Research Article

Effect of the Emulsifier Polymers and the Concentration of Drug on the Viscosity and Antifungal Activity of Clotrimazole Cream

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Abstract

The preparation of emulsions without heating is an ideal production process for the heat-sensitive ingredients and energy saving. This study investigated the utilization feasibility of emulsifying polymers in cream base prepared without heating for clotrimazole**.** A stable and acceptable cream base readily for mixing with clotrimazole was prepared at room temperature using isopropyl isostearate as an oil phase, emulsifying polymer as an emulsifier, concentrated paraben as a preservative, polyethylene glycol 400 as a solubilizer and distilled water as a water phase at a ratio of 15:3:1:5:75, respectively. Clotrimazole creams comprising emulsifying polymer were evaluated for their viscosity and pH. The evaluations were also performed on the drug release using Franz diffusion cells and the inhibition of *Candida albicans* using agar diffusion method compared with a commercial product. The drug loading and the viscosity of cream influenced the drug release and the antifungal activity of this developed clotrimazole cream. The types of emulsifying polymer also affected the drug release but not the antifungal activity. The drug release and antifungal activity of this clotrimazole cream were not significantly different from Canesten® cream. There was a possibility to prepare clotrimazole cream without heating using the emulsifying polymer.

Key Words: Cream; Clotrimazole; Emulsifying Polymer

Introduction

Emulsifying polymer is a polymer based on hydro-swelling droplets polymer technology which is classified as a gelling and thickening agent (Anchisi, 2001). Oil, acrylate-acrylamide polymer, water and surfactant are the main components of this emulsifying polymer. This pre-neutralized polymer contains non-ionic surfactant catching around it and being dispersed in oil phase. By adding water, it is inverted and the polymer network expands instantly. Thereafter, the polymer forms a macromolecular network around each droplet of dispersed oil. Emulsifying polymer could be employed to create the gel-emulsions without heating and high energy supply based on principle of low energy emulsification. The advantage of the product prepared with this

polymer is its good stability because of cold processing, which is an ideal production process for the heat-sensitive ingredients. Additionally, it composes with a non-ionic emulsifying agent in formulation therefore it has been suggested as a non-irritant alternative to skin. While the conventional emulsion sometimes exhibited disadvantages for its instability, skin irritation from composition in formulation and time consuming for production. Emulsifying polymer has been widely used in many cosmetics. A component comprising a mixture of polyacrylamide, C13-14 isoparaffin and laureth-7 (Sepigel 305®) has been reported to be used for creams containing vegetable extracts from *Salvia officinalis*, *Centella asiatica* and *Calendula spp*. (Anchisi, 2001) and vitamins E and A (Thais et al., 2006). Emulsifying polymer is designed for all skin and hair care preparations, formulated as gels (Anna et al., 2006), cream gels (Anchisi, 2001), shampoo and after-sun product (Claude & Daniele, 1995). Type and amount of these emulsifying polymers or solvent and order of mixing notably affected viscosity of cream base as previous reported by our research group (Juntawong et al., 2009). However, there was no scientific publication on the research of using emulsifying polymers in pharmaceuticals.

Superficial fungal infections caused by dermatophytes, yeasts and nondermatophyte molds are among the most common skin diseases affecting in both healthy and immunocompromised persons (Cohn, 1992; Gupta et al., 2006). Typically, the topical antifungal treatments often have a broad spectrum of action on dermatophytes and yeast. Clotrimazole [1-[(2-chlorophenyl) diphenyl methyl]-1-H-imidazole] is a lipophilic drug with an antimycotic action that is used both locally and systemically (Ahmed & Gibaly, 1998). It is an odorless, white to pale yellow, crystalline powder. It is practically insoluble in water, but freely soluble in alcohol and soluble in polyethylene glycol 400. It is active against dermatophytes, yeasts, dimorphic fungi, and bacteria (Borgers, 1980; Shadomy, 1971). Its antimycotic effect is due to the inhibition of ergosterol synthesis and the promotion of the fungal plasma membrane leakage (Burgess and Bodey, 1972; Ritter et al., 1982). Several dosage forms of this drug were prepared and used in topical (Souto et al., 2004), oral (Pandey et al., 2005), esophagal (Janet et al, 1986) and vaginal candidiasis (Abdel-Moety, 2002). Clotrimazole has been reported to use as an active compound in solid lipid nanoparticle (Souto et al., 2004), complex with cyclodextrin (Ahmed et al., 1998), liposome (Zeljka et al., 2005), and mucoadhesive gel (Chang et al., 2002). Clotrimazole cream has been used in the management of skin mycoses. However, clotrimazole has not yet been reported to be used as active compound in cream prepared from emulsifying polymer.

