RESEARCH ARTICLE

Factors Affecting Foam Stability of Clotrimazole Vaginal Foam

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ABSTRACT

Clotrimazole (CLT) is a broad-spectrum antifungal, synthetic imidazole derivative, used for *Candida albicans* the major cause of vaginitis. Vulvovaginal candidiasis (VVC) symptoms can cause discomfort and lower a women's quality of life. Foams are used to apply formulation without the use of fingertips, the more stable the foam the better for coverage of larger surface area.

CLT 2% vaginal foam were prepared as an O/W emulsion using Tween 20 and Span 20, Lemon oil, PEG 400, SLS, cetyl alcohol, and the formulas were evaluated for foamability and foam stability, foam density, cycles of freezing and thawing, heating, and cooling, and the impact of the chosen formula on *Candida* culture are all taken into consideration.

The results showed that the CLT prepared successfully as vaginal foam, and the selected formula (F24) considered as the best formula which has good miscibility, texture and acceptable homogeneity, pH (4.8), drug content (97.5%), acceptable foamability and foam stability; foam expansion FE (70%), foam liquid stability (FLS) (40%), foam volume stability FVS (23.5%), gas fraction (GF) (35 mL), acceptable foam density (0.90), good stability at temperature changes, freeze–thaw cycle (pass), heating–cooling cycle (pass) with no phase separation, fast complete drug release (100% in about 40 min), no interaction between the solid components of the formula and acceptable inhibition zone against *Candida* strains.

Finally, we can conclude that formulation of CLT as vaginal foam is an optimum method to improve patients' compliance and cure the disease with low recurrence possibility due to fast release and long contact time with the affected area.

Keywords: Clotrimazole, Stability, Vaginal foam.

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INTRODUCTION

Foams are supersaturated dispersions of gas in a solid (solid foam) or in a liquid (liquid foam), foams, have a physicochemical structure that allows for a wide range of therapeutic applications.[1-3] There are two types of foams stable or breakable foam.[1,3-5] Methods of foam production, include whipping, shaking, bubbling, etc.[6,7]

Advantages and properties of medicated foams[8] It is painless to apply to hurting, inflammatory skin because there is no need to rub it in. This also makes it easier to apply to larger, hirsute, or sensitive inflamed areas and for a short time after expulsion, stable foams do not collapse or drain when being manipulated, such as raising a surface with an applicator for skin application. In the event that it is required, it is simple to remove, and due to their good spreadability, fast absorption, and easy application (even on broad or hirsute areas), foams are preferable to cream or ointments because of their good spreadability, fast absorption, and easy application. These factors lead to patient acceptance and increased patient compliance and adherence.

Vulvovaginal candidiasis (VVC) is common among women who visit healthcare facilities. Nearly 75% of all women suffer from fungal vulvovaginitis at some point in their lives. VVC occurs in around 40–50% of women at some point in their lives.[9,10] Most typical clinical signs are pruritus, hyperemia, vaginal discomfort and leucorrhea, abnormal discharge, dyspareunia, and erythema in both the vagina and the vulva, which can cause marital and sexual issues.

Clotrimazole (CLT) is of low solubility and cannot be taken orally because of the risk of severe adverse effects.[11]

The work aims to study the factors affecting CLT foam stability to enhance the therapeutic effect by filling of vaginal cavity and reach all folds for longer contact time.

MATERIALS

CLT purchased from Hangzhou hyper chemicals, China, cetyl alcohol (CA) , sodium acetate Alpha chemika, India , Span 20 (HLB=8.6), Tween 20(HLB=16.7), polyethylene glycol (PEG) 400, glacial acetic acid from Thomas Baker, India, Sodium

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lauryl sulfate (SLS) from HI media India, lemon oil from Avonchem Ltd. UK. Methanol, Scharlau, Spain (Table 1).

METHODS

Preparation of CLT Vaginal Foam

Total 30 CLT 2% vaginal foam formulas were prepared as an O/W emulsion, in which the oil phase was added gradually to the water phase. The oil phase is prepared by addition of warm lemon oil to warm cetyl alcohol (CA) (about 40°C) with continuous mixing while on the hot plate, Span 20 then CLT were added. The water phase consists of water, PEG, Tween 20, and SLS mixed and was heated 2–3°C higher than the oil phase. Then the oil phase was added to the water phase drop by drop while the water phase was still on the hot plate gradually (drop by drop) with continuous high-speed mixing, after all the oil phase was added the mixture was removed from the hot plate (Staut, England) and allowed to cool down to room temperature.[12,13]

Evaluation of CLT Vaginal Foam

Visual Examination

The formulations were tested for a series of characteristics (consistency, homogeneity, miscibility, and color appearance), by visual inspection and were tested for their appearance and presence of any aggregates and immiscibility (Table 2).

pH Measurement

The vaginal preparation pH is important, mainly to stop the growth of fungi, bacteria and other microorganisms, prevent mucosa irritation, and maintain normal physiological environment. At room temperature, a pH meter (Hanna, Italy) was used to test the pH of the chosen formulations, by inserting the electrode through into produced foam and measuring the pH using a pH meter, the readings were tabulated after 2 minutes.

