguarding them against degradation, and regulating their release kinetics. In addition, it is worth noting that niosomes possess biocompatible and biodegradable properties, rendering them amenable to modifications for precise targeting of particular tissues or cells [4]. Niosomes have found significant utility in the field of medicine and pharmaceuticals, particularly in the realm of drug delivery for diverse therapeutic applications encompassing cancer treatment, gene therapy, vaccination, and dermal/transdermal delivery. The design and optimisation of niosomal formulations encompass various factors, including the selection of surfactants, techniques for drug loading, and approaches for vesicle preparation [5].

Butenafine hydrochloride is a pharmacological compound of synthetic origin that exhibits antifungal properties. Its primary route of administration is topical, making it suitable for the treatment of cutaneous fungal infections [6]. This substance is classified within the category of pharmaceutical compounds referred to as allylamines [7]. Butenafine hydrochloride is commercially accessible under several brand names, such as Lotrimin Ultra, Mentax, and Butop. Upon topical application, butenafine hydrochloride exerts its pharmacological effect through the inhibition of ergosterol synthesis, a crucial constituent of the fungal cell membrane. The aforementioned disturbance results in the deterioration of the cellular membrane, ultimately causing the demise of the fungus and subsequent resolution of the infection [8].

Butenafine hydrochloride is frequently employed in order to treat various dermatological ailments, including jock itch (tinea cruris), ringworm (tinea corporis) and athlete's foot (tinea pedis) [9]. Fungal

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infections of the skin, hair, or nails are frequently attributed to dermatophytes, a type of fungi that infiltrate and proliferate within these anatomical structures [10]. The pharmaceutical product is available in various formulations such as creams, gels, or sprays, which are topically administered to the specific region of the skin requiring treatment. The precise dosage and duration of treatment are contingent upon the particular condition under consideration, and it is imperative to adhere to the guidelines provided by one's healthcare provider or as stipulated on the product packaging.

The tolerability of butenafine hydrochloride is generally favourable; however, as with any pharmaceutical agent, it may be associated with certain adverse effects. Frequently encountered adverse effects may encompass mild dermal irritation, pruritus, a sensation of burning, or erythema at the site of application. Serious adverse effects are infrequent, albeit encompassing severe allergic reactions or exacerbation of symptoms. In the event of encountering any worrisome or enduring adverse reactions, it is imperative to promptly seek medical assistance.

Prior to utilizing butenafine hydrochloride, it is imperative to seek guidance from a healthcare practitioner, particularly if one possesses any documented allergies, medical ailments, or is concurrently using other pharmaceutical substances. The healthcare professionals possess the capability to offer individualized guidance and assess the appropriateness of this antifungal medication in relation to your particular circumstances.

The provided information serves as a broad summary of butenafine hydrochloride and should not be considered a substitute for the guidance and instructions provided by a healthcare professional or the details outlined on the medication packaging.

MATERIAL AND METHODS

Butenafine hydrochloride (BT HCl) was Purchased from Tokyo Chemical Industries, Toshima, Japan. Cholesterol, span 20, Span 40, Span 60 and Span 80 were purchased from Central drug house, New Delhi India. All the solvents used in the study was of analytical grade and were procured from KCP store.

Preformulation studies

Melting point: Melting point of BT HCl was determined by digital melting point apparatus (RellGlass) by capillary method.

Fourier transforms infrared (FTIR) spectroscopy: ATR-FTIR investigations facilitate the identification of diverse functional groups that are present within a given molecule. The aforementioned process will generate a profile image of the specimen, which represents a unique molecular pattern. The Fourier Transform Infrared (FTIR) spectra of Butenafine hydrochloride, Cholesterol, Span 20, Span 40, Span 60, and Span 80 were obtained individually and in combination using a Shimandzu IR Spirit-A224160 analyzer manufactured in Japan. A 1 mg sample was selected and affixed to the adhesive layer in contact with the ATR prism. Subsequently, spectral analysis was conducted within the 400-4000 cm□1 range. The data was gathered and analyzed utilizing laboratory solution software developed by Shimandzu Corporation.

Differential scanning calorimetric (DSC): DSC was employed to acquire the DSC curve, which depicts the rate of heat absorption in relation to temperature variation. Differential scanning calorimetry (DSC) curves were acquired for the individual constituents, specifically Butenafine hydrochloride. In order to examine the melting characteristics of BT HCl, the DSC; 7020 instrument from Hitachi, Japan was employed. The investigation involved subjecting the sample to heating and cooling processes within the temperature range of 150-240°C, with a heating and cooling rate of 10°C/min. The experiments were conducted under a consistent flow of N2 atmosphere at a rate of 50 mL/mi. In a concise manner, a quantity of 5 mg of the specimen was collected within an airtight aluminium container. A pan of the same type that was empty was utilized as a reference. The data was collected and analysed utilizing the Nexta software.

The analysis of BT HCl was conducted utilising the potentiometric titration technique. A quantity of 300 mg of the drug was introduced into a sterile and desiccated 100 ml conical flask, followed by dissolution in 5 mL of formic acid. The experiment involved the addition of 80 mL of acetic anhydride, which was subsequently titrated against a 0.1 M perchloric acid solution. The molar concentration of perchloric acid is 0.1 M, and each millilitre of this solution corresponds to a mass of 35.39 mg of BT HCl.