The aim of this work was to investigate the effect of the emulsifier polymers and the concentration of drug on the viscosity and antifungal activity of clotrimazole cream prepared without heating. The commercial 1% w/w clotrimazole cream (Canesten® cream) was used for comparison.

Materials and Methods

Materials

Clotrimazole (ctz) (batch no. 20001304, Lambrochem, Italy) and Canesten® cream (batch no. 6B23, Bayer Thai Co., Ltd., Bangkok, Thailand) were used as received. Sepiplus 265® (Se 265) (Ammonium acrylate/Acrylamide copolymer & Polyisobutene & Polysorbate 20) (batch no. T44031), Sepigel 305® (Sg 305)(Polyacrylamide + C13-14 Isoparaffin + Laureth-7) (batch no. T52135), Sepiplus 400® (Se 400)(Polyacrylate & Polyisobutene & Polysorbate 20) (batch no. T43131), Simulgel EG® (Si EG)(Sodium acrylate / Sodium acryloyidimethyl taurate + Isododecane + Polysorbate 80) (batch no. T51411), Simulgel NSÒ (Si NS) (Hydroxyethylacrylate / Sodium acryloyidimethyl taurate copolymer & squalane & Polysorbate 60) (batch no. 32631) were purchased

from Seppic, Paris, France. Isopropyl isostearate (Prisorine 2021®) (batch no. 1129023, Uniqema, U.K.), methyl hydroxyl benzoate (MP) (batch no. A16/18), propyl hydroxyl benzoate (PP) (batch no.000130), polyethylene glycol 400 (PEG 400) (batch no.P077241) and propylene glycol were supplied by P.C. Drug Center Co., Ltd., Thailand. Cellulose acetate membrane with a pore size of 0.45 mm (Whatman®, Brentford, English), and methanol (HPLC grade) (batch no. 0605570, VWR International, EC) were used as received. Potassium hydrogen orthophosphate (batch no. AF501340), sodium hydrogen orthophosphate (batch no. AF405300) and citric acid (batch no. AF411021) were purchased from Ajax chemicals, Australia. Syringe filter 13 mm disposable filter device and nylon filter with a pore size of 0.45 mm (Lot no.L231 Whatman®, Brentford, English) were used as received. Sabouraud dextrose agar (batch no. 6166081), sabouraud dextrose broth (SDB) (batch no. 6345690), tryptic soy agar (TSA) (batch no. 7341698) and tryptic soy broth (batch no. 1121004) were purchased from Becton, Dickinson and company, France.

Methods

Preparation of ctz cream

The component of cream base is shown in Table 1. An oil phase (phase A: isopropyl isostearate (Prisorine® 2021)) and an aqueous phase (phase B: water and emulsifying polymer) were weighed into separate container. Five emulsifying polymers were used in this study as following: Sepiplus 265® (Se 265), Sepigel 305® (Sg 305), Sepiplus 400® (Se 400), Simulgel EG® (Si EG), Simulgel NS® (Si NS). Phase A was gradually added to phase B (A to B) at room temperature with glass stirrer to form the emulsion. Finally, the remaining ingredients of phase C (concentrated paraben solution containing 1:10 PP:MP in propylene glycol) and/or drug were added to the bulk. The emulsion was mixed until it was homogenous. The ctz dissolved in PEG (at amount of 5% w/w of formula) was gradually mixed with the cream base. The effect of type of emulsifying polymers and drug loading were investigated. To investigate effect of drug loading on physical properties, drug release and antifungal activity, the selected cream base loaded with 0.125-3 % w/w ctz was prepared and evaluated.

Table 1 Composition of the cream base

Composition	% w/w
Emulsifying polymer	3
Isopropyl isostearate	15
Paraben concentrated solution	1
PEG 400	5
Water	q.s.

