Drug Development and Industrial Pharmacy, 34:478–484, 2008

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040701743873

informa
healthcare

Percutaneous Absorption of Metopimazine and Effect of Cyclodextrins

Bounoure Frédéric and Lahiani-Skiba Malika
Laboratoire de Pharmacie, UFR Médecine Pharmacie, IFR (Institute for Biomedical Research), Université de Rouen, Rouen, Cedex, France

Hubert Marie
Laboratoire de Spectrométrie de Masse Bio-Organique, Université de Rouen, Mont-Saint-Aignan, Cedex, France

Mallet Eric
Département de Pédiatrie, Hôpital Charles Nicolle, Rouen, Cedex, France

Arnaud Philippe
Laboratoire de Pharmacie Galénique, Université René Descartes, UFR des Sciences Pharmaceutics et Biologiques, Paris, France

Skiba Mohamed
Laboratoire de Pharmacie, UFR Médecine Pharmacie, IFR (Institute for Biomedical Research), Université de Rouen, Rouen, Cedex, France

Metopimazine (MPZ) is used to prevent emesis during chemotherapies. A transdermal delivery system of MPZ may present a great advantage in patients to improve compliance. Hydroxypropyl cyclodextrin (HP CD) and partially methylated cyclodextrin (PM CD) were tested to enhance the percutaneous absorption of MPZ through pig skin using Franz's cells. The MPZ hydrochloride flux was low with 0.176 0.054 g/h/cm and no flux was detected with a suspension of MPZ (base). The used characterization analyses demonstrated the formation of an inclusion complex with cyclodextrin and this complex improved percutaneous absorption of MPZ. Flux was increased to 0.240 0.032 g/h/cm and 0.566 0.057 g/h/cm for HP CD and PM CD, respectively, with a concentration of 20%. This study has shown that HP CD and PM CD improved the percutaneous penetration of MPZ. Cyclodextrin complexes increased MPZ bioavailability at the skin surface and PM CD was also able to extract cutaneous fatty acids.

Keywords cyclodextrin; metopimazine; Franz's cell; percutaneous absorption

Address correspondence to Skiba Mohamed, Laboratoire de Pharmacie Galénique, UFR de Médecine Pharmacie, Aden Upres Ea 3234, Université de Rouen, 22 bd Gambetta, 76136, Rouen, Cedex, France. E-mail: Mohamed.skiba@univ-rouen.fr

INTRODUCTION

Metopimazine (MPZ) is a phenothiazine derivative with dopamine D2-receptor antagonist propriety (Herrstedt, Hyttel, & Pedersen, 1996), which presents an antiemetic activity. Many studies have reported that metopimazine is an effective drug in combination with ondansetron to prevent nausea and vomiting during chemotherapy (Bloch et al., 2005; Nathan et al., 2006; Sigsgaard et al., 2001). The chemical structure of MPZ is represented in Figure 1. Oral administration of drugs is generally the route of choice (Vianna, Bently, & Riebeiro, 1998), but in this case, oral absorption is often compromised by nausea and vomiting and MPZ is administered by perfusion. The transdermal route has a potential interest in those situations in which oral administration may be inadvisable.

The transdermal route also can be used in the treatment of nausea and vomiting. Indeed, scopolamine may be administered by transdermal route in the treatment of motion sickness. Calpena and colleagues (1994) have studied the metopimazine transdermal absorption in Franz's cells on rat skin. The predicted range of MPZ permeated amounts during the first 24 h was inferior to the theoretical daily transdermal dose. The lag time of MPZ has been reported to be 28 h, which is unacceptable to obtain an immediate therapeutical effect (Calpena et al., 1994).

