ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Clotrimazole Soft Lozenges Fabricated with Melting and Mold Technique

Phaechamud T[1*] and Tuntarawongsa S[1]

Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Nakorn Pathom 73000, Thailand.

ABSTRACT

Polyethylene glycol (PEG) has potentially been utilized as a matrix component prepared with fusion and mold method as a inert carrier to improve the solubility of an poorly water-soluble drugs. The clotrimazole soft lozenges were prepared and investigated the factors affecting physical properties of soft lozenges base; PEG, polymer, glycerine, sweetener, talcum, flavouring and colouring agents. The hardness was increased as the amount of PEG1500, xanthan gum or xylitol was increased. The disintegration time was increased as the amount of clotrimazole or hardness was increased. The system comprising 9:1 PEG1500:glycerin, 15% w/w talcum, 15% w/w xanthan gum, 15% w/w xylitol, 0.12% w/w saccharin sodium, 2% w/w citric acid, 1.67% w/w orange oil and 0.0067% w/w sunset yellow FCF No.2 was the suitable carrier for clotrimazole. The antifungal activity against *Candida albicans* was tested by agar diffusion method. The developed clotrimazole soft lozenge exhibited the antifungal activity similar to the positive control (Candinas®) ensured that the developed clotrimazole soft lozenges has potential to be used as antifungal dosage form.

Keywords: Soft lozenges, clotrimazole, mold tablet, polyethylene glycol

Corresponding author
Email:thawatchaienator@gmail.com

ISSN: 0975-8585

INTRODUCTION

For poorly water-soluble drugs, solubility is a major factor affecting the drug bioavailability. Therefore many efforts were investigated to solve the solubility problem of the poorly water-soluble drugs. Solid dispersion (SD) is one of dosage forms that capable to increase solubility of the incorporated drug. The inert carrier in the solid state could be prepared by melting, dissolution in a solvent, or melting solvent method to increase the apparent solubility or enhance the bioavailability of poorly water-soluble compounds [1, 2]. The solid polyethylene glycols (PEGs) have been employed as drug carriers and have potentially been utilized as a matrix component prepared with fusion and mold method [3-7]. Mold tablets prepared using molten PEG combined with hydroxypropyl methylcellulose or xanthan gum as main components both to enhance the solubility and to prolong release the hydrophobic drug have been reported previously [8,9].

Clotrimazole is a hydrophobic broad-spectrum antifungal agent used both locally and systemically [10]. Clotrimazole, [1-[(2-chlorophenyl) diphenyl methyl]-1-H-imidazole] is an odorless, white to pale yellow, crystalline powder and is practically insoluble in water, freely soluble in alcohol and soluble in polyethylene glycol 400. It is active against dermatophytes, dimorphic fungi, yeasts and antibacteria due to the inhibition of ergosterol synthesis and promotion of the plasma membrane of fungi leaky [11, 12]. Clotrimazole lozenge is indicated for the local treatment of oropharyngeal candidiasis. Because this drug can be soluble in PEG it is interesting to use as model drug for development into lozenge prepared with melting and mold technique. The aim of this study is to develop the clotrimazole soft lozenges in the form of SD tablets prepared with melting and mold technique. Effect of molecular weight of PEG and amount of other ingredient (glycerin, sweetener, talcum and xanthan gum) on physical properties of the developed clotrimazole lozenges were investigated.

MATERAILS AND METHODS

Materials

Clotrimazole tablets (Candinas® 5,10 and 20 mg/tablet)(Thai-Japan Company, Bangkok, Thailand) were kindly supported from Department of Pharmacy, Huayplu hospital, Nakhon Pathom, Thailand. PEG4000 (lot no. 504907), PEG1500 (lot no. 504909) and PEG400 (lot no. PO76049), acacia, glycerin, sucrose, xylitol, monopotassium phosphate and sodium phosphate were purchased from P. C. Drug Center Co., Ltd., Bangkok, Thailand. Xanthan gum (Xantural 75® , lot no. 01-100, CP Kelco US., Inc. USA.). Hydroxypropyl methylcellulose (HPMC) type K 15 M, lot no. PH26012N31, (Dow Chemical, Michigan, USA.) and sodium chloride (lot no. AF 407256, Ajax Finechem, Australia) were used as received.

Methods

Preparation and Evaluation of Soft Lozenges Base

ISSN: 0975-8585

Preparation of Soft Lozenges

Soft lozenges were prepared by melting and mold technique as described previously[8]. PEG was melted on water bath and mixed with the other ingredients to form a homogeneous mixture. Subsequently, the mixture was poured into the stainless steel mold which size of each mold of tablet was 12 mm diameter and 6.8 mm height as shown in Fig. 1.