Study of physical properties

The physical appearance of prepared creams was visually observed. The viscosity of formula was measured using brookfield helipath viscometer (Model: DV-I, Brookfield Engineering Laboratories, INC., USA) at room temperature with constant shear rate for 5 min. The pH of formula was measured using a pH meter (Professional Meter PP-15 Sartorius, Goettingen, Germany). All measurements were performed at room temperature in triplicate for each sample. The physical stability of prepared creams was also tested after 6 cycles temperature cycling. For one cycle, all formulations were kept at 4° C for 24 h in the refrigerator and then at 40°C for 24 h in the hot air oven (FED 720, Scientific promotion, Bangkok, Thailand). Viscosity alteration and phase separation were used to indicate the physical stability. The criteria of selection included a good appearance with a homogeneous, smooth, white creamy texture without the phase separation or without the high viscosity change after temperature cycling.

Drug release study

A. *In vitro* release study

The Franz® diffusion cells were used for the drug release study comprising the donor compartment with 2.1 cm diameter orifice and the receptor phase was stirred by a constantly spinning magnetic bar at 100 rpm. Since ctz was slightly soluble in water, a mixture of 0.1 M citrate-phosphate buffer pH 5.5: ethanol at a ratio of 1:1 at 37 ± 0.5°C was used as receptor solution. The receptor compartment was filled with 15 mL of receptor solution. The membrane used in this study was cellulose acetate membrane with a pore size of 0.45 mm. One gram of cream was added into the donor compartment. Cellulose acetate membrane was previously soaked with the receptor solution for 30 min to obtain the equilibrium with this medium. Then it was placed between the donor and receptor compartments. At appropriate time intervals (1, 2, 3, 4, 6, 8, 12 and 24 h), 1 mL of receptor solution was withdrawn. The amount of drug released was measured using HPLC. The volume of sample solution removed was replaced with an equal volume of fresh receptor solution. The extract amounts of ctz released at each time interval were calculated using a calibration curve. All of the experiments were performed triplicate, and the mean release rate ± S.D. was calculated. The release rate through membrane was calculated by plotting the cumulative amount of drug per area against the square root of time. The slope of linear portion of the curve and the X-intercept values were determined by linear regression analysis.

B. Determination of ctz

Chromatographic separation was carried out at ambient temperature on a LiChrospher® 100 (125, 4 mm) C_{18}, 5 mm. The compounds were separated with a mobile phase consisting of a mixture of methanol: dibasic potassium phosphate buffer pH 6.5 (3:2). The pH of the binary solvent mixture was finally adjusted to 4.0 with *o*-phosphoric acid. The mobile phase was filtered through 0.45 mm membrane filter and degassed for approximately 15 min in the sonicator bath prior to use. The flow rate was 1 mL/min. An injection volume was 20 mL, and eluted analyses for ctz were traced by UV-detection at 254 nm. The ctz cream containing 10 mg of ctz was extracted with mobile phase about 50 mL by warming at 50°C using water bath and occasionally shaking until it was completely dissolved and was then removed from the bath, shaken vigorously for 5 min. Afterward, the extractive was cooled in an ice bath for 15 min, and filtered through filter paper into a 100 mL volumetric flask. The volume was finally adjusted to 100 ml with the mobile phase. The acceptable percentage of recovery from the true value was within 90 to 110 %.

Antifungal activity test

Antifungal activity against *Candida albicans* (*C. albicans*) ATCC 17110 of prepared creams was determined using agar cup diffusion method. An isolated colony of *C. albicans* from sabouraud dextrose agar (SDA) was inoculated into sabouraud dextrose broth (SDB) and incubated at 37°C for 24 h. An amount of culture was obtained by comparing the culture turbidity to standard 0.5 M MacFarland (Lorian, 1991). The adjusted culture was spread over the SDA by a sterile cotton swab. Sterilized cylinder cups were placed carefully on the surface of the swabbed agar. The ctz cream was filled into a cylinder cup. Each plate was placed with cylinders containing the cream with varying concentrations of ctz (0.125, 0.25, 0.5, 1 and 3 %) in selected cream base incubated at 37 °C for 72 h. The 1% ctz in PEG 400 was also tested as a control group since this drug dissolves completely in this solvent. For studying the effect of cream base, the various types of emulsifying polymers with 1% ctz were also used since the commercial cream contains 1%w/w of ctz. The cylinders were then removed and antifungal activity was measured as the diameter (mm) of clear zone. The tests were carried in triplicate and the mean inhibition zone ± S.D. were calculated.