Table 1: Composition of CLT 2% Vaginal Foam (expressed as W/W%) to 100 g

Formula	*CLT*	*SAA Tween 20 +Span 20*	*Lemon oil*	*PEG 400*	*SLS*	*CA*
F1	2	2	20			
F2	2	3	20			
F3	2	4	20			
F4	2	5	20			
F5	2	6	20			
F6	2	7	20			
F7	2	6	20	1		
F8	2	7	20	1		
F9	2	7	20	3		
F10	2	7	25	3		
F11	2	7	25	3		2
F12	2	7	25	3		2
F13	2	8	25	3		2
F14	2	9	25	3		2
F15	2	10	25	3	2	2
F16	2	11	25	3	2	2
F17	2	12	25	3	2	2
F18	2	13	25	3	2	2
F19	2	13	25	4	2	2
F20	2	13	25	5	2	2
F21	2	13	25	5	2	2.5
F22	2	13	25	5	2	3
F23	2	13	23	5	2	4
F24	2	13	23	5	2	4.5
F25	2	13	23	5	2	5
F26	2	7	25	3	2	5
F27	2	13	20	5	2	6
F28	2	13	20	5	2	7
F29	2	13	20	5	2	8
F30	2	13	20	5	2	10

Drug Content

Accurately, 1-mL of the formulation (equivalent to 20 mg/mL CLT) from selected formulas was diluted to 100 mL with methanol. A 1-mL of this formula was diluted again to 10 mL with methanol. The absorbance was measured at the maximum absorption wavelength using UV spectrophotometer. Finally, the CLT content (as %content) was determined by applying the equation of calibration curve of CLT in methanol.[14]

Freeze Thawing Cycle

Three cycles of 48 hours each were spent storing the chosen formulations at -20 and 25°C temperature changes.[15]

Heating-cooling Cycle

The formulations were kept for 48 hours at alternate temperature of 4 and 45°C during six heating-cooling cycles The cylinder foam test was applied to the formulae that showed no signs of phase separations, creaming, or cracking.

Foamability and Foam Stability (Cylinder Method)

As 50 mL of chosen formulations were dispensed as foam into a 100 mL glass cylinder. The initial amount of foam, matured foam volume, and evacuated liquid quantity were all measured at predetermined time intervals. The dissociation of the liquid due to liquid drainage was assessed after 30 minutes to understand the stability of the foam over this time period.

This test may evaluate foam expansion (FE%, Equation 1), foam liquid stability (FLS%, Equation 2), foam volume stability (FVS%, Equation 3), and foam gas fraction (GF, mL, Equation 4).[16] Finally, the computations were completed using the following equations,

$$FE(\%) = \frac{V_{foam} - V_{formulation}}{V_{formulation}} \times 100\% \quad \text{Eq.1}$$

$$FLS(\%) = \frac{V_{liquid\ 30\ min}}{V_{formulation}} \times 100\% \quad \text{Eq.2}$$

$$FVS(\%) = \frac{V_{foam30\ min}}{V_{foam}} \times 100\% \quad \text{Eq.3}$$

$$GF(mL) = V_{foam} - V_{formulation} \quad \text{Eq.4}$$

V_{foam};volume of created foam mL, generated from $V_{Formulation}$; volume of formulation mL, $V_{liquid\ 30\ min}$; the volume of liquid emptied after 30 minutes, and $V_{foam\ 30\ min}$; foam volume after 30 minutes. The difference between the volume of the foam and the capacity of the enlarged formulation may be used to calculate the foam gas percentage.

The greater the FE, the more foam-able the formulation. The created foam is more stable the lower the FLS. The created foam is more stable the greater the FVS.

Foam Density

The density of foam was obtained by filling (100 mL cylinder) with water and then the weight of water was determined (m water), after that the same cylinder have been filled with the foam formula and obtain its weight (m foam). This method of determining the foam density is described in the European Pharmacopoeia (Monograph:1105),[17] and the results obtained by using this equation:

$$FD = \frac{m_{foam}}{m_{water}} \quad \text{Eq. 5}$$

Differential Scanning Calorimetry (DSC)

A sample of pure CLT weighing 8–10 mg and physical mixture of CLT and SLS powder were placed in the DSC (DSC-60 Shimadzu, Japan). This was performed using a reference aluminum pan and a dry nitrogen flow rate of 100 mL/min. The temperature for a DSC was raised from 30 to 300°C, the temperature of sample container rises linearly with time (10°C of heating per minute). Thermograms for the substances were produced, indicating their DSC peaks. The sharper the peaks for the tested substances, the more crystalline the analyzed substances are.

