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Research Article

Development and Characterization of Butenafine Hydrochloride Solid Lipid Nanoparticles for Skin Targeting

Anis.J.Kazi, Dr. Sameer Shafi, Dr. Vishweshwar M. Dharashive, Harsh. A.Waghmare, Mukta.R.Rudrurkar

Shivlingeshwar College of Pharmacy, Almala Tq. Ausa Dist. Latur – 413520, Maharashtra [MH], India.

A B S T R A C T

Fungal infections are a common cause of skin diseases and their occurrence is increasing worldwide. Oral therapy for fungal infections can have toxic effects, require long treatment durations, and may not be well tolerated by patients. On the other hand, topical therapy for superficial fungal infections faces challenges such as poor solubility of drugs, skin irritation, and limited permeability through the skin.

To address these challenges, solid lipid nanoparticles containing antifungal drugs, specifically Butenafine solid lipid nanoparticles (BUTE-SLN), were prepared for improved drug penetration, minimized side effects, and rapid relief from fungal infections. These nanoparticles were incorporated into a Carbapol gel base to enhance drug penetration through the skin and improve therapeutic activity. The BUTE-SLN was prepared using a modified solvent emulsification technique, and its formulations were evaluated for particle size, polydispersity index, zeta potential, entrapment efficiency, and drug loading. Furthermore, stability studies as per ICH guidelines confirmed the stability of the SLN dispersions. The BUTE-SLN were then incorporated into Carbapol gel in order to improve drug penetration and provide an additive effect in the treatment of fungal infections. The BUTE-SLN gel exhibited non-Newtonian pseudoplastic flow, excellent spreadability, ease of application, and adhesion. Furthermore, it was found to be occlusive, preventing transmembrane water loss, and showed greater skin hydrating potential than a marketed cream. In vitro drug release studies revealed a biphasic release pattern, with initial burst release followed by sustained release, indicating quick onset of action and prolonged antifungal effect. Skin retention studies demonstrated the maximum concentrations of drug in the stratum corneum.

The BUTE-SLN gel exhibited enhanced antifungal activity and stability over the study period. The formulation of antifungal drugs into solid lipid nanoparticles for topical drug delivery proves to be a promising carrier for drug delivery, offering enhanced penetration and proven safety and compatibility

Keywords: Butenafine Hydrochloride, Solid lipid nanoparticles loaded Gel, Drug Content, pH of the Gel, In-vitro drug release study

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*Address for Correspondence:
Aman Shrivastava, Madhyanchal professional University, Bhopal, M.P.

INTRODUCTION

Fungal infections are one of the most common skin diseases, affecting approximately 25% of the population. It is estimated that 40 million people in developing and developed countries are affected by fungal infections. Studies have shown that vaginal mycosis is one of the three most common infections in humans. The number of fungal infections increases with changes in age, climate and disease. People taking antibiotics, corticosteroids, immunosuppressive drugs, and birth control pills are more susceptible to fungal infections[1]Until now, fungal infections were fought with oral antibiotics. While antifungal drugs are commonly used to enhance the effect of the drug in the treatment of rare fungal infections, oral therapy is often

associated with side effects such as nausea, vomiting, headache, and nephrotoxicity and hepatotoxicity. Therefore, primary care is a suitable treatment method for infectious diseases, which has the advantages of targeting the site of infection, reducing systemic side effects, improving treatment effectiveness, and improving patient compliance. The effectiveness of antifungal treatment depends onkey factors such as penetration of the drug into the target area and residence time for effective absorption of the drug through the skin. In central administration of anti-inflammatory drugs, the drug must penetrate the stratum corneum. In this context, selectivity may play an important role in drug penetration into the skin. This method of treating infections involves the use of ointments, creams, gels, & lotions that require large quantities, and frequent use due to the short residence time on the skin and long duration of use. Therefore, there is a need for an innovative delivery system that can accurately deliver drugs to the target site and effectively distribute them to different parts of the skin.

Solid Lipid Nanoparticles (SLN)

SLNs were introduced in the late 20th century. They have been used to replace traditional drug carriers such as emulsions, liposomes, microemulsions, and other polymer-containing formulations. Solid lipid nanoparticles were first developed for oral administration [2]. They are not without the problem of lipid toxicity and industrialization. It is a nano-sized drug contained in lipid that remains solid at room/body temperature. They can be produced in small sizes from 50 nm to 500 nm. Their size increases their surface area, causing them to exhibit more drug. They provide the potential for diffusion of chemicals and nutrients. Additionally, solid lipid nanoparticles produce less toxicity than other methods due to their biocompatibility [3].

Butenafine Hydrochloride is a novel, broad-spectrum,benzylamines antifungal agent primarily used for the topical treatment of superficial fungal infections, including tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm). Approved by regulatory agencies for its potent antifungal activity, luliconazole demonstrates a high level of efficacy against dermatophytes and certain non-dermatophyte fungi, offering advantages over traditional antifungal agents. Although the mechanism of action has not been fully established, it has been suggested that butenafine, like allylamines, interferes with sterol biosynthesis (especially ergosterol) by inhibiting squalene monooxygenase, an enzyme responsible for converting squalene to 2,3-oxydo squalene. As ergosterol is an essential component of the fungal cell membrane, inhibition of its synthesis results in increased cellular permeability causing leakage of cellular contents. Blockage of squalene monooxygenase also leads to a subsequent accumulation of squalene. When a high concentration of squalene is reached, it is thought to have an effect of directly kill fungal cells.

MATERIAL AND METHOD:

Butenafine Hydrochloride API was supplied byGlenmark Pharmaceutical, Nashik India, as a gift sample. Steric acid was purchased from Merck Chemical Company (Mumbai, India). Carbopol 934 was purchased from LobaChemie, Mumbai, India. Tween 80 was purchased from S D Fine-Chem Limited, Mumbai. Thermo Fisher Scientific India Pvt. Ltd. Mumbai purchased methyl paraben and propyl paraben. All other chemicals and solvents were used without further purification and were of analytical grades.