Data evaluation

A significance of the differences between the viscosity, the drug release rate constant and the inhibition zone (where $p < 0.05$) of the prepared cream and Canesten® cream was analyzed using ANOVA and pair *t*-test from SPSS for window version 11.0. Each data point represents an average of three determinations.

Results and Discussion

Physical properties of drug-loaded creams

The most stable and elegant cream base included isopropyl isostearate as an oil phase, emulsifying polymers, PEG 400 (5%w/w) as a solubilizer, paraben concentrated solution as a preservative and distilled water as a water phase at a ratio of 15:3:5:1:75. PEG 400 at the amount of 5 % (w/w) was selected as a solvent to dissolve the drug because ctz can dissolve in PEG 400 (AHFs Drug information, 2005). The viscosities of the prepared ctz creams were in the range of 176,889 ± 4,682 to 260,889 ± 5,048 cps (Figure 1). The viscosity of 1 %ctz cream prepared using different emulsifying polymers could be ranked in the following descending order: ctz 1% (Si 265) > ctz 1% (Se 400) > ctz 1% (Si EG) > ctz 1% (Sg 305) > ctz 1% (Si NS). The rank order for the viscosity of ctz cream prepared using different drug loading was ctz 0.125 % cream > ctz 0.25 % cream > ctz 0.5% cream > ctz 1 % cream > ctz 3 % cream (Figure 2). The viscosity of creams was not significantly different as the drug concentration was increased. It was probably due to the low drug content and the limit of drug solubility at high drug loading therefore the dispersed drug slightly influenced the cream viscosity. The viscosity of the formulation was varied depending on the types of emulsifying polymer. The pH of all prepared creams was in the range of 6.30 ± 0.08 to 7.40 ± 0.04 (Tables 2 and 3) which was not different from the acceptable cream base (Mehling, 2007). The viscosity of all cream bases after 6 cycles of temperature cycling was not significantly different ($p > 0.05$) from freshly prepared cream base. All cream bases before and after 6 cycles of temperature cycling presented a good appearance with homogeneous texture and smoothness and there was no phase separation or color change. The translucent characteristic of the above formula could be ranked in the following descending order: ctz 1% (Si EG), ctz 1% (Si NS), ctz 1% (Sg 305) > ctz 1% (Se 400) and ctz 1% (Se 265). The viscosity value of all creams after 6 cycles of temperature cycling was not significantly different ($p>0.05$) from freshly ctz cream.

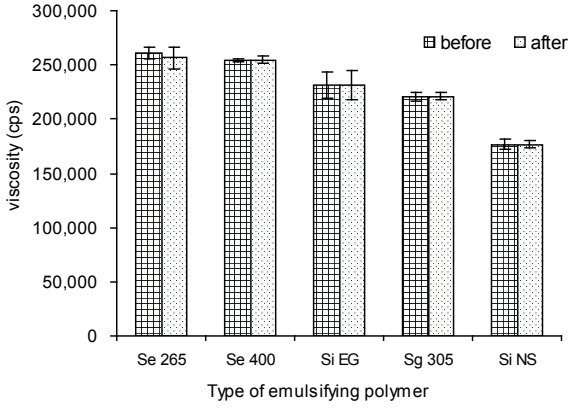
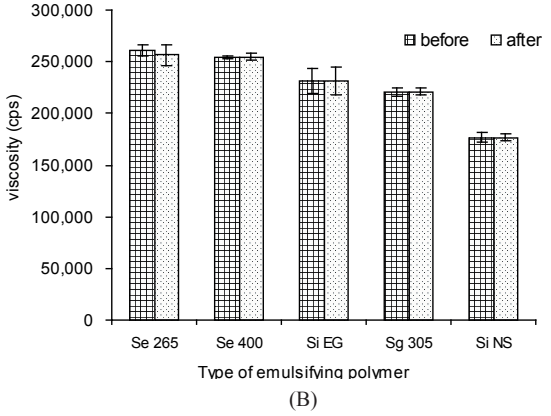


Figure 1 The viscosity of ctz cream prepared using different emulsifying polymers both before and after temperature cycling (n=3)