FTIR and Drug–Excipients Compatibility Studies

In order to look into potential interactions between the CLT and SLS, the physicochemical compliance between CLT and SLS used in the vaginal foam formula, was investigated using FTIR. The spectrums were contrasted with the CLT spectrum on its own. The drug sample and the dry physical mixture was combined with (1:100) potassium bromide KBr in a mortar and then squeezed into a tiny disc using a hydraulic press with 14 tons of force.[18] Using a FTIR spectrometer (FTIR -43000 Shimadzu, Japan), the absorbance between 4000 and 400 cm^{-1}, and the spectral band were recorded to evaluate the data.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to assess correlation at which significant results ($p < 0.05$) and non-significant ($p > 0.05$).

RESULTS AND DISCUSSION

Evaluation of Prepared 2% CLT Vaginal Foam Formulas

Visual Examination Results

CLT 2% foam was formulated in lemon oil as it was the best oil to solubilize the drug, the initial formulas were not emulsions, as the surfactant mixture was insufficient for emulsification (F1-F10), upon increasing the concentration of surfactant mixture and addition of cetyl alcohol the emulsion started to appear but were unstable (F11-F14) even with addition of SLS (F15-F17) as phase separation was seen upon standing until the surfactant mixture was increased to 13% then the foams showed homogeneity with no phase separation (F18-F25), further increase in cetyl alcohol (above 5%) increased the consistency of the foams, as they turned into thick creams (F27-F30) (Table 3).

Increasing stirring time during formulating increases stability (decrease phase separation)

The pH of CLT Vaginal Foam

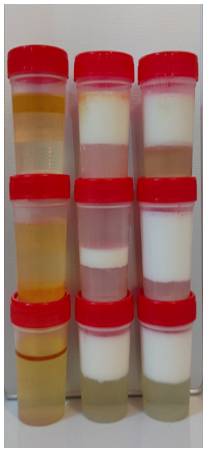
The pH of formulas F18-F25 ranged between 4.8 and 5.3, the pH was ideal to be prepared as a vaginal foam since all formulas were with pH close to the pH of the vaginal cavity (4.5) and cause no irritation.[19]

Drug Content Results

The selected formulations F18-F25 were found to have acceptable drug content (93.15–97.53%), indicating that the method adopted for making the formulation is suitable.

Table 2: Visual Appearance of CLT 2% vaginal foam

Formula	*SAA Tween 20 +Span 20*	*PEG 400*	*SLS*	*CA*	*Appearance*
F1	2				
F2	3				
F3	4				
F4	5				
F5	6				
F6	7				
F7	6	1			
F8	7	1			
F9	7	3			
F10	7	3			
F11	7	3		2	
F12	7	3		2	
F13	8	3		2	
F14	9	3		2	
F15	10	3	2	2	
F16	11	3	2	2	
F17	12	3	2	2	
F18	13	3	2	2	
F19	13	4	2	2	
F20	13	5	2	2	
F21	13	5	2	2.5	
F22	13	5	2	3	
F23	13	5	2	4	
F24	13	5	2	4.5	
F25	13	5	2	5	
F26	7	3	2	5	
F27	13	5	2	6	Thick
F28	13	5	2	7	Thick
F29	13	5	2	8	Thick
F30	13	5	2	10	Thick



The results were acceptable within the USP monograph (90–110%).[20]

Thermodynamic Stability Studies of 2% CLT Vaginal Foam

As noticed the formulas with less amounts of (PEG 400, CA) showed less stability and phase separation.[12,13,21]

Foam Stability and Foam Density

The results obtained from cylinder method were acceptable and reflecting good foamability and foam stability[22,23] as showed in Table 4 The results showed significant correlation between CA concentration and foamability parameters since *p-value* (< 0.05). The foam density results were acceptable (between 0.892–0.913) and reflects good spreadability. Using CA increase foamability and stability of the formula, and using SLS increases the foamability of the formula.