Study of Physical Properties

Hardness of the soft lozenges were determined using a hardness tester (Pharmatest, Ontario, Canada)(n=10). Thickness and diameter of the soft lozenges were measured using a thickness tester (Teclock, Kyoto, Japan)(n=10). Weight variation was evaluated using analytical balance (Sartorius)(n=20). Disintegration time was measured using disintegration apparatus. 500 ml artificial saliva was used as a disintegration medium and temperature was keep constant at 37$\pm$2^{o}C (n=6).

Study of Antifungal Activity

The antifungal activity was investigated using agar diffusion method. *Candida albicans* ATCC 17110 was used as a pathogen model. The test was performed by incubating *C.albicans* in sabourad dextrose broth at 35-37^{o}C for 18-24 hours then diluted the inoculate as the same concentration as Mcfarland No.0.5 and swab on sabourad dextrose agar. The developed clotrimazole soft lozenges were placed on and incubated for 72 hours at 37^{o}C. Commercial clotrimazole tablet (Candinas® 5,10 and 20 mg/tablet) and placebo soft lozenge were used as positive and negative controls, respectively. The clear zone was measured and used to indicate the antifungal activity (n=3).

Factors Affecting Physical Properties of Soft Lozenges Base Formulation

Effect of Sweetener

PEG 4000:400 with a ratio 7:3 was used as a basic soft lozenges base. The soft lozenges base were prepared by melting PEG 4000 on the water bath then mixed with PEG 400 and 20% w/w sucrose or 20% w/w xylitol, respectively to form a homogeneous mixtures and then the mixtures were poured into the stainless steel mold. The study of the physical properties of prepared lozenges was conducted as mentioned previously.

Effect of PEG and Polymers

PEG 1500:glycerin with a ratio 7:3 were also used as a basic soft lozenges base and polymer using in each formulation was 10% w/w acacia, xanthan gum or HPMC. The soft lozenges base were prepared by melting PEG 1500 on the water bath and mixed with polymer and glycerin, respectively until a homogeneous mixtures was formed then the mixtures were poured into the stainless steel mold. Physical properties of prepared lozenges were investigated.

Effect of Glycerin Content

Ratio of PEG 1500 and glycerin was varied as 7:3, 8:2, 9:1 and 9.5:0.5. 10 % w/w xanthan gum was used as polymer. The soft lozenge base were prepared and then the mixtures were poured into the stainless steel mold. Physical properties of prepared lozenges were investigated.

Effect of Talcum Content

PEG 1500:glycerin (9:1) and 10 % w/w xanthan gum were used as soft lozenges base and amount of talcum was varied as 1, 5, 10 and 15 % w/w. The soft lozenges bases were prepared by melting PEG 1500 on the water bath and mixed with xanthan gum, talcum and glycerin, respectively, and then the mixtures were poured into the stainless steel mold. Physical properties of prepared lozenges were investigated.

Effect of Xanthan Gum Content

PEG 1500 : glycerin (9:1) and 15 % w/w talcum were used as soft lozenges base and amount of xanthan gum was varied as 10, 15 and 20 % w/w. The soft lozenges bases were prepared and then the mixtures were poured into the stainless steel mold. Physical properties of prepared lozenges were investigated.

Effect of Xylitol Content

PEG 1500:glycerin (9:1), 15 % w/w talcum and 15 % w/w xanthan gum were used as soft lozenges base and amount of xylitol was varied as 10, 15 and 20 % w/w. The soft lozenges base were prepared by melting PEG 1500 on the water bath and mixed with xanthan gum, talcum, glycerin and xylitol, respectively, and then the mixtures were poured into the stainless steel mold. Physical properties of prepared lozenges were investigated.

Physical Properties and Antifungal Activity

PEG 1500 : glycerin (9:1), 15% w/w talcum, 15% w/w xanthan gum, 15% w/w xylitol, 0.12% w/w saccharin sodium, 2% w/w citric acid, 1.67% w/w orange oil and 0.0067% w/w sunset yellow FCF No.2 were used as soft lozenges base. The amount of clotrimazole in each formulation was varied as 5, 10 and 20 mg/lozenge. The soft lozenges base were prepared by melting PEG 1500 on the water bath and mixed with xanthan gum, talcum, glycerin, xylitol, saccharin sodium and citric acid, respectively. When temperature of mixture was dropped to 40-45 ^{o}C, clotrimazole, orange oil and sunset yellow FCF No. 2 were added and then the homogeneous mixtures were poured into the stainless steel mold. The study of the physical properties of medicated lozenges was conducted as mentioned previously.