(B)

Figure 2 The viscosity of ctz cream containing different concentration of ctz before and after temperature cycling (n=3)

Table 2 pH Value of 1 % ctz creams prepared with different emulsifying polymers (n=3)

Types of emulsifying polymer	pH ± S.D.	
	Freshly prepared	After temperature cycling
Se 265	7.40 ± 0.04	7.32 ± 0.07
Se 400	7.34 ± 0.15	7.32 ± 0.12
Si EG	6.39 ± 0.14	6.36 ± 0.10
Sg 305	6.44 ± 0.09	6.44 ± 0.07
Si NS	6.35 ± 0.25	6.30 ± 0.08

Table 3 pH Value of creams prepared with Se 265 containing different amount of ctz (n=3)

ctz (%w/w)	pH ± S.D.	
	Freshly prepared	After temperature cycling
0.125 %	7.33 ± 0.02	7.32 ± 0.02
0.25 %	7.35 ± 0.10	7.34 ± 0.08
0.5 %	7.34 ± 0.10	7.36 ± 0.05
1%	7.33 ± 0.03	7.36 ± 0.03
3%	7.32 ± 0.08	7.30 ± 0.04

Drug release from creams

Effect of emulsifying polymer types on drug release

The release of ctz from cream bases containing different emulsifying polymers is shown in Figure 3. The rank order of release of ctz cream prepared by using different emulsifying polymers was Si NS > Se 305 > Si EG > Se 400 > Se 265. The effect of different emulsifying polymers among Se 265, Se 400, Si NS, Si EG, Si 305 on the release rate was significantly different ($p<0.05$) (Table 4). The types of emulsifying polymer affected

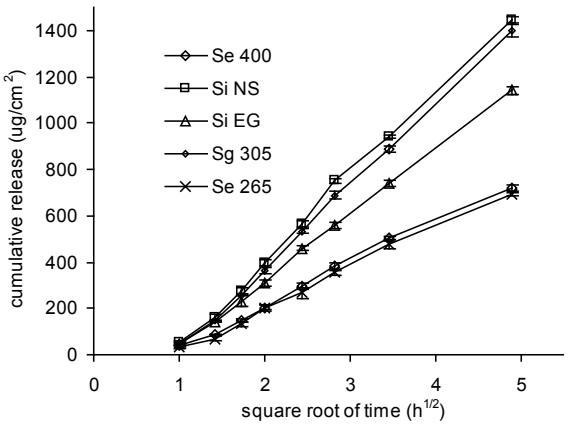


Figure 3 Release profiles of ctz cream prepared using different emulsifying polymers (n=3)

the drug release from cream base. The variation in amount and types of acrylate polymer, oil, and the surfactant incorporation in the emulsifying polymers could probably influence the viscosity of the prepared dosage forms. Generally, the greater the viscosity of the formulation, the lower the release of drug (Chowdary and Kumar, 1994; Tehrani and Mehramizi, 2000; Salamon et al., 1979; Lindner and Lippold, 1995; Kim and Fassihi, 1997; Reynolds et al., 1998). The viscosity of cream base prepared using the different emulsifying polymers was ranked as followed: Se 265 > Se 400 > Si EG > Se 305 > Si NS. The release rate of ctz cream with emulsifier as Se 265, Se 400, Si EG, Se 305 or Si NS was 176.38, 182.27, 285.34, 353.69, or 365.63 mg/cm^2/h$^{1/2}$, respectively. Therefore, the higher viscosity of the emulsion system retarded the drug release. The utilization of emulsifying polymer led to the formation of a dense polymer matrix structure, resulting in smaller pores and a more tortuous structure. Thereafter, the diffusion of incorporated drug through the network was difficult. The lag times of drug release from creams containing different types of emulsifying polymers showed no significant difference ($p>0.05$).