Determination of λmax

In methanol: A solution of BT HCl with a concentration of 5µg/ml was prepared in methanol. The solution was then subjected to scanning for the maximum wavelength (λmax) within the range of 200-400nm using a UV spectrophotometer (Shimadzu, UV-1900, Japan).

Preparation of standard curve in methanol: A precise measurement of 50 mg of BT HCl was conducted, followed by its transfer to a volumetric flask with a capacity of 10 mL. The BT HCl was then diluted using methanol. A volume of 1 mL of the initial stock solution was subjected to additional dilution, resulting in 10 mL aliquots. These aliquots were then pipetted and further diluted to generate a standard mixture with a drug concentration ranging from 5 to 50 µg/mL. The measurement of absorbance at a wavelength of 280 nm was conducted using a UV-visible spectrophotometer for the final solutions.

Solubility studies: The solubility of BT HCL in different surfactants was assessed by introducing 50 mg of the drug into 1 ml of molten surfactant within glass vials. The vials were subjected to vortexing using a Remi Cyclo mixer CM-101 for duration of 30 seconds. The \A volume of 525 µl of the supernatant sample was extracted and subsequently diluted with methanol. The diluted sample was then subjected to spectrophotometric analysis using a Shimadzu UV-1900 spectrophotometer from Japan, with a wavelength of 280 nm.

Preparation of BT HCl loaded niosomes: Niosomes containing BT HCL were synthesised using the thin film hydration technique. A drug solution was prepared by dissolving 100 mg of Butenafine HCl in methanol. The mixture of methanol and chloroform was used as a solvent to dissolve surfactant and cholesterol at varying ratios. Subsequently, this solution was introduced into the drug solution contained in a round bottom flask. The organic solvent was separated from the mixture using a rotary evaporator while maintaining a temperature of 60°C. A solid mixture is observed to have formed as a thin film layer at the bottom of the flask. The thin film was collected and subsequently hydrated by gently agitating it with a 10 ml aqueous phase consisting of distilled water at a temperature of 60°C. The niosomal preparation was subjected to vortex mixing for duration of 10 minutes, followed by sonication for a period of 20 minutes. The niosomal dispersion was incubated at a temperature of 40°C in a refrigerated environment for duration of one night.

Physiochemical characterization of NLC dispersion

Vesicle morphology: The morphology of the niosomes that were optimised was assessed through the utilisation of Olympus microscopy. The niosomes were diluted using distilled water and subsequently affixed onto a glass slide for examination under a microscope. The confirmation of vesicle formation was achieved using a resolution of 40X.

Particle size and poly dispersity index

The measurement of particle size and polydispersity index for the prepared niosomes was conducted using the Zetasizer instrument. The analysis of particle size was conducted using the Aton paar litesizer-500 instrument. A volume of approximately 1 millilitre of prepared niosomes was extracted, subjected to filtration, and subsequently diluted by a factor of 10 using distilled water. The diluted niosomes were placed in a disposable cuvette and subjected to laser light diffraction at a 90° angle for the purpose of analysing particle size.

Zeta potential and entrapment efficiency

The zeta potential was determined using the Malvern Zetasizer v7.11 instrument. The niosomes that had been prepared were introduced into a folded capillary, which was supported by platinum electrodes. Subsequently, the capillary was positioned within the sample holder of a Zetasizer instrument for the purpose of analysis.

Entrapment efficiency: A 2.0 ml sample of prepared niosomes was subjected to centrifugation at a speed of 15000 revolutions per minute (rpm) for duration of 30 minutes. Next, the supernatant was diluted using methanol and passed through a 40 µm filter paper. The concentration of the drug was subsequently measured using a UV-visible spectrophotometer at a wavelength of 280 nm. The entrapment efficacy of niosomes was calculated as follows

In-vitro analysis: The in vitro release pattern of the prepared niosomes was determined using the dialysis bag (Sigma, St. Louis, USA) method, employing a dialysis bag with a molecular weight cutoff of 12,000. The formulations were introduced into the dialysis bag, which served as the donor compartment, with a length of 5 cm. A dialysis bag was introduced into a beaker containing 100 ml of pH 7.4 phosphate buffer and ethanol (80:20) solution, serving as the receptor compartment. The temperature of the receptor medium was maintained at 37±1°C, and agitation of the medium was achieved by using a magnetic stirrer set at a speed of 50 rpm. Samples of 2 mL were collected at predetermined intervals and promptly replaced with an equivalent volume of ethanolic buffer. The samples that were gathered were subjected to spectrophotometric analysis at a wavelength of 280 nm using a UV-Visible Spectrophotometer. Every experiment was conducted in triplicate, with a sample size of three (n = 3). The in vitro release studies were conducted for the commercially available formulation (cream) using the same methodology and were subsequently compared with the niosomes that we prepared**.**

In-vitro release kinetics: The release kinetics was investigated using several kinetic models, including the zero-order, first-order, Higuchi, and Korsmeyer-Peppas plots. In order to investigate the release kinetics of the formulation, data acquired from in vitro drug release studies was utilised to construct plots based on different kinetic models. The zero-order model represents the relationship between the cumulative amount of drug released and time, expressed as a percentage. The first-order model, on the other hand, describes the logarithmic relationship between the cumulative percentage of drug remaining and time. The Higuchi model illustrates the cumulative percentage of drug released as a function of the square root of time. Lastly, the Korsmeyer-Peppas model depicts the logarithmic relationship between the cumulative percentage of drug released and the logarithm of time. The model that provided the best fit was determined by the correlation coefficient, which exhibited a value in close proximity to 1.