Preformulation Studies

1. **Morphological Characterization:**
   The physical characteristics of Butenafine Hydrochloride, including color, Odor, taste, and nature, were evaluated.
2. **Melting Point Determination**:
   The melting point of Butenafine Hydrochloride was determined using a capillary tube sealed at one end and placed in a paraffin-filled melting point apparatus. The temperature was recorded from the start to the complete melting of the drug.
3. **Solubility**:
   Solubility was assessed by dissolving 50 mg of Butenafine Hydrochloride in 3 mL of various solvents (methanol, ethanol, acetone, chloroform, water, PBS pH 7.4) and shaking for 24 hours. After centrifugation, the supernatant was analyzed for solubility.
4. **Partition Coefficient**:

   The partition coefficient (Log P) was determined by shaking luliconazole (1 mg/mL in water) with octanol. The concentrations in both phases were measured using UV spectrophotometry at 254 nm, and Log P was calculated as the ratio of drug concentration in the organic phase to the aqueous phase.
5. **UV-Visible Spectroscopy**:
6. **λ max Determination**: Luliconazole dissolved in ethanol was analyzed using UV spectrophotometry to identify its maximum absorbance (λ max) in the range of 200-400 nm.
7. **Calibration Curve**: Calibration curves in methanol and phosphate buffer (pH 7.4) were prepared by measuring the absorbance of dilutions (2-12 µg/mL) at λ max 254 nm.
8. **Fourier Transform Infrared Spectroscopy (FTIR)**:
   FTIR spectra of luliconazole were recorded over a range of 4000–400 cm^{-1}. The spectra were analyzed to confirm functional groups and assess interactions with excipients.
9. **Compatibility Studies**:
   Compatibility studies were performed by comparing the FTIR spectra of pure Butenafine Hydrochloride with physical mixtures of the drug and excipients.
   Characteristic peaks of Butenafine Hydrochloridewere observed at specific wave numbers.

Preparations of Butenafine Hydrochloride solid lipid nanoparticles (SLN)

Solid lipid loadedButenafine Hydrochloridedrug was prepare by using melt emulsification method. In the lipid phase, a known amount of drug and steric acid were taken and dissolved in small quantities of methanol in a beaker to obtain a lipid-drug matrix. Aqueous phase was prepared by taking tween 80 in 10 ml distilled water and heated to 70^0C under continuous stirring. Aqueous phase was poured dropwise to lipid phase using a magnetic stirrer at 1000rpm for 15 min. The resulting dispersion was probe sonicated for

10 min. The mixed solution was transferred in ice water bath and stirring for 4 hours at 3000 rpm. Different formulation of drug loaded SLN were prepared by varying concentration of steric acid and surfactant.

Table 1: Composition of Different Solid Lipid Nanoparticles

Batch	Drug	Steric acid	Cholesterol	Tween 80	PEG 400
SLN1	10	0.5	-	1.5	1.5
SLN2	10	1.5	-	1.5	1.5
SLN3	10	2.5	-	1.5	1.5
SLN4	10	-	0.5	1.5	1.5
SLN5	10	-	1.5	1.5	1.5
SLN6	10	-	2.5	1.5	1.5

Evaluation of SLN

a. Evaluation of entrapment efficiency

Drug EE of drug can be calculated by weight amount of Butenafine Hydrochloride added SLN were added in phosphate buffer 7.4 and diluted with 100ml phosphate buffer 7.4 solution. And sonicate for 10 minutes, then centrifuged at 1000 rpm for 15min then the supernant was withdrawn, and further diluted by buffer 7.4 solution and analyses at wavelength max at 254 nm of luliconazole using UV spectroscopy.

EE % = W (Added drug) −W (free drug) / W (Added drug) x 100

Where, W (added drug) is quantity of drug added during preparation of SLN, and W (free drug) is quantity of free drug measured in supernatant after centrifugation.

b. Physicochemical property

Physicochemical Properties of SLN dispersions were characterized as colour, odour, pH, and solubility of SLN-6 in aqueous medium.

c. Particles Size analysis and PDI:

At room temperature, mean particle size and PDI of Butenafine Hydrochloride-loaded SLN analysed using a nanoparticle analyser and (DLS). Sample dissolved in water and sonicated for 20 minutes. After that this solution can be diluted and analyse the size of solid lipid nanoparticles.

Zeta Potential:

The charges on the surface of Butenafine Hydrochloride-loaded SLN was determine at room temperature, by using Malvern nanoparticle analyser was determined using solid lipid nanoparticles. The ZP was determined after dilution of sample with Distilled water at room temp.

Scanning Electron Microscopy:

SEM used to examine the surface structure of SLN (SEM). An SEM image of a solid lipid nanoparticles can also be used to show its structure. SEM used to examine the morphology of lButenafine Hydrochloride-loaded SLN.

Formulation of Solid lipid nanoparticles loaded topical gel:

The gel developed as per referenced protocol with slight modification. Briefly, Carbopol 934P placed in defined quantity of distilled water while constant stirring at 600 rpm and followed by adding of methylparaben (0.02% w/v) and propylparaben (0.1% w/v) and remained undisturbed with continuous stirring for 30 min. Prepared gel base set aside for 24 hrs. Next, SLN F6 disseminated with measured quantity of propylene glycol (5% w/w) and 1% ethanol (20% w/w) and far ahead it added to carbopol gel bases with continuous shaking at 1000 rpm and followed by churning for 30min. Tri-ethanol amine (TEA) subjected to the final stage to maintain pH (5.5 - 6.5) for drug stabilization and stirred thoroughly to obtain clear gel**.**

The same procedure applied to get three formulations having varying amount of carbopol and aim is associated to prepare different forms of gel is to obtain best homogeneous anduniform texture with stable physicochemical reliability in respect of % release of leading moiety. Different formulations of SLN gel are enlisted as in Table;

Table 2: Preparation of different formulations of solid lipid nanoparticles containing gel

Formulation code	Carbopol 934 % (w/v)
G1	1%
G2	2%
G3	3%

Characterization of gel

a. Appearance:

The visual appearance, odour, texture, of the SLN-based topical gels were evaluated upon application, including grittiness, consistency, and uniformity.

b. pH determination:

pH of each SLN Gel was determined using digital pH meter. Each 50 mg formulation was added in beaker and pH of formulation was determined by using calibrated pH meter**.**

c. Gel strength:

20 ml of formulation was placed in 25 ml graduated cylinder and gelled in thermostatically controlled water bath at 37°C. A weight of 5 g was placed onto the gel. The time required to travel 2 cm distance for the 5 g weight through gel was determined.

d. Viscosity:

Viscosity of the gel formulation was calculated using a Brook-field viscometer and a suitable spindle number and RPM.T-bar spindle (Spindle-R/S, S-75) was lower perpendicularly into the gel in a beaker, being careful not to touch the bottom of beaker. The spindle was rotted at 60 rpm, and the readings were taken after 60 seconds, when the gel level had stabilised.

e. Spreadability:

Using the spread ability apparatus, spread ability was calculated. The device consists of 2 slides, one of which is fastened firmly in a wooden frame and the other of which may easily be placed on top of the fixed slide. Two grams of extra gel are sandwiched between the equipment' two slides. The slides can support a weight of 1 kg before being discharged. Slide edges that have extra gel are carefully

cleaned off. The top slide is pulled by 80 gm of weight while the bottom slide is securely fastened. The top slide must travel 5 cm in the specified number of seconds. Better spread ability is indicated by a shorter interval. Following that, spread ability was determined using the following formula:

$$S = \frac{M \times L}{T}$$

Where,

S = is the Spreadability,

M = weight pan (tied in the upper pan),

L= length moved by the glass slide,

T = Time in seconds taken to separate the slide completely.

a. Drug Content:

The drug content of SLN loaded gel was determined by diluting 1mL of the formulation with100 mL methanol, further diluted 10ml to 50ml with methanol followed by analysis with UV-visible spectrophotometer

b. *In-Vitro* drug diffusion Study:

In Vitro drug diffusion study was performed on the Franz diffusion cell using cellulose acetate membrane. Phosphate buffer pH 7.4 was used as diffusion medium and previously put in contact with membrane 30 min before placing the sample.Phosphate buffer pH 7.4 was placed in receptor compartment of franz diffusion cell. The receptor compartment was continuously stirred using magnetic bar and the temperature was kept at 37±0.5 °Cusing water bath. The experiment was started with the even application of 0.5 gm of SLN gel on the surface of cellulose acetate membrane from donor compartment side. Sampling was performed after 0.5, 1, 2, 6, and 12 hr and the fresh diffusion medium was added with each withdrawal of sample. The samples were diluted and analysed at 296 nm UV Visible spectrophotometrically.

c. *In vitro* antifungal activity

In vitro antifungal activity study was performed against *Candida albicans* species using modified agar diffusion method. Sabouraud's dextrose agar (SDA) was used for the preparation of cultures and incubation of fungal species. Cultivation/incubation media was prepared and sterilized (by autoclaving at 15 psig pressure, 121°C for 15 min). Fresh cultures of *C. albicans* were prepared and incubated at 37±2°C for 48 hr in dark condition. Sterilized SDA plates were prepared and a spherical well was made with a sterile borer in an aseptic area. Each formulation (SLN gel, and marketed formulation) was mixed thoroughly with the medium and poured into the wells on an agar plate under sterile conditions. The plates were dried and incubated at 37±2°C for 48 hr. The zone of inhibition was measured at the end of incubation.

d. Stability studies:

Optimized formulation was subjected to stability as per ICH guidelines at the following conditions (ICH, 2003).

Samples were kept in stability chamber at following conditions for 3 months-

1. 40± 2°C and 75 ± 5% RH (Accelerated temperature)
2. Room temperature

Formulations were analysed at 1, 2 and 3 months for following tests-

i. Visual appearance
ii. pH
iii. Gel Strength
iv. Spreadability
v. *In vitro* drug release

RESULT AND DISCUSSION

Preformulation Studies

1. Morphological Characterisation:

The pure API sample of Butenafine was found to be white, odourless, amorphous powder.

Table 3: Result of Organoleptic properties

Sr No.	Parameters	Specification	Observation
1	Nature	Amorphous	Amorphous
2	Colour	White	White
3	Odour	Odourless	Odourless

2. Melting point determination

Melting Point of Butenafine was found range of 149-151^{0}c, while as per literature standard it is reported to be 150-152^{0}c.As per practical value it could be concluded that Butenafine Hydrochloride was in pure state.

3. Determination of Solubility:

The solubility of the drug in different solvents was studied and a solvent to be used in the final formulation was selected. The solubility was analysed using UV-VIS spectrophotometer at 254nm.

Table 4: Result of Solubility of Butenafine

Solvent	Solubility in (mg/ml)
Water	0.009_0.000
DMSO	17.55_0.000
Ethanol	70.57_0.000
Acetone	17.794_0.038
Methanol	23.538_0.628

4. Partition coefficient:

Partition coefficient is normally used to determine the lipophilic and hydrophilic nature of a substance. Compounds with log p more than 1 are lipophilic in nature whereas those with less than 1 are hydrophilic.

Table 5: Partition coefficient of Butenafine

Partition coefficient of drug	Solvent system	Log P Values
Butenafine Hydrochloride	n-octanol: water	6.77

UV-VIS Spectrophotometric method for Butenafine Hydrochoride: Determination of λ max

A. Preparation of Calibration Curve of Butenafine Hydrochlorie

- **Calibration curve of Butenafine Hydrochlorie in**

- **Methanol**

❖ **Preparation of standard stock solution:**

accurately weight 100mg of pure Butenafine Hydrochloridedrug was diluted in 100ml Methanol. (1000µg/ml). From this solution remove out 10 ml and transferred to another 100 ml volumetric flask and adjust vol. up to 100ml by using methanol. (100 µg/ml).

❖ **Preparation of Working Solution:**

From Stock solution (100µg/ml), pipette out 0.2,0.4, 0.6, 0.8, 10, into 10ml volumetric flask and adjust the volume up to 10 ml to get concentration in the ranges from 2-12 µg/ml. then the absorbance of above dilution was recorded by uses UV Visible Spectrophotometry at λ max 254 nm. The absorbance of Butenafine Hydrochlorie was plotted against conc. in MS excel and slope and Intercept was determined. Result as shown in **table no 6**and **fig no 1.**