Table 4 Estimate parameters from cure fitting with Higuchi's equation of drug release from different cream bases and different drug concentration (n=3)

Formula	Correlation Coefficient (r^2)	Release rate ($ug/cm^2/h^{1/2}$)	lag time (h)
		Mean±S.D.	Mean±S.D.
Canesten® cream	0.9951	177.56±4.21	0.67±0.06
1 % ctz (Se 265)	0.9945	176.38±2.27	0.80±0.05
1 % ctz (Se 400)	0.9940	182.27±2.80	0.71±0.03
1 % ctz (Si EG)	0.9993	285.34±4.25	0.78±0.04
1 % ctz (Si NS)	0.9971	365.63±4.61	0.81±0.05
1 % ctz (Sg 305)	0.9985	353.69±5.06	0.89±0.04
0.125% ctz cream*	0.9976	46.25±1.63	0.32±0.07
0.25% ctz cream*	0.9974	65.13±2.04	0.27±0.03
0.5% ctz cream*	0.9971	166.39±0.96	0.72±0.03
1% ctz cream *	0.9944	174.66±1.04	0.68±0.10
3% ctz cream*	0.9946	185.01±1.93	0.56±0.07

*cream base containing 3% Se 265 as an emulsifier, 15 % isopropyl isostearate as an oil, 1% paraben conc. solution, 5% PEG400 and distilled water.

Effect of drug loading on drug release

By comparison at the same concentration, Se 265 provided cream which showed the highest viscous and stable therefore this emulsifying polymer was selected to prepare the cream base loaded with different amount of ctz. The drug release was increased depending on drug concentration in the cream (Figure 4). The release rate was enhanced as a drug concentration was increased. The release rate of cream containing different drug loading was significantly different ($p<0.05$). The similar result was also reported by Yan-Fei et al. (2007). Increased release rate with an increment of a loading dose might be due to an increase in thermodynamic activity of the drug, which is related to its concentration in the cream base (Vlachou et al, 1992).

In vitro drug release studies of creams containing ctz demonstrated a prolonged release characteristic following Higuchi's model (Higuchi, 1962) with a correlation coefficient ranging from 0.9940 to 0.9993 (Table 4), which signified an excellent model fit. This finding indicated that the rate-controlling stage in the release process was the diffusion of the dissolved drug through the polymeric network of the external medium. Thus, the drug release increased linearly along the increasing concentration until it reached the same limiting value which was the value of the saturated solution. However, the *in vitro* release results obtained under artificial stirring conditions and buffer medium might not directly mimic the *in vivo* situation. The *in vitro* release results, however,

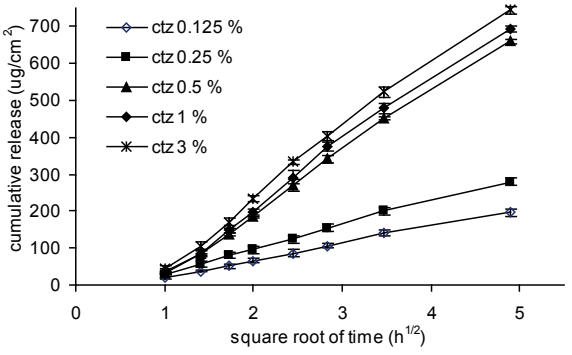


Figure 4 Release profiles of ctz creams prepared with Se 265 containing different amount of drug (n=3)

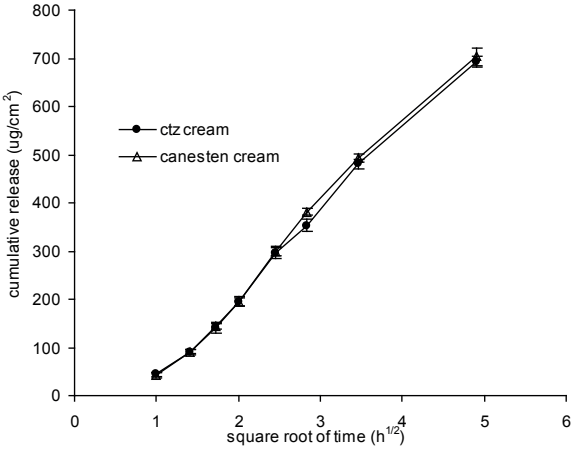


Figure 5 Release profiles of ctz from developed clotrimazole cream prepared with Se 265 and Canesten® cream (n=3)

provided information of the release rate of ctz from cream base. Only about 40 % of drug content was released from Franz diffusion cell at 24 hour, the rest might be hold by emulsifying polymer or absorbed on membrane (Shantha and Harding, 2003).