RESULT AND DISCUSSION

Preformulation studies

Melting point: Melting point of BT HCl was determined by melting point apparatus (ReliGlas) by capillary method.

FTIR analysis: Fourier Transform Infrared (FTIR) spectra were acquired for Butenafine hydrochloride, Cholesterol, span 20, Span 40, Span 60, and Span 80 in their pure forms, as well as for physical mixtures (Butenafine hydrochloride + cholesterol, Butenafine hydrochloride + span 20, Butenafine hydrochloride + span 40, Butenafine hydrochloride + span 60). The purpose of this analysis was to investigate any potential incompatibilities between the excipients and active ingredients during and after the preparation of niosomes. Due to its high solubility in surfactants, the physical mixture spectrum did not exhibit any discernible peaks corresponding to the drug. The absence of discernible drug peaks in the FTIR analysis can be attributed to the drug's solubilization within the surfactant.

Differential scanning calorimetry: The DSC thermogram exhibited a distinct endothermic peak at a temperature of 222.1□, which was observed at approximately 15-minute intervals. The measured value was consistent with the reported value of the BT HCl pure reference material, indicating the sample's purity and integrity. The phase transition of BT HCl necessitates the absorption of energy, thus indicating an endothermic reaction. Therefore, based on the findings of the physical characterization and identification studies conducted on Butenafine HCl, it can be concluded that the drug sample is devoid of any impurities

Lambda max. The UV spectrophotometer was utilised to scan BT HCl in order to determine its maximum wavelength (□ max). The wavelength at which maximum absorption (□ max) was observed was determined to be 280.0 nm, as indicated in the data provided.

Solubility studies: To achieve optimal drug loading in niosomes, it is essential to prioritise drugs solubility within the lipids and surfactants used. The drug showed highest solubility in span 60 (40.96), followed by span 40 (34.18) and span 80 (31.63). The selection of the span series for further studies was based on solubility studies. The results are given

Particle size, polydispersity index and zeta potential: The Zetasizer instrument was utilized to measure the particle size and polydispersity index of the prepared niosomes. The analysis of particle size was conducted utilizing the Anton Paar Litesizer-500 instrument, which operates on the principle of photon correlation spectroscopy. Presents the average particle size, PDI, zeta potential, and entrapment efficacy of the prepared niosomes. The particle size was determined to fall within the range of 236.2 to 486.4. The zeta potential is a term used to describe the electrical potential that exists between the medium and the layer of fluid that is in contact with the dispersed particles. The zeta potential is a fundamental

parameter that influences stability, as it quantifies the strength of the electrostatic repulsion or attraction between particles. The zeta potential of the prepared niosomes was observed to fall within the range of -20.2 to -39.0 mV. The research revealed that an increase in zeta potential leads to a decrease in particle aggregation, primarily due to the presence of electric repulsion. Consequently, this results in enhanced stability of niosomes. The zeta potential value of batch NS8 was measured to be -39.0 mV. The effectiveness of the Entrapment was observed to range from 80.558±0.448% to 88.492±0.206%. The relationship between the concentration of surfactant and both the drug content and encapsulation efficiency was found to be significant. NS8 was optimised based on particle size, polydispersity index (PDI), zeta potential, and entrapment efficacy.

CONCLUSION

Niosomes have emerged as a highly viable approach for drug delivery due to their exceptional biocompatibility, improved stability, controlled release characteristics, and targeted delivery capabilities. They have also generated significant interest in industries, cosmetic and pharmaceutical, as they can improve the rate of encapsulation and bioavailability of bioactive compounds. In the current study, an attempt to formulate Butenafine HCl-loaded niosomes was made by adopting a thin film hydration method. Niosomes prepared utilizing varying concentrations of surfactant and cholesterol (NS8) showed great physical stability, with high EE value (80.558 to 88.492%), lower PS (236.2 to 486.4 nm), PDI (0.145to 0.989) and optimal zeta potential (-28.3 to -39.0 mV). The in vitro studies demonstrated that optimized niosomes showed sustained drug release over the duration of 6 hours (92.77%), which is much improved than the marketed formulation of BT HCl which releases 92% of drug in 4 hours. In this work, the in vitro drug release followed the Higuchi Model. This indicates that the regulated drug release from the niosomes occurred via the porous matrix. From the above results it was concluded that optimized niosomes demonstrate slow and extended release profile to maintain the concentration of drug with the skin for a longer duration hence gives patient compliance.

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