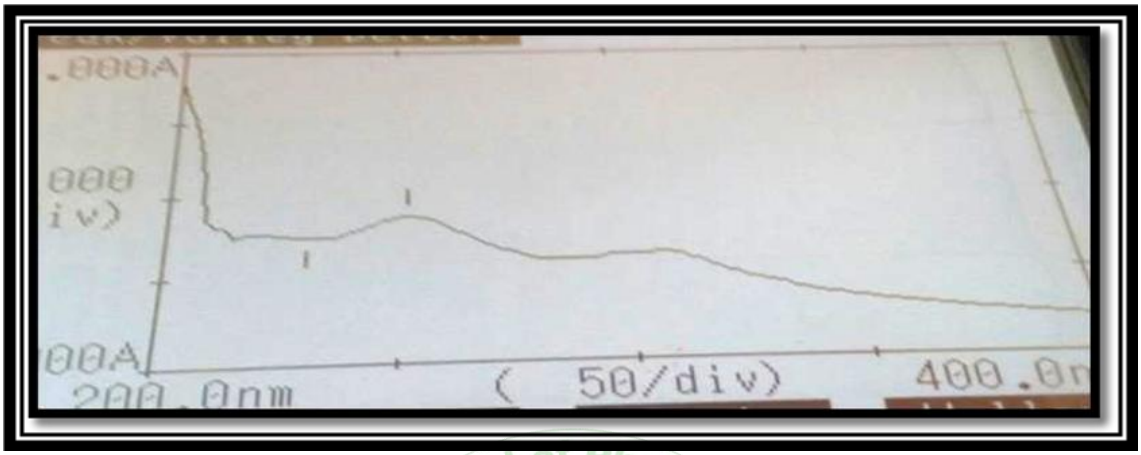

Figure 1: Wavelength max of Butenafine Hydrochloride.

Preparation of Calibration Curve of Butenafine Hydrochloride:

Calibration Curve of Butenafine Hydrochloride in Methanol

The calibration of Butenafine Hydrochloride in methanol was found to be linear in conc. range at 0, 2, 4, 6, 8, 10 µg/ml having a coefficient of regression (R2) value 0.9945.

Table 6: Absorbance of Butenafine Hydrochloride in methanol

Concentration µg/ml	Absorbance
2	0.324
4	0.523
6	0.735
8	0.967
10	1.125

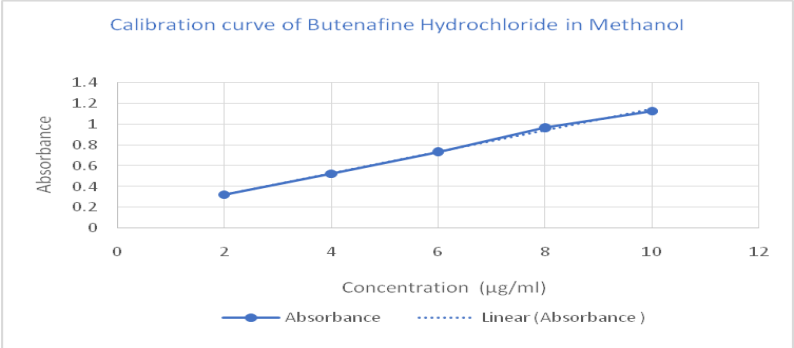

Figure 2: Calibration Curve of Butenafine Hydrochloridein Methanol

5. Fourier Transform Infrared Spectroscopy (FTIR)

The infrared spectrum of pure luliconazole recorded by FTIR spectrometer is shown in fig 19 which was compared with standard functional group frequencies of ButenafineHydrochlorideshows in table show that functional group frequencies of Butenafine Hydrochloride were the reported range which indicate the purity of Butenafine Hydrochloride.

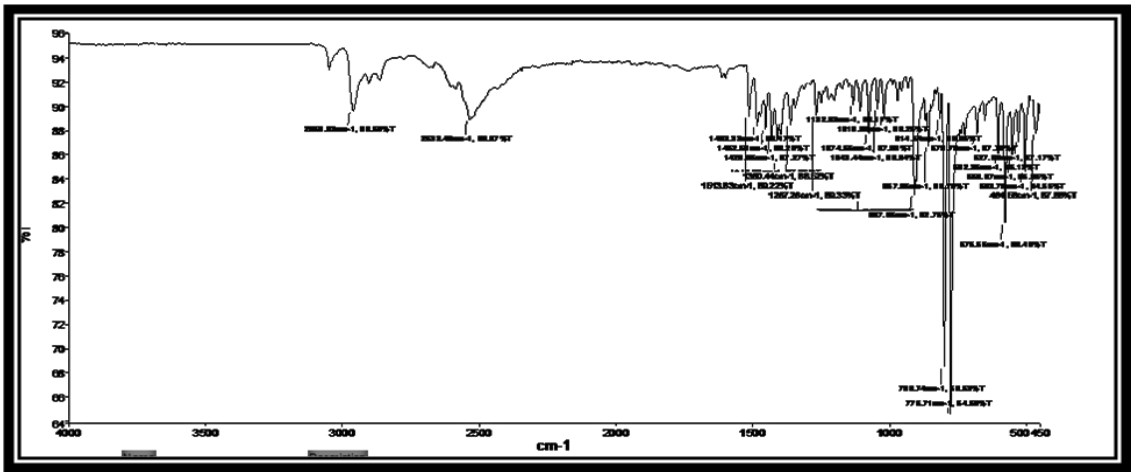

Figure 3: FTIR Spectrum of pure Butenafine Hydrochloride drug.

Table 7: Interpretations of Butenafine Hydrochloride (Pure Drug) FTIR Spectra

Functional Group	Standard frequencies cm-1	Observed frequencies cm^{-1}
C-H Aromatic stretch	690-900cm-1	857 cm-1
C-H Alkane	2850-3000cm-1	2961.76 cm-1
C-N Amines	1000-1350cm1	1074.97 cm-1
C=C aromatic	1475-1600cm-1	1483.66 cm-1
CH3 ,bending	1375-1450cm-1	1410.43 cm-1
O-H bend (alcohol/phenol)	1310-1360 cm-1	1309.60 cm-1
C-Cl Stretching	600-800 cm-1	790.96cm-1