The relative impermeability of the stratum corneum provides the principal resistance to percutaneous absorption of

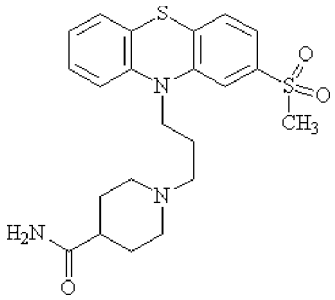

FIGURE 1. Chemical structure of MPZ.

most drugs. Attempts have been made using penetration enhancers to reverse or reduce this barrier resistance. Conventional penetration enhancers, such as alcohols, disrupt the lipid layers of the biological barrier (Arellano, Santoyo, Martin, & Ygartua, 1998; Levang, Zhao, & Singh, 1999). Cyclodextrins are bucket-shaped oligosaccharides produced from starch. As a result of their molecular structure and shape, they possess a unique ability to act as molecular containers by entrapping guest molecules in their internal cavity. The resulting inclusion complexes offer a number of potential advantages. Cyclodextrins increase the water solubility of poorly soluble drugs and also can be used as penetration enhancers. They act by increasing drug availability at the surface of the biological barrier (Masson, Loftsson, Masson, & Stefansson, 1999). Partially, methylated β cyclodextrin (PMβCD) may extract lipids from the stratum corneum, which can cause increased permeation of many drugs across skin, but the effect of hydroxypropyl β cyclodextrin (HPβCD) on the skin is less clear (Bently, Vianna, Wilson, & Collett, 1997; Williams, Shatri, & Barry, 1998). Authors have shown that, HPβCD increased the in vitro transdermal permeation of corticosterone by a pre-treatment of the skin (Shaker, Ghanem, Li, & Warner, 2003) and PMβCD also increased the percutaneous absorption of liarozole by a pre-treatment (Vollmer et al., 1993).

The purpose of the research presented in this paper was to study the influence of PMβCD and HPβCD on the MPZ transdermal absorption. These cyclodextrins are used as percutaneous penetration enhancers. The complex formation was characterized by physical methods and the effect of these cyclodextrins on percutaneous absorption of MPZ was tested in Franz's cells on pig skin. The choice of skin used could influence the percutaneous absorption results. Catz and Friend (1990) have shown that the use of animal skin is a good predictive model to estimate the percutaneous absorption, but the absorption result is often more important than with the human skin. Pig skin is the more interesting skin to predicte the absorption of drug. Sato and coworkers (1991) have demonstrated that porcine skin presents the absorption paramaters more similar to human skin.

MATERIALS AND METHODS

Materials

Schwartz Pharma AG (Boulogne Billancourt, France) provided metopimazine. Partially methylated β-cyclodextrin (PMβCD) and hydroxypropyl β-cyclodextrin (HPβCD) were gifts from Wacker (Lyon, France). All other chemicals were obtained from Acros (Noisy le Grand, France).

Methods

Phase Solubility Studies

Phase solubility studies were assessed according to the method described by Higuchi and Connors (1965). An excess amount of MPZ was mixed in an aqueous solution containing increasing amount of HPβCD or PMβCD. The amount of MPZ in solution after equilibrating for 3 days was determined by UV detection at 264 nm. The apparent stability constant (Kc) of the 1:1 and 2:1 complexes (drug/cyclodextrin) was determinated from the slope (R) and aqueous solubility of the drug (S_0) of the phase solubility diagram according to the equations (Higuchi & Connors, 1965) below:

$$K_{C\,1:1} = R/S_0 \times (1 - R) \quad (1)$$

$$K_{C\,2:1} = R/S_0 \dagger \times (2 - R) \quad (2)$$

Each sample is in triplicate.

Preparation of Skin

Pig ears were obtained from a slaughterhouse and were frozen at –20°C before to be used during a maximum of 2 months. The skin was carefully removed, leaving the fat tissue behind. The hair was clipped as close as possible to the skin without damaging it. The skin was examined for damage or diseases conditions. Any skin in which the barrier was disrupted was not used in this study. The skin was cut into 2 cm × 2 cm samples for permeation studies. The skin was directly used with any pretreatment.

For FT-IR studies, the epidermis was separated from full thickness skin using the procedure described by Scott and colleagues (1989). The stratum corneum was peeled off from the skin after soaking in 2 M potassium bromide solution for 12 h at 37°C. The epidermal sheet was then dried in a vacuum desiccator for 3 days before using. The stratum corneum was treated with a solution of cyclodextrins at 10% (w/v) for 4 h. The epidermal sample was dried with tissue paper at room temperature.