Comparison of drug release from Canesten® cream and prepared ctz cream

The release of ctz from Canesten® cream and selected ctz cream was investigated. The release pattern of ctz from prepared cream (1% ctz cream prepared using 3% Sepiplus 265® as an emulsifier, 1% paraben concentrated solution and 15 % isopropyl isostearate as an oil) resembled that of commercial ctz cream (Canesten® cream) as shown in Figure 5. The release rate (Table 4) of Canesten® cream and ctz cream was insignificantly different ($p>0.05$). Therefore, the release of drug from prepared cream was similar to a commercial ctz cream (Canesten® cream). The lag time of drug release from prepared cream and Canesten® cream showed no significant difference ($p>0.05$).

Antifungal activity test

Effect of emulsifying polymer types on antifungal activity

The antifungal activity of ctz creams prepared using different emulsifying polymers is shown in Table 5. The cream bases did not exhibit the inhibition of *C. albicans* growth (data not shown). Antifungal activities of all 1 % ctz creams prepared using different emulsifying polymers were insignificantly different ($p<0.05$). However, they were significantly different ($p<0.05$) from 1 % ctz solution prepared in PEG 400. This result was not corresponding to the *in vitro* drug release. Therefore the antifungal activity depended on the drug concentration whereas the type of emulsifying polymer did not play important role on this activity.

Table 5 Inhibition diameter (mm) of 1% ctz cream containing different emulsifying polymers (n=3)

Type of emulsifying polymer	Inhibition diameter ± S.D. (mm)
Si NS	16.4 ± 0.5
Sg 305	16.0 ± 0.5
Si EG	16.1 ± 0.9
Se 265	15.2 ± 0.8
Se 400	15.3 ± 0.7
1 % ctz solution*	32.0 ±1.0

*1 % ctz solution prepared in PEG 400

Effect of drug loading on antifungal activity

The antifungal activity of cream containing different amount of ctz against *C. albicans* is shown in Table 6. Increasing the amount of ctz from 0.125-0.50 % tended to enhance the antifungal activity of ctz cream. Due to the limit of ctz solubility in this cream base the drug loading higher than 0.5% did not apparently increased the antifungal activity. The inhibition clear zone of creams containing 0.5-3% ctz was significantly wider ($p<0.05$) from those containing 0.125-0.25% ctz. The greater the drug content, the wider the inhibition zone. In comparison between the different concentrations of ctz cream and 1% ctz solution, the cream 0.5-3 % ctz showed the significantly lower antifungal activity than the solution.

Antifungal activity of Canesten® cream and ctz cream

The antifungal activity of ctz cream prepared using 1 % w/w ctz, 3% w/w Sepiplus 265®, 1% paraben concentrated solution and 15% w/w isopropyl isostearate is shown in Table 7. The inhibition zone of ctz cream was not significantly different ($p>0.05$) from Canesten® cream which was corresponded to their *in vitro* release results. It was suggested that the antifungal activity against *C. albicans* of the Canesten® cream and prepared cream was not different.

Table 6 Inhibition diameter (mm) of ctz creams containing different amount of ctz (n=3)

Clotrimazole	Inhibition diameter ± S.D. (mm)
0.00%	0.0 ± 0.0
0.125 %	10.9 ± 0.7
0.25 %	11.7 ± 0.3
0.5 %	16.4 ± 0.2
1 %	16.5 ± 0.5
3 %	17.2 ± 0.3
1 % ctz solution*	32.0 ±1.0

* 1 % ctz solution prepared in PEG 400

Table 7 Inhibition zone diameter (mm) of ctz cream and Canesten® cream (n=3)

Type of cream	Inhibition diameter ± S.D. (mm)
Canesten® cream	15.1 ± 0.4
1% ctz cream	14.9 ± 0.2

Conclusion

The ctz cream could be prepared without heating using the emulsifying polymer. The most stable and elegant cream base included isopropyl isostearate as an oil, ammonium acrylate/acrylamide copolymer & polyisobutene & polysorbate 20 (Se 265) as an emulsifier, paraben concentrate as a preservative, PEG 400 (5%w/w) as a solubilizer and distilled water as a water phase at a ratio of 15:3:1:5:75. The formulation was shown to have a highly effective antifungal activity. From this investigation, the emulsifying polymer could be considered as choice materials in preparation of cream base for ctz.

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