ISSN: 0975-8585

RESULTS AND DISCUSSION

Factors Affecting Physical Properties of Soft Lozenges Base

The soft lozenges prepared with the melting and mold technique has been previously reported that the system comprising ratio 7:3 PEG4000:PEG400 was the most suitable for use as carrier since it could be formed into tablet with easily removed from the mold [8,9]. In this study, factors affecting physical properties were investigated. The sweeteners used in this study were sucrose and xylitol. In melting process sucrose was changed to brown colour, some was recrystalize and appeared as a white dot on tablets surface. On the other hand, the soft lozenge comprising xylitol exhibited a better appearance than that using sucrose but the hardness and disintegration time was less than that using sucrose due to xylitol was less crytallinity than sucrose (Table 1).

Since the desired hardness could not be obtained form this formula, the soft lozenge base was changed to 7:3 PEG1500: glycerin containing different polymer. The only one system that could be molded into a tablet was the system comprising 7:3 PEG1500: glycerin and 10 % w/w xanthan gum. Hardness and disintegration time of this system was higher than that of 7:3 PEG4000:PEG400 system due to a more rigidity of the tablet (hardness, 24.15$\pm$ 6.11 N; DT 16.00 $\pm$ 1.11 min). Other systems comprising other polymers (10% w/w acacia and HPMC) were too soft and sticky and could be not completely removed from the mold.

The hardness of the soft lozenges base was improved by adjusting the PEG1500: glycerin ratio. The hardness of lozenge was increased as the amount of PEG1500 was increased whereas disintegration time of the system was decreased as the amount of PEG1500 was increased (Table 2).

The system comprising PEG1500: glycerin (9:1) was chosen as a suitable carrier since the desired hardness could be obtained. However the difficult removal from the mold was found thus talcum was attempted to add into the system as an anti-adherence agent. Plate-like talcum [13] can reduce the stickiness between lozenge and stainless steel mold. Amount of talcum had no significant effect on lozenge hardness. Whereas disintegration time tended to increase as the amount of talcum was increased owing to a hydrophobic property of talcum (Table 3).

To prolong the disintegration time, the different amounts of xanthan gum were added. An addition of xanthan gum increased disintegration time and hardness of the lozenges since xanthan gum could apparently enhance the viscosity of the lozenge matrix [9]. However the white dots were obtained on lozenges surface when 20% w/w xanthan gum was used which might be the residual of xanthan gum that not completely swelled (Table 4).

An addition of xylitol in the system comprising 9:1 PEG1500:glycerin, 15 % w/w talcum and 15 % w/w xanthan gum notably increased the hardness and disintegration time of the system which might be owing to the high crystallinity of xylitol. The white dot on

ISSN: 0975-8585

lozenges surface was obtained for the tablet containing 20% w/w xylitol which might be the undissolved xylitol in the system (Table 5).

The system that was selected as basic soft lozenge base contained 9:1 PEG 1500:glycerin, 15% w/w talcum, 15% w/w xanthan gum and 15% w/w xylitol. The taste, flavour and color of lozenges were improved by adding 0.12% w/w saccharin sodium, 2% w/w citric acid, 1.67% w/w orange oil and 0.0067% w/w sunset yellow FCF No.2. Clotrimazole was added into this lozenge base as an antifungal agent. The clotrimazole content did not significantly affect the hardness and disintegration time of the prepared lozenges (Table 6).

Table 1 Appearance, hardness and disintegration time of soft lozenges base comprising the different sweetener, sucrose and xylitol.

Sweetener	Appearance	Hardness (N)	Disintegration time (min)
Sucrose 20 % w/w	Brown and white dot	18.74 ± 2.37	6.55 ± 0.39
Xylitol 20 % w/w	White and smooth	14.35 ± 1.73	5.59 ± 0.21

Table 2 Appearance, hardness and disintegration time of soft lozenges base comprising the different ratio of PEG1500 and glycerin

PEG1500:glycerin	Appearance	Hardness (N)	Disintegration time (min)
7:3	White and smooth Little sticky	24.15 ± 6.11	16.00 ± 1.11
8:2	White and smooth Little sticky	24.89 ± 1.62	11.68 ± 1.33
9:1	White and smooth, but adhere to the mold	34.02 ± 4.81	6.36 ± 0.52
9.5:0.5	White and smooth, but adhere to the mold	32.62 ± 2.46	6.48 ± 1.30

Table 3 Appearance, hardness and disintegration time of soft lozenges base comprising different amount of talcum.

Talcum	Appearance	Hardness (N)	Disintegration time (min)
1	White and smooth, little sticky	34.16 ± 1.28	7.12 ± 0.39
5	White and smooth, not sticky, easily removed from the mold	33.46 ± 4.48	7.38 ± 0.99
10	White and smooth, not sticky, easily removed from the mold	35.71 ± 2.43	7.20 ± 0.67
15	White and smooth, not sticky, easily removed from the mold	35.23 ± 1.96	8.03 ± 2.23

ISSN: 0975-8585

The antifungal activity of developed clotrimazole soft lozenge was slightly less than a commercial clotrimazole tablet (Table 7). This might be due to the limited diffusion property of clotrimazole from developed lozenges. Solubility and diffusion rate into agar were the rate limiting step for antifungal action of this drug [10]. The placebo (soft lozenge base) had no antifungal activity.