Differential Scanning Calorimetry

Inclusion compounds were prepared in purified water at room temperature over 3 days by mixing appropriate amounts of MPZ and PMβCD or HPβCD with 1:1 molar ratio. Then,

complexes were obtained by freeze drying solutions. Physical mixtures were obtained by mixing the equivalent amount of reagents. Differential scanning calorimetry of the samples was conducted on a Perkin Elmer instrument DSC-6. The heating rate was 5°C/min in a dynamic nitrogen environment between 30°C and 250°C. The sample weighed 2 mg and was contained in closed aluminum pans. Cyclodextrins, MPZ, physical mixture (1:1) and inclusion compounds (1:1) were scanned to observe the melting of solid phase.

Infrared Spectroscopy Studies

Infrared absorption spectra of the samples were recorded using a Perkin Elmer Spectrophotometer, Spectrum One. The diffuse reflectance technique was utilized in the mid-IR (600–4000 cm^{-1}) spectral region. The samples were prepared by the same method described in DSC study.

For skin studies, the stratum corneum was treated with a solution of cyclodextrins at 10% for 4 h. The epidermal sample was dried with tissue paper at room temperature. Infrared absorption spectra were recorded between 3000–2800 cm^{-1} and 1750–1500 cm^{-1}. All spectra analyzed represented an average of 50 scans with resolution of 4 cm^{-1}. To estimate the lipid extraction caused by cyclodextrins, the increase of transmission of asymmetric (near 2850 cm^{-1}) and symmetric C-H (near 2920 cm^{-1}) stretching bands due to alkyl chains of the lipids was studied. The changes of the amide I stretching vibration at 1650 cm^{-1} also were studied to investigate an interaction with skin proteins. The spectrum was recorded before and after treatment with the enhancer.

Partition Coefficient Determination

A 100 μg/ml MPZ solution in n-Octanol and 3 buffer solutions at pH 5.5, 7.4 (phosphate buffer), and 10.3 (carbonate buffer) were prepared. These pH have been chosen because 5.5 is the pH of skin surface, 7.4 is the physiological pH, and 10.3 is to obtain only in solution of the non ionized form. Then, 2 ml of n-Octanol solution were mixed with 2 ml of buffer solution. The solutions were agitated for 24 h at 25°C. The concentration of MPZ in aqueous phase was analyzed by UV quantification after separating each phase by centrifugation at 4.000 rpm for 20 min. Each sample is in triplicate.

In Vitro Skin Permeation Studies

Franz type diffusion cells were used in this study to determine the MPZ permeation. The excised skin was mounted between the donor and the receptor chambers with epidermal side facing the donor fluid. The diffusion cell was clamped and immersed in a water bath maintained at 37 ± 0.5°C on a magnetic stirrer. The volume of donor and receptor chambers were respectively 4 ml and 5 ml and the effective surface area available for permeation of drug was 1 cm^2. 2 ml of MPZ solution with a concentration of 2 mg/ml was placed on the donor side. For preparation of MPZ/CD solutions, HPβCD and PMβCD were added to water to obtain clear aqueous solutions. To these solutions, MPZ was added and the mixture was stirred for 12 h. Large concentration of cyclodextrin is used to solubilize the entire quantity of MPZ base. The receptor chamber was filled with 5 ml of acetate buffer solution (pH 5.5; 300 mOsm). This buffer was used to ensure sufficient drug solubility in the receptor phase. The experiments were repeated six times.

Analytical Procedure

For complex characterization and solubility study, the amount of metopimazine was assayed with an UV spectrophotometer (Beckman) at 264 nm. The absorbance of calibration curve was linear in the range 1–25 μg/ml (r^2 = 0.9998). In permeation study, MPZ was determined using HPLC apparatus (Kontron) equipped with a variable wavelength UV monitor according to Angelo and coworkers (1989) method. The column was a 5 μm Supersil® CN 25 cm × 4.6 mm ID used at room temperature. The mobile phase was methanol 0.1 M ammonium acetate (50:50). The flow rate was 1.5 ml/min and the detection was at 264 nm.

Statistical Analyses

Statistical data analyses were performed using the Student's test with $p < 0.05$ as the minimal level of significance.

