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INTRODUCTION

Onychomycosis is fungal infection of nail plate. In Thailand, nondermatophyte molds (NDM) such as *Aspergillus spp., Fusarium spp., Scytalidium spp.* are leading cause of onychomycosis.[1] Standard treatment of onychomycosis is orally administration of antifungal agents for example terbinafme, itraconazole, or fluconazole. The nail plate is several layers of dead and compacted keratin supported by nail bed, viable dermis with capillaries. Delivery therapeutic quantity of oral administered drugs to the nail plate requires high oral dose and long therapeutic regimen. Therefore, treatment failure in onychomyosis is due to low availability of drugs at the infection site (nails), high hepatotoxicity of the antifungal drugs, and low patient compliance.[2,3] Nail preparation containing antifungal drugs is not commercially available in Thailand. In order to overcome the above drawbacks, the ultimate goal of this research is to develop a topical nail formulation containing the high concentration of permeation enhancer. The secondary objective of this research is to compare stabilities. Since the nail plate contained water more than lipid structure, the nail formulations should be an o/w emulsion (o/w) or the hydrophilic formula.[4] In addition, the topical nail formulations must adhere to the nail plate for a reasonable time so that permeation enhancer can facilitate drug permeation into the nail plate. Dimethylsulfoxide (DMSO) is known to enhance the nail permeability.[5] DMSO is slightly hazard to human. DMSO can cause formulation problems since it is an organic solvent by nature. Thus, development of formulations containing high concentration of DMSO is quite a challenge. An objective of this present work was to develop three stable based formulations, i.e. ointment, o/w emulsion, and gel, containing DMSO to be used as nail formulations.

MATERIALS AND METHODS

Formulation of cream base The o/w emulsions were modified by varying concentration of various ingredients as shown in Table 1.[6,8] The cream base was prepared using a beaker method. Oil phase consisted of glyceryl monostearate, cetyl alcohol, stearyl alcohol, mineral oil, and span®60 were heated to 75°C. Water phase consisted of purified water, tween®60, and DMSO were heated to 80°C. The oil phase was added into the water phase and gently stirred until it was congealed.

Formulation of hydrophilic ointment base The hydrophilic ointment bases were prepared by varying concentration of ingredients as shown in Table 2.[7,8] In short, stearyl alcohol and white petrolatum were fused at 75°C and the mixture was stirred until it became homogeneous. The aqueous phase composed of sodium lauryl sulfate, propylene glycol, DMSO and purified water was heated to 75°C. The oil phase was added to the aqueous phase. The hydrophilic ointment base was stirred gently until it was congealed.

Formulation of gel base The formulation of gel base was shown in Table 3.[8] Poloxamer 407 was slowly dispersed in cold mixture (5°C) of propylene glycol, DMSO and purified water. The mixture was gently stirred until the gel was formed.

Physical stability evaluation Physical stability of selected preparations were evaluated by heating-cooling method. Samples were stored in a refrigerator (Kelvinator, Australia) at 4°C for 48 hours, and then kept in an incubator (Memmert, Thailand) at 45°C for 48 hours. The preparations were redone all steps mentioned above for 6 cycles prior to organoleptic evaluation.

RESULTS AND DISCUSSIONS

The freshly prepared o/w cream bases containing 5-50% DMSO were opaque thick cream (Figure 1A). After passing through 6 heating-cooling cycles, o/w cream based containing DMSO less than 30% showed no any significant physical changes (Figure 1B). However, o/w cream based containing DMSO more than 35% showed translucent layer at the bottom of the cream. The translucent layer was due to high concentration of DMSO that could dissolve wax and oil in the formulation.

Table 1 The formulation of cream base

Ingredients	Functions	% w/w
Glyceryl monostearate	Emollient, emulsifying agent	1-5
Cetyl alcohol	Stiffening agent	1-5
Stearyl alcohol	Stiffening agent	1-5
Mineral oil	Emollient	5-10
Tween®60	Emulsifying agent	1-10
Span®60	Emulsifying agent	1-10
Dimethyl sulfoxide	Penetration enhancer	5-50
Purified water	Vehicle	q.s. to 100

Table 2 The formulation of hydrophilic ointment base

Ingredients	Functions	% w/w
Sodium lauryl sulfate	Emulsifying agent	0.5-2.5
Propylene glycol	Humectant	5-15
Stearyl alcohol	Stiffening agent	1-5
White petrolatum	Emollient	5-50
Dimethyl sulfoxide	Penetration enhancer	5-30
Purified water	Vehicle	q.s. to 100