6. Drug and Excipient Compatibility Study:

FTIR analysis of SLN-6 performed to determine possible interaction between drug and drug additives. spectral data reveal principal absorption peaks of luliconazole at 2955.75 cm-1 for C-H stretching, 2523 & 2647 cm-1 for S-H stretching, 2201.52 cm-1 for C≡N stretching, 1556.90 cm-1 for C=N stretching, 1471.88 cm-1 for C=C aromatic ring stretching and 720.33and 1101.29 cm-1 for C-Cl stretching. Whereas, principal absorption peaks of stearic acid were found at 2914.97cm-1& 2848.05 cm-1 in high-frequency region attributed to -CH2- band asymmetric and symmetric stretching vibrations, whereas and 1698.03 cm-1 for -COOH stretching is attributed in low-frequency region. Spectral analysis of optimized SLN confirmed that there are no more changes in luliconazole after successful formation of SLN. Spectral The FTIR spectral analysis of SLN gel G3 performed successfully to determine possible interaction between drug and drug additives and obtained spectral data matched with spectral data of Butenafine Hydrochlorideand stearic acid. Findings of spectral analysis show principal absorption peaks at 3331.36cm -1 for N–H stretching, 2971.88 cm-1 for C-H stretching, 2193.49 cm-1 for C≡N stretching, 619.26 & 1044.56 cm-1 for C-Cl stretching for Butenafine Hydrochloride.Whereas, principal absorption peaks of stearic acid were ascribed to 2932.49cm-1& 2895.16 cm-1 in high-frequency region attributed to -CH2- band asymmetric and symmetric stretching vibrations, and 1639.31 cm-1 for -COOH stretching is attributed in low-frequency region. Spectral analysis of optimized formulation

G3 reveals that no more possible interaction between drug and drug additives even after successive formation of topical gel. Hence it can be said that spectra show purity and authenticity of SLN G3 gel .

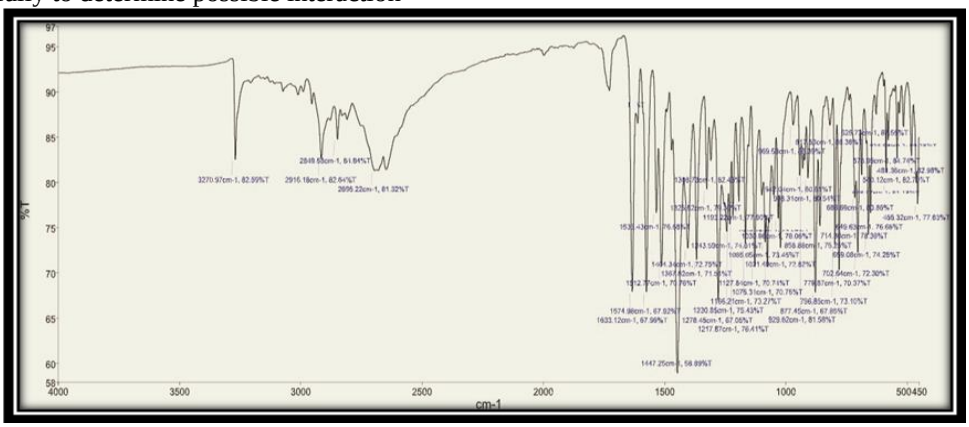

Figure 4: FTIR Spectrum of pureButenafine Hydrochloridedrug + Excipient

Table 8: Interpretations ofButenafine Hydrochloride+ Steric Acid

Functional Group	Standard frequencies cm-1	Observed frequencies cm^{-1}
N-H stretc	3300 – 2400 cm-1	2895.43 cm-1
C=C stretch	1638 – 1648 cm-1	3331.36 cm-1
CO - O – CO stretch	1450 - 1650 cm-1	1144. 56 cm-1
C – Cl stretch	550 – 850 cm-1	619. 26cm-1

Preparation of SLN Dispersion:

The lipid selected was stearic acid according to the solubility studies of various lipids. The particular concentration of lipid was melted above at a low concentration, resulting in a smaller particle size. stearic acid was selected for further evaluation. its melting point, and the drug was added to form a clear mixture; this is the oil phase. The aqueous phase was prepared by dissolving the selected surfactant, *i.e.*, tween 80 in the required quantity of distilled water under the same temperature as the oil phase. The aqueous phase is incorporated into the oil-phase dropwise under magnetic stirring while maintaining the temperature constant. This solution was homogenized for 5 min under 8000 rpm and then sonicated for 5 min. This nano-dispersion was allowed to cool to room temperature to yield nanoparticles.

Further, in optimization of SLN, method archived step by step with alternate changes in concentration of stearic acid and tween80 (w/v). All prepared groups of SLN were coded successfully and proceed to quantitate percent entrapment of active moiety spectrophotometrically at 254 nm. Obtained data were evaluated statistically. SLN which deal with high entrapment of Butenafine Hydrochloride chosen as optimized SLN and proceed for further evaluation.

Figure 5: Prepared SLN batches of Butenafine Hydrochloride

Evaluation of SLN

1. Determination of entrapment efficiency

Varying concentrations of lipid and organic solvent showed significant effect on EE and DL of butenafine. EE of BUTE was found to be higher in the selected formulation. The EE of four formulations run B1 to run BS5 were found to be in between 85.45±2.26 % to 88.65±1.69 % and drug loading in between 15.05±0.58 % to 22.86±0.46 %. The EE and DL of optimized BS6 BUTE-SLN was found to be 90.38±2.35 % and 17 .692±0.95 % respectively.

Table 9: Entrapment Efficiency of SLN Formulation

SR. NO.	FORMULATION	% ENTRAPMENT EFFICIENCY
1	SLN1	83.01±2.71
2	SLN2	85.45±1.21
3	SLN3	87.87±1.93
4	SLN4	88.65±3.10
5	SLN5	89.53±1.58
6	SLN6	90.38±2.17

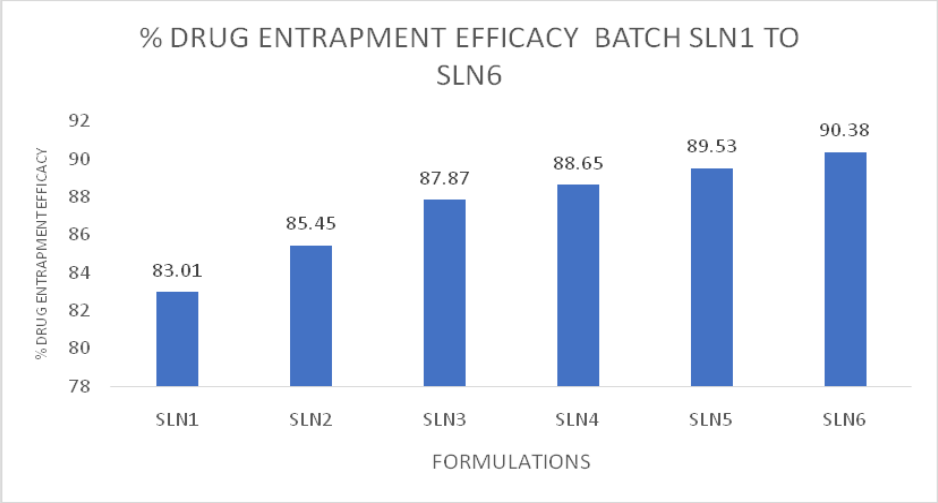

Figure 5: Percentage entrapment efficiency of Butenafine Hydrochloride in SLN

2. Physicochemical property

The SLN F( ) evaluated based on their physicochemical characteristics such as colour, odour, pH stability, and aqueous solubility. physicochemical results reveal that SLN has white transparent colour with homogeneous and uniform texture, aromatic odour, better stability at 7.4 pH, and water solubility found 0.153 ± 0.035 mg/ml, i.e. much enough than Butenafine Hydrochloride solubility