RESULTS AND DISCUSSION

Partition Coefficient Determination (logP)

Partition coefficient (logP) is a predictive factor to percutaneous absorption and depends on hyphophilicity and hydrophobicity of drug. Partition coefficient is depending on pH of the solution and on pKa of the drug (8.4). The data are shown in Table 1. At pH 5.5, MPZ ionization increases the hydrophilicity and logP is at –0.15. At pH 10.3, non-ionized MPZ is the dominant form and logP is at 2.77. The logP value was of the same order as that of fentanyl (4.05) and of scopolamine (1.66), molecules already used by transdermal route and that have similar general features as MPZ. These latest results were encouraging for a transdermal application to the lipophilic MPZ molecule. Better percutaneous absorption could be predicted with MPZ base, nevertheless its lower water solubility should limit the drug penetration.

Phase Solubility Studies

The phase solubility diagram of MPZ with HPβCD and PMβCD were represented in Figure 2. The MPZ solubility increases with the concentration of HPβCD and PMβCD. The

TABLE 1
Partition Coefficient of MPZ Between n-Octanol and a Buffer at Different pH (n = 3)

pH	5.5	7.4	10.3
P	0.71 ± 0.4	13.2 ± 2.8	591 ± 80.3

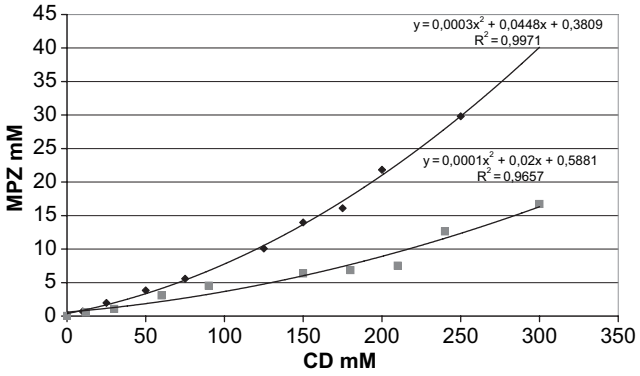

FIGURE 2. Solubility diagram of MPZ with HPβCD (■) and PMβCD (✦) at room temperature (n = 3).

two diagrams are Ap type of phase solubility diagram. This may indicate the formation of 1:1 and 1:2 stochiometric ratios of inclusion complexes. The Kc of the two complexes (1:1) and (2:1) is calculated respectively to 1512 and 156 M^{-1} for PMβCD and to 658 and 52 M^{-1} for HPβCD.

Physical Characterization of Complexes

The MPZ complexes were prepared with HPβCD and PMβCD and characterized with DSC and IR spectra. DSC thermogram for HPβCD and PMβCD are represented in Figures 3 and 4. MPZ shows a melting point at 188°C. The physical mixtures present a DSC thermogram with an endothermic peak of MPZ at 189°C for HPβCD and at 214°C for PMβCD. For the physical mixture between PMβCD and MPZ, this endothermic peak is increased showing an interaction between this cyclodextrin and MPZ. In case of inclusion complexes, the melting point peak of MPZ has disappeared, which also shows an interaction. However, DSC thermograms of physical mixture and inclusion complexes are different, proving the formation of the complex between cyclodextrin and MPZ. IR

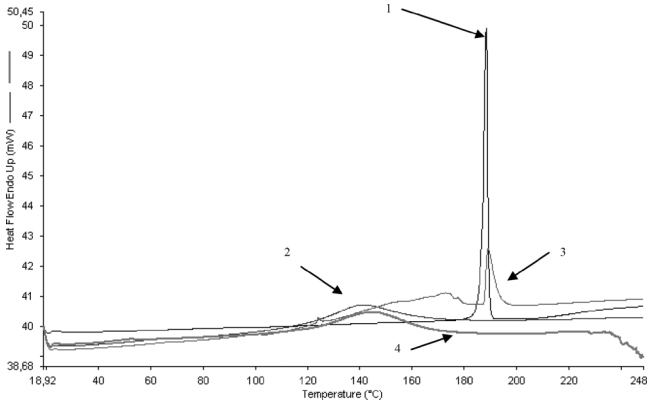

FIGURE 3. (1) Differential scanning calorimetric thermogram of MPZ, (2) HPβCD, (#) physical mixture between MPZ and HPβCD 1:1, and (4) inclusion complex between MPZ and HPβCD 1:1.