DSC

The DSC of pure CLT powder is The DSC thermogram of the pure CLT showed an endothermic peak of 146.0°C,

Table 3: Evaluation parameters of F18-F25 CLT vaginal foam

Formula	*pH*	*Drug content%*	*Thermodynamic stability*
F18	5.3	95.27	Stable
F19	5.1	93.15	Stable
F20	5.2	93.37	Stable
F21	5.1	96.16	Stable
F22	5.1	95.97	Stable
F23	5.2	96.82	Stable
F24	4.8	97.53	Stable
F25	4.9	97.01	Stable

Table 4: Results of foamability and foam stability parameters

Formula	*FE%*	*FLS%*	*FVS%*	*GF (mL)*	*Foam density*
F18	30	65	18	15	0.892
F19	40	60	20	15	0.895
F20	40	65	19.5	25	0.897
F21	50	60	20.5	25	0.900
F22	50	60	20	30	0.902
F23	60	45	21.5	30	0.902
F24	70	40	23.5	35	0.904
F25	40	50	22	20	0.913

Finally, after testing all formulas by these parameters F24 (4.5% CA) had the best results, with high FE (70%), low FLS (40%), high FVS (23.5%) and good GF (35 mL).

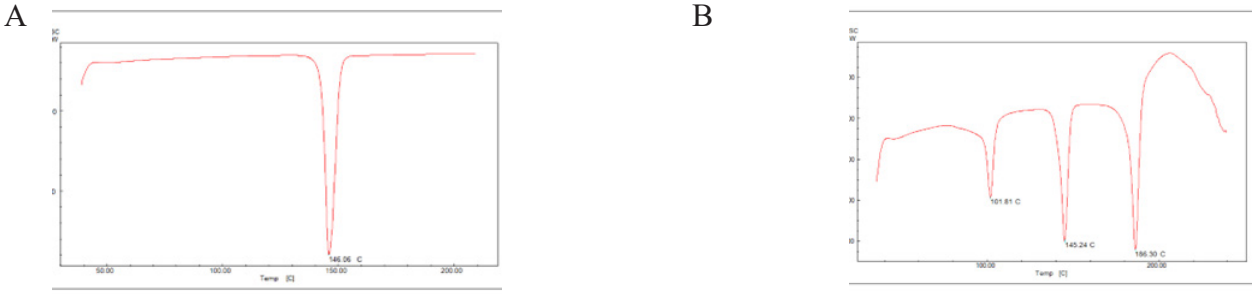


Figure 1: The DSC thermogram of CLT (A) and CLT with SLS (B).

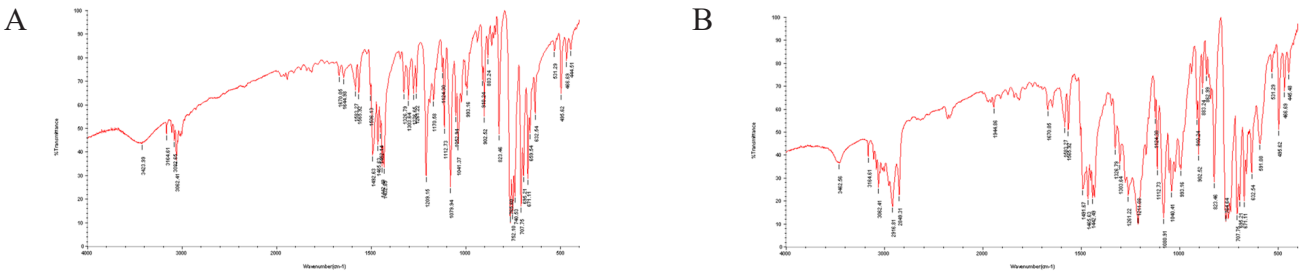


Figure 2: FTIR spectrum of CLT (A) and physical mixture of CLT and SLS (B).

corresponding to the melting point of the crystalline form of the drug[24] as shown in Figure 1A and complied with reference, the DSC of solid formula components showed three peaks as showed in Figures 1B one peak for CLT (145.24°C) and the two other peaks for the SLS 101.8 and 186.3°C.

FTIR and Drug-excipients Compatibility Studies

The FTIR of CLT displayed distinctive peaks of CLT at 3062.41 cm^{-1} (Aromatic C-H Stretching), 1583.27 cm^{-1} (Aromatic C=C stretching), 1565.92 cm^{-1} (C=N stretching), 1079.94 cm^{-1} (C-N stretching) and 1052.94 cm^{-1}(C-N stretching), and 765.60 cm^{-1} (Aromatic C-H bending), which comply with the literature.[25] The FTIR spectrum of the physical mixture of CLT and SLS showed the same bands of CLT in same positions (Figure 2).

CONCLUSION

The main parameters affecting foam stability are the concentration of surfactant and the percent of cetyl alcohol present, cetyl alcohol stabilized the foam but a certain limit,

above which the foam turned into a thick un-sprayable cream.

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