States to high stability of nanosystem. In particle size analysis, SLN unveiled with mean particle diameter by ~261.3 nm, unimodal size distribution, polydispersity index (PDI) by 0.268, intercept value 0.98 and 92% peak intensity. PDI is parameter that represents dissemination factor with low aggregation of nanoparticles when PDI value would be < 0.5.

The particle size, zeta potential and polydispersity index of the prepared SLN batches are reported in table. The particle size analysis of Butenafine Hydrochloride SLN suspension revealed that the particle size measured by laser light method is around to 287 nm with low polydispersity index. All the SLN formulation shows particle sizes in the nano range (< 1 µm). The reduced particle size and polydispersity index could be attributed to the stabilization of colloidal system.

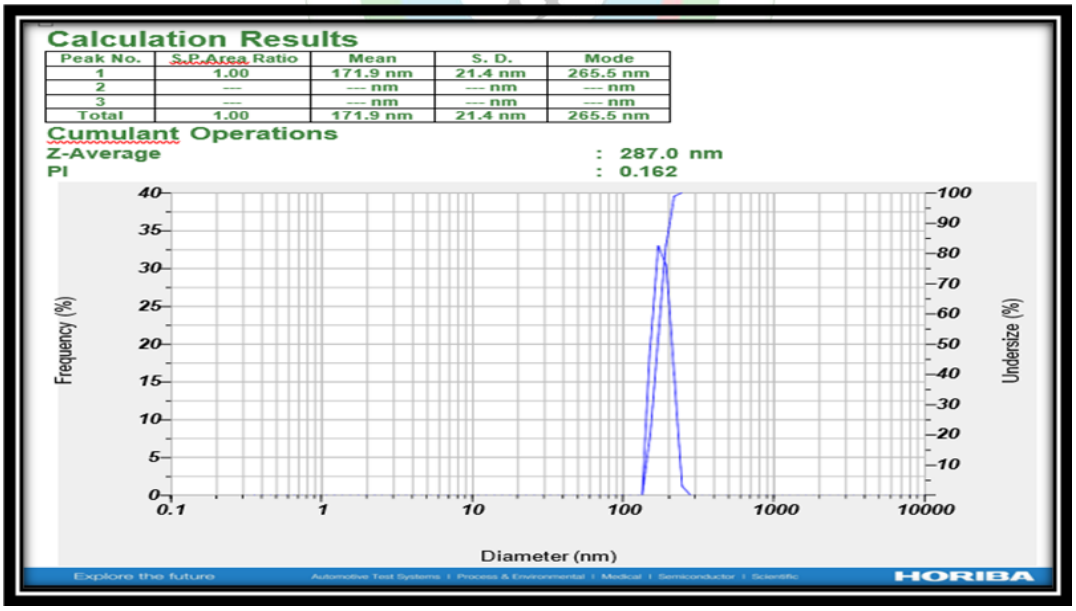

Figure 6: Result of Particle Size.

3. Zeta Potential

The charges on the surface of ButenafineHydrochlorie-loaded SLN was determine at room temperature, by using Malvern nanoparticle analyzer was determined using solid lipid nanoparticles. The ZP was determined after dilution of sample with Distilled water at room temp. the results are shown in **Figure No 7.**

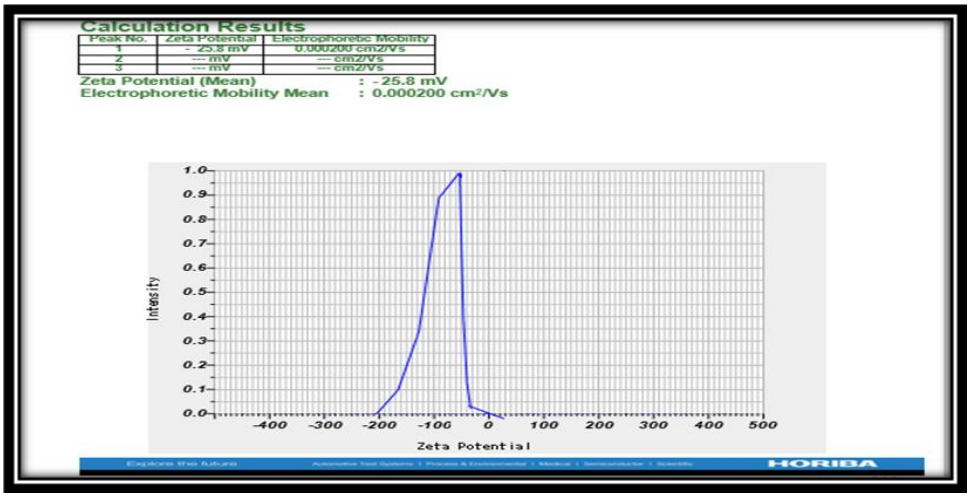

Figure 7: Result of Zeta Potential

The zeta potential is in the ideal range. The high zeta potential was found to reduce the tendency for particle aggregation due to higher magnitude of repulsive forces.

4. Scanning Electron Microscopy:

The SEM image of optimized SLNs (F6) is shown in Figure 5. The SLNs were observed to be spherical in shape, with a smooth surface. It was noticed that particles adhered together, probably due to the nature of the steric acid used in the formulation.