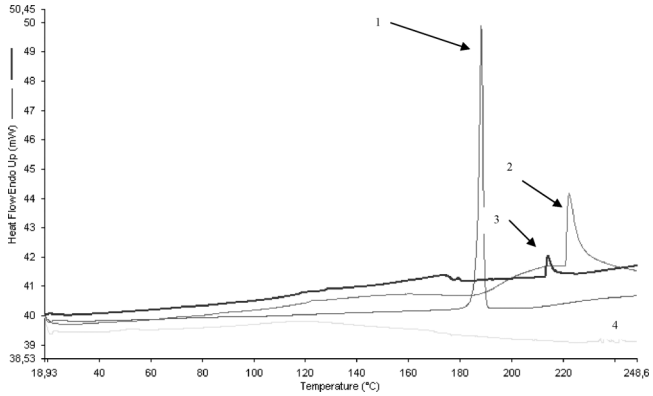

FIGURE 4. (1) Differential scanning calorimetric thermogram of MPZ, (2) PMβCD, (3) physical mixture between MPZ and PMβCD 1:1, and (4) inclusion complex between MPZ and PMβCD 1:1.

spectroscopy is a useful technique to confirm the formation of an inclusion complex. Ahmed et al. (1991) used IR to support the evidence for a complex formation between bropirime and β cyclodextrin. IR spectra of MPZ, CD, inclusion complex, and physical mixture are represented in Figure 5 for HPβCD and for PMβCD. MPZ is characterized with 4 absorption peaks:

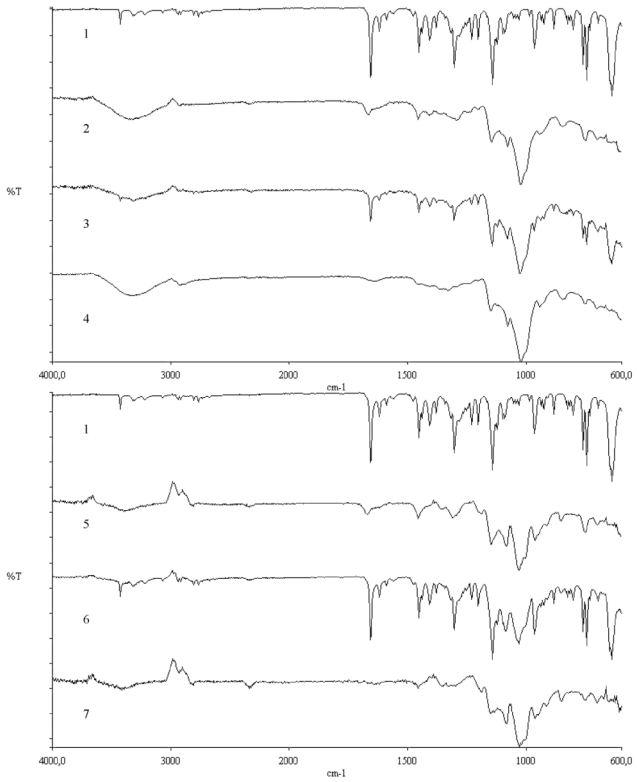

FIGURE 5. (1) Infrared absorption spectra of MPZ, (2) inclusion complex between MPZ and HPβCD 1:1, (3) physical mixture between MPZ and HPβCD 1:1, (4) HPβCD, (5) inclusion complex between MPZ and PMβCD 1:1, (6) physical mixture between MPZ and PMβCD 1:1, and (7) PMβCD.

3431 cm^{-1} for vibration N-H function, 1700 cm^{-1} for vibration C=O function, and 1307 cm^{-1} and 1144 cm^{-1} for vibration S=O function. The IR spectra of the physical mixture for PMβCD and HPβCD show no significant differences from the respective spectra of HPβCD or PMβCD and MPZ. IR spectroscopy of inclusion complexes shows no absorption peak at 3431 cm^{-1} and a small absorption peak at 1700, 1307 and 1144 cm^{-1}. This result is consistent with the results obtained from DSC and the phase solubility.