Table 4 Appearance, hardness and disintegration time of soft lozenges base comprising the different amount of xanthan gum.

Xanthan gum (% w/w)	Appearance	Hardness (N)	Disintegration time (min)
10	White and smooth	35.23 ± 1.96	8.03 ± 2.23
15	White and smooth	59.38 ± 4.71	14.95 ± 2.26
20	White and smooth, white dots on lozenges surface were obtained.	58.44 ± 4.55	19.30 ± 0.78

Table 5 Appearance, hardness and disintegration time of soft lozenges base comprising the different amount of xylitol.

Xylitol (% w/w)	Appearance	Hardness (N)	Disintegration time (min)
10	White and smooth	53.83 ± 5.43	24.97 ± 1.46
15	White and smooth	63.77 ± 6.41	30.74 ± 3.64
20	White and smooth, white dots on lozenges surface were obtained.	77.02 ± 4.53	33.79 ± 3.56

Table 6 Physical properties of clotrimazole soft lozenges

Clotrimazole (mg/soft lozenge)	Appearance	Hardness (N)	Disintegration time (min)
5	Orange and smooth	32.79 ± 4.13	37.01 ± 7.27
10	Orange and smooth	32.79 ± 4.13	35.91 ± 2.15
20	Orange and smooth	30.04 ± 3.90	41.47 ± 4.79

Table 7 Clear zone of clotrimazole soft lozenges

Clotrimazole (mg/soft lozenge)	Clear zone (cm)		
	Developed lozenge	Candinas®	Placebo
5	4.13 ± 0.21	4.23 ± 0.15	0.00 ± 0.00
10	4.03 ± 0.35	4.33 ± 0.20	0.00 ± 0.00
20	3.90 ± 0.25	4.50 ± 0.18	0.00 ± 0.00

ISSN: 0975-8585

Figure 1. Stainless steel mold.

CONCLUSION

The soft lozenge prepared by mold technique has potential to improve the solubility of clotrimazole since it was dispersed in PEG system. Hardness of the lozenges was increased as the amount of PEG1500, xanthan gum or xylitol was increased. System comprising 9:1 PEG1500:glycerin as a basic base, 15% w/w talcum was used as an anti adherence and 15% w/w xanthan gum as gelling agent was fabricated to prolong the soft lozenge disintegration. 15% w/w xylitol, 0.12% w/w saccharin sodium, 2% w/w citric acid, 1.67% w/w orange oil and 0.0067% w/w sunset yellow FCF No.2 were used as flavouring agents. This lozenge base was used as the suitable carrier for clotrimazole. The antifungal activity of the developed clotrimazole soft lozenges and Candinas® was slightly different.

ACKNOWLEDGEMENTS

This research work was kindly supported by the Faculty of Pharmacy, Silpakorn University. The author would like to thank Leaungjuntawong T., Suwanajitr T. and Churasree Y. for their help.

REFERENCES

[1] Craig DG. Drug Dev Ind Pharm 1990;16:2501-26.
[2] Fujii M, Okada H, Shibata Y, Teramachi H, Kondoh M, Watanabe Y. Int J Pharm 2005;293:145-53.
[3] Trapani G, Franco M, Latrofa A, Pantaleo MR, Provenzano MR, Sanna E, *et al*. Int J Pharm 1999;184:121-30.
[4] Wang X, Armasa HN, Blaton H, Michoel A, Van dan Mooter G. Int J Pharm 2007;123:163-9.
[5] Fini A, Moyano JR, Gines JM, Perez-Martinez JI, Rabasco AM. Eur J Pharm Biopharm 2005;60:99-111.
[6] Leonardi D, Barrera MG, Lamas MC, Salomon CJ. AAPS PharmSciTech 2007;8(4) Article 108 (http://www.aapspharmscitech.org) [last accessed on 2009 Jan 4].
[7] Ahuja N, Katare OP, Singh B. Eur J Pharm Biopharm 2007;65:26-38.
[8] Mesnukul A, Yodkhum K, Phaechamud T. Indian J Pharm Sci 2009;71:413-20.
[9] Mesnukul A, Yodkhum K, Mahadlek J, Phaechamud T. Indian J Pharm Sci 2010; 72(1):92-100.
[10] Ahmed MO, El-Gibaly I, Ahmed SM. Int J Pharm 1998;171:111-121.
[11] Burgess MA, Bodey, GP. Chemother 1972;2:423–426.
[12] Borgers M. Rev Infec Disease 1980;2:520–534.
[13] Okhamafe AO, York P. Drug Delv Ind Pharm 1985;11(1):131-146.