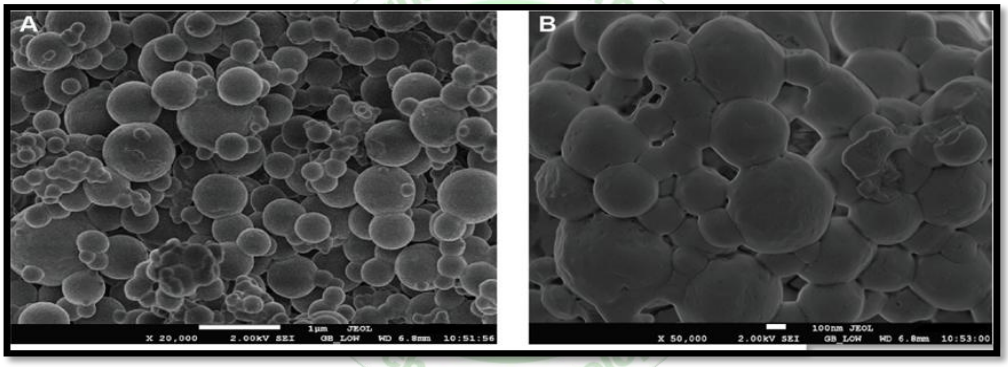

Figure 8 SEM images of optimized Butenafine Hydrochloride loaded SLNs

Evaluation of SLN loaded topical gel

SLN-6 batch was found to be optimized which is used further for preparation of gel from optimized SLN and evaluated for following parameters.

Figure 9: Visual appearance of SLN gel

a. Appearance:

Table 10: Physical evaluation of Butenafine Hydrochloride SLN based gels

Formulation	Appearance	Consistency	Grittiness	Uniformity
G1	Whitish	Smooth	None	Good
G2	Whitish	Smooth	None	Good
G3	Whitish	Smooth	None	Good

b. pH measurement:

pH of BUTE-SLN based gels was found in range of 5.4 – 5.8 which is was near to the physiological pH of the skin. Hence it concludes that the gel formulation is safe to use topically. Results are shown in below table no 15.

Table 11: pH of BUTE-SLN based gel

Batch	G1	G2	G3
pH	6.6	6.7	6.8

c. Gel Strength:

Gel strength was determined by visually observing and measuring the time required for travel of 5 gm weight up to 2 cm distance through gel. These observations were graded as +++ if time required is more than 4 hr, ++ if time is 2.5 - 4 hr and + if time is less than 2.5 hr. + indicate low gel strength and the gel may get dissolved and cleared off faster from skin surface, ++ and +++ indicate good and very good respectively and will help to hold drug for prolonged period of time. The gel strength for the formulation was found to be ++ indicates good gel strength which will help desired drug release and may get easily cleared off from skin when required. The results are shown in table no--.

d. Viscosity:

The viscosity of luliconazole based SLN gel formulation was found to be in the range of 13941±6.55cpsto 12521±5.56cps. showing good consistency of the formulation. The results are shown in Table No --.

Table 12: Viscosity of BUTE-SLN based gels

Batch	Viscosity (cps)	Gel Strength
G1	13941	++
G2	12521	++
G3	13947	+

+++ if time required is more than 4 hr, ++ if time is 2.5-4 hr and + if time is less than 2.5hr

e. Spreadability:

The consistency and adhesive property of semi solid dosage form was studied by the spreadability values. Nanometric monodisperse particles showed good spreadability and forms a uniform layer on the skin. The presence of BS3 BUTE-SLN did not show any significant change in spreadability. The spread ability value of BS3BUTE-SLNwasfound tobe4.4±0.37gm.cm/sec and for plaingel base 4.06±0.41gm.cm/sec.

Table 13: Spreadability of BUTE SLN based gels

SLN BUTE-SLN	PLAIN GEL BASE
4.4±0.37gm.cm/sec	4.06±0.41gm.cm/sec.

f. Drug content:

All the prepared BUTE loaded batches shows good drug content, the drug content is within the range of 78% - 86.3%.

Batch	Drug Content (%)
G1	94.49
G2	96.54
G3	82.39

g. *In-Vitro* drug diffusion study:

All the prepared batches show good drug release. Table no 15 shows the drug release of the SLN based gel batches.

Table 14: Drug Content BUTE SLN formulation

Time	G1	G2	G3
0	0	0	0
0.5	3.29±0.59	3.75±0.57	4.02±0.64
1	11.16±1.08	8.52±1.16	9.93±1.04
2	18.32±1.29	14.92±1.27	19.6±1.18
4	27.74±1.27	29.56±1.16	31.62±1.28
6	41.81±1.35	37.84±1.64	39.53±1.34
8	44.66±1.48	43.91±1.47	44.48±1.85
12	54.04±1.86	51.26±1.92	46.27±2.17

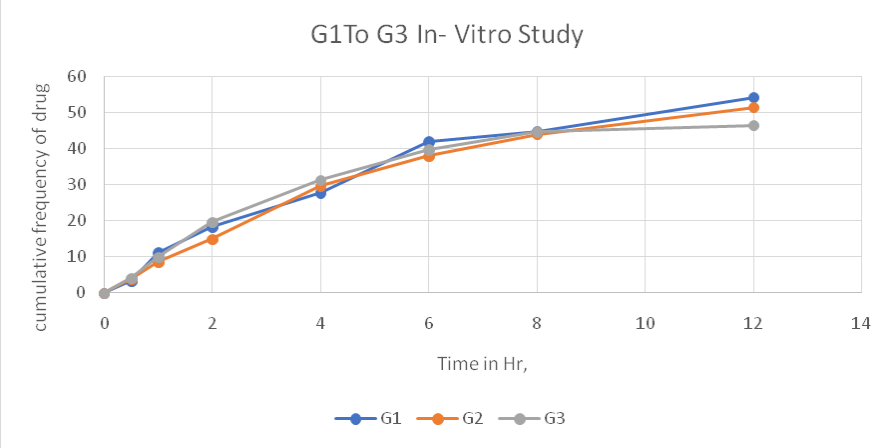

Figure 10: *In vitro* drug diffusion of gel

Table 15: Drug Content BUTE SLN formulation

TimeinHr	BS3 BUTE-SLN Gel%	Reference%
0	0	0
1	23.15±1.76	4.27±1.29
2	44.34±1.55	8.53±1.86
5	58.29±2.06	13.69±1.39
7	66.71±2.78	19.35±1.51
9	68.52±2.91	25.46±2.76
12	72.43±2.96	32.95±1.94