Percutaneous Penetration

The parameters of percutaneous absorption of MPZ with different concentrations of HPβCD and PMβCD are represented in Table 2. The MPZ hydrochloride flux was low with 0.176 ± 0.054 μg/h/cm^2. This result is lower than the flux obtained with rat skin by Calpena and coworkers (1994) report with 5.02 μg/h/cm^2 in the first 24 h. No flux was detected with the suspension of MPZ base. This result is explained because of the low solubility of MPZ. The skin absorption of MPZ is modified by the presence of cyclodextrins. After 24 h, the amount of permeated MPZ was 4.52 ± 0.53 μg/cm^2 with 20% HPβCD (w/v) and 10.92 ± 0.90 μg/cm^2 with 20% PMβCD (w/v). A better percutaneous absorption of MPZ was obtained with PMβCD. The quantity of dissolved MPZ increases with the amount of cyclodextrin. Thus, a greater quantity of MPZ is available to the skin surface to pass through the cutaneous barrier. Loftsson and Masson (2001) also have reported that cyclodextrins enhanced topical drug delivery by increasing the drug solubility, and this availability at the barrier surface and drug delivery from aqueous cyclodextrin solutions was both diffusion controlled and membrane controlled.

TABLE 2
Parameters of Percutaneous Permeation of MPZ with Different Concentrations of HPβCD and PMβCD (n = 6)

Drug (2 mg/ml)	% HPβCD (w/v)	% PMβCD (w/v)	Amount Permeated (24 h) μg/cm^2	Flux μg/cm^2/h
MPZ base			Not detected	Not detected
MPZ HCl			2.77 ± 0.98[b]	0.176 ± 0.44[c]
MPZ HCl	5		3.04 ± 0,61[b]	0.140 ± 0.029[c]
MPZ HCl	10		4.07 ± 1.07[a,b]	0.152 ± 0.079[c]
MPZ HCl	20		4.54 ± 0.23[a]	0.179 ± 0.008[c]
MPZ base	20		4.52 ± 0.53	0.240 ± 0.031
MPZ HCl		5	8.83 ± 0.23*	0.449 ± 0.175[d]
MPZ HCl		10	7.96 ± 0.65*	0.435 ± 0.031[d]
MPZ HCl		20	9.36 ± 0.80*	0.474 ± 0.054[d]
MPZ base		20	10.91± 0.89	0.570 ± 0.058

*, a, b, c, and d: no statistical difference between two values with the same letter.

Complexation with cyclodextrins has been variously reported to both increase and decrease skin absorption. Many works report an increase of drug absorption with use of cyclodextrins. Lopez and colleagues (2000) have studied the influence of complexation of dexamethasone with βCD and HPβCD on the in vitro permeation through hairless mouse skin. Complexation with cyclodextrins increased the amount of dexamethasone permeated and protected the drug against cutaneous metabolism. Babu and Pandit (2004) have shown that PMβCD or HPβCD enhanced bupranolol permeation through rat skin at concentration of 2% and 5% (w/v). At concentration of 10% (w/v), PMβCD decreased the permeation of bupranolol.

Contrary to these reports, Williams and coworkers (1998) have shown that the βCD and HPβCD did not enhance flux of estradiol or fluoro-uracil through skin. Drug permeation was reduced following membrane pre-treatment with cyclodextrins. They have suggested that cyclodextrins may be incorporated into a formulation to reduce percutaneous absorption of toxic drugs on occupational exposure. In this work, Williams and coworkers found that the pre-treatment of skin with βCD and HPβCD resulted in reduced permeation of toluene through human skin. Simeoni and associates (2004) also investigated the effects of HPβCD and sulfobutylether-β-CD on in vitro human skin penetration of the butyl-methoxydibenzoylmethane. A low amount of the applied dose of butyl-methoxydibenzoylmethane penetrated within the skin tissue. But no drug was detected in the dermis and was absorbed. Vollmer and colleagues (1993) have shown that HPβCD was an ineffective enhancer of liarozole at a concentration of 5% (w/v) and moderate enhancer at a concentration of 20% (w/v). The absorption of liarozole in 20% (w/v) aqueous solution of PMβCD was slightly decreased by a factor of 0.6 (Felton, Wiley, & Godwin, 1993).