Table 3 The formulation of gel base

Ingredients	Functions	% w/w
Poloxamer 407	Gelling agent	12.5-20
Dimethyl sulfoxide	Penetration enhancer	5-30
Purified water	Solubilizer	q.s. to 100

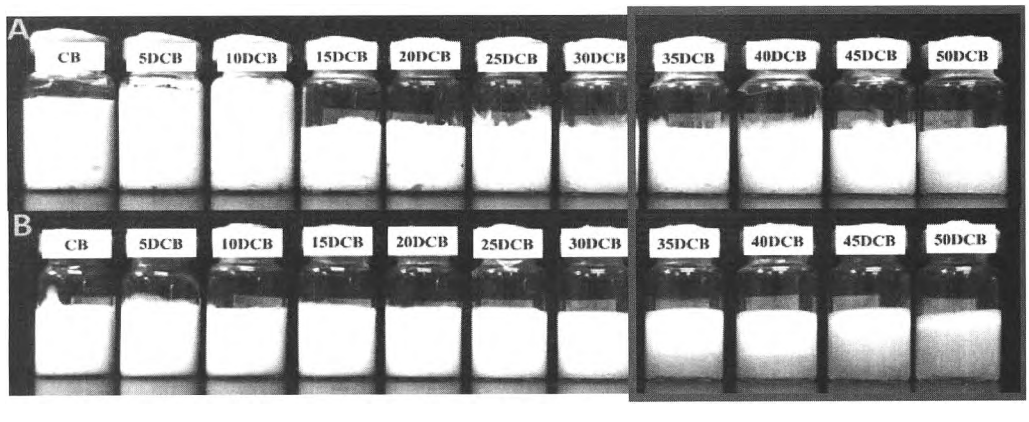

Figure 1 Physical appearance of freshly prepared o/w cream base (A) and cream base after 6 cycles of heating-cooling cycle (B). The numbers represent DMSO concentration presented in each formulation where CB represents cream base formulation.

The hydrophilic ointment and gel bases were formulated in the presence of 5-30% DMSO. The hydrophilic ointments were thick opaque cream with no significant changes in physical appearance after keeping at 4°C and 45°C for 6 cycles (the data was not shown). The obtained gels were opaque viscous gels. The surface active properties of Poloxamer 407 gave rise to formation of air bubbles after gently stirring. As a result, the air bubbles were entrapped inside the viscous gels. DMSO is solidified at temperature lower than 18 °C; therefore, elimination of air bubbles by keeping the gels in a refrigerator in order to lower the gel viscosity led to formation of DMSO crystal. However, the gels showed no significant changes in their physical appearance after passing through 6 heating-cooling cycles.

CONCLUSION

In this present work, three based formulations; i.e. o/w emulsion, hydrophilic ointment and gel, containing 30%DMSO were developed. All of them showed reasonable physical stability after passing through 6 heating-cooling cycles. In the further studies, an antifungal agent will be incorporated into these based formulations. The formulations will subject to both physical and chemical tests prior to determination of the nail permeability.

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REFERANCES

1. Ungpakorn, R., 2005. Mycoses in Thailand: current concerns. Japanese Journal of Medical Mycology, 46(2), 81-86.
2. Rodgers, P. and Bassler, M., 2001. Treating onychomycosis. American Family Physician, 63(4), 663-672.
3. Welsh, O., Vera-Cabrera, L., and Welsh, E., 2010. Onychomycosis. Clinics in Dermatology, 28(2), 151-159.
4. Murdan, S., 2002. Drug delivery to the nail following topical application. International Journal of Pharmaceutics, 236(1-2), 1-26.
5. Vejnovic, I., Simmler, L., and Betz, G., 2010. Investigation of different formulations for drug delivery through the nail plate. International Journal of Pharmaceutics, 386(1-2), 185-194.
6. Niazi, S.K., 2009. Handbook of pharmaceutical manufacturing formulations: semisolid products. vol.4. 2nd ed. New York: Informa Healthcare.
7. The United States pharmacopeia USP24: the national formulary NF19. 2000. Rockville, MD: United States Pharmacopeial Convention.
8. Rowe, R.C., Sheskey. P.J., Quinn, M.E., eds. 2009. Handbook of pharmaceutical excipients. 6th ed. London: Pharmaceutical Press.