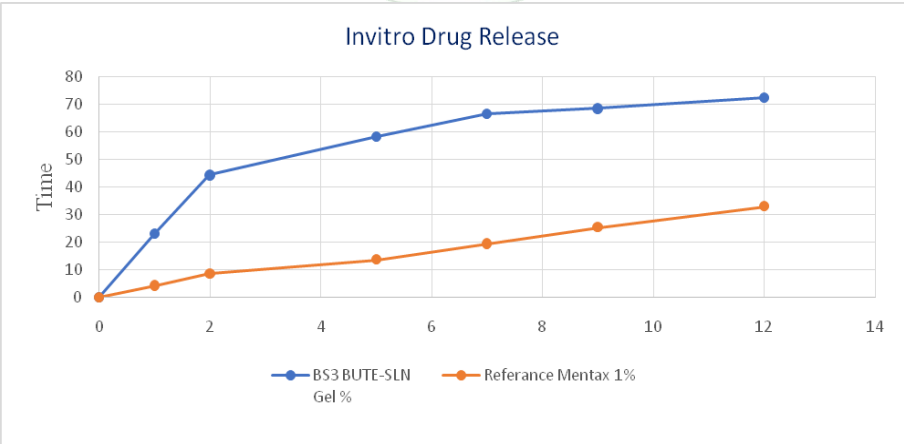

Figure 11: *In-vitro* drug diffusion profile of BS3BUTE-SLNgel and reference marketed Mentax Cream 1%.

h. *In vitro* antifungal activity:

The antifungal activity was evaluated on the basis of zone of inhibition. Zone of inhibition interprets the effectiveness of formulation against the microbial species taken. Here *C Albican*is used as a reference as it is responsible for various skin infections. The zone of inhibition measured after 72 hr BUTE-SLN was found to be higher when compared with marketed preparation. This is due to the permeability of SLN to cross the fungal cell membrane and releases the drug inside the cell. The result reveals the enhanced potential of BUTE-SLN gel to act against *Candida* species as compared to marketed cream and the standard dilutions of Butenafine Hydrochloride.

There was no significant difference between zone of inhibition of control and 1% luliconazole marketed cream. Whereas, optimized SLN gel exhibited larger zone as the small particle size of SLN results in better diffusion through membrane pores in the gel network. and (Table 20) A large amount of Butenafine Hydrochloride was found to be localized within the same isotropic media, resulting in strong antifungal activity compared to commercial preparations. The zone of inhibition for optimized SLN gel was greater than microemulsion based gel as reported by *Kansagra et al.*

In-vitro antifungal study clearly depicts that optimised SLN formulation exhibits better anti-fungal activity as it portrays larger zone of inhibition against *CAlbicans* in comparison to marketed luliconazole cream.

Table 17: Zone of Inhibition diameters for *In-vitro* antifungal studies

Sample	ZOI of C. Albicans diameter (mm)
Control	87
1% Luliconazole marketed cream	83
SLN of Butenafine Hydrochloride Gel	93

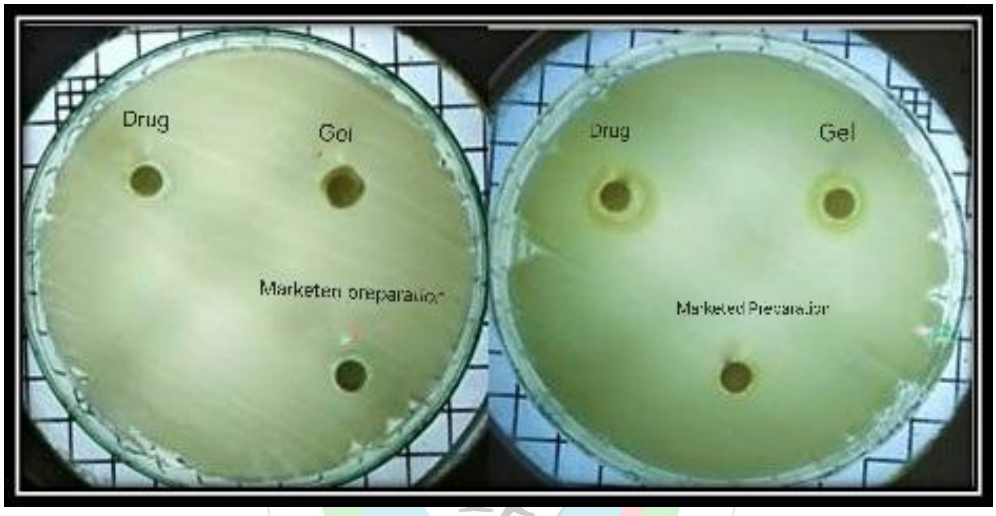

Figure: 12 As compared with Marketed Preparation BUTE-SLN Gel Shows Higher Zone of Inhibition

i. Stability studies:

The optimized formulation F2 was subjected for stability studies as per the ICH guidelines for 1 month. Stability study's results indicated that the there was no significant change in the visual appearance, floating behavior, and drug content as shown in Table. (Room temperature of 25°C±2°c).

Table 18: Stability Study.

Month	Temperature	Appearance	pH	Gel Strength	% Drug Release
1	R.S.T. Acc. S.T.	No change No change	5.5 5.3	++ ++	89.5 89.4
2	R.S.T. Acc. S.T.	No change No change	5.6 5.5	++ +++	88.8 88.2
3	R.S.T. Acc. S.T.	No change No change	5.7 5.8	+++ +++	88.4 88

CONCLUSION

A topical drug delivery system aims to guarantee that the intended area in the body receives a therapeutic dose of medication and that the desired effects are maintained for a specific duration. Our research has resulted in the development of solid lipid nanoparticles (SLN) that contain luliconazole, which enhances skin permeation and provides targeted, controlled drug release. These particles were incorporated into a carbopol 934 topical gel with excellent skin retention. Standard protocols were followed to determine the physicochemical properties of the gel, ensuring its compliance after patient use. Spectroscopic analysis revealed no chemical interaction between the drug and excipients. Optical and scanning electron microscopy examinations demonstrated that the SLN was evenly distributed throughout the gel and that the drug release kinetics were well-ordered. Consequently, we can conclude that the SLN gel system provides controlled drug release and can serve as an excellent drug carrier system for lipophilic drugs and as a bioavailability enhancer for poorly water-soluble drugs via nanoparticle drug delivery.

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