Skin enhancer effect of cyclodextrins could be attributed not only to an increase of solubility and availability of MPZ. For a concentration of cyclodextrin at 20% (w/v), no significant difference is observed between MPZ hydrochloride and base. The MPZ permeation obtained in presence of cyclodextrin is statistically more important than with a solution of MPZ hydrochloride. The permeated amount and flux of MPZ were, respectively, 8.82 ± 0.23 μg/cm^2, 7.96 ± 0.64 μg/cm^2, and 9.35 ± 0.8 μg/cm^2 after 24 h, and 0.449 ± 0.175 μg/cm^2/h, 0.435 ± 0.031 μg/cm^2/h, and 0.474 ± 0.054 μg/cm^2/h for PMβCD at 5, 10, and 20% (w/v). For HPβCD, the permeated quantity and flux of MPZ were, respectively, 3.04 ± 0.61 μg/cm^2, 4.07 ± 1.07 μg/cm^2, and 4.54 ± 0.23 μg/cm^2 after 24 h and 0.140 ± 0.029 μg/cm^2/h, 0.152 ± 0.079 μg/cm^2/h, and 0.179 ± 0.008 μg/cm^2/h for HPβCD at 5, 10, and 20% (w/v). The MPZ absorption is statistically more important with PMβCD than with HPβCD. MPZ absorption also increases with the concentration of cyclodextrin but only the difference between HPβCD at 5% and 20% (w/v) was statistically significant. HPβCD doesn't statistically modify the MPZ flow. In this case, solubility of MPZ hydrochloride was not modified by cyclodextrin; skin penetration enhancement may be attributed only to extraction

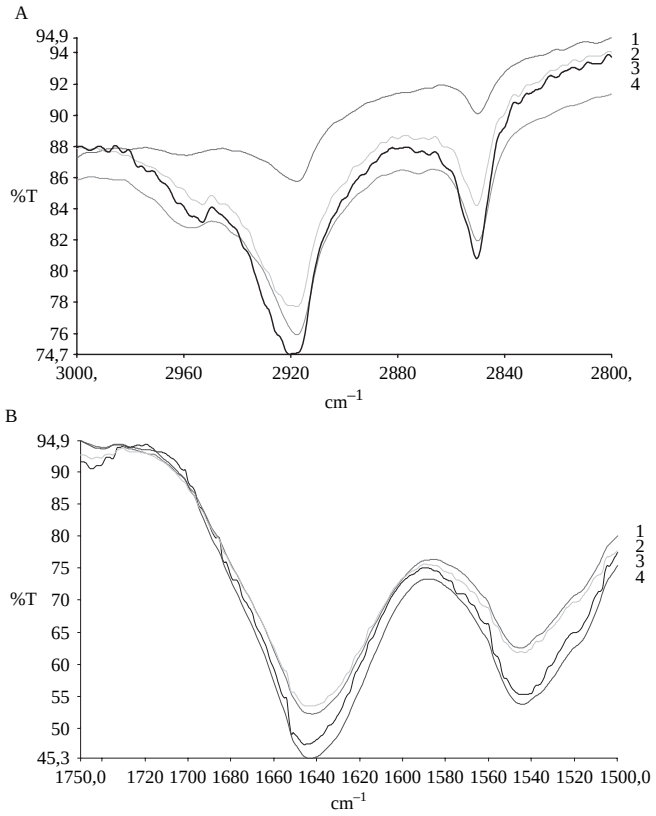

FIGURE 6. FT IR spectra before and after treatment with cyclodextrin. (A) Changes in lipid C-H stretching: 2840 and 2920 cm^{-1}; (B) Changes in amide I stretching: 1640 cm^{-1}(1) After treatment with PMβCD 10% (w/v); (2) Before treatment with PMβCD 10% (w/v); (3) After treatment with HPβCD 10% (w/v); (4) Before treatment with HPβCD 10% (w/v).

of stratum corneum lipids by cyclodextrins. The FT IR spectra from 3000 to 2800 cm^{-1} and to 1750 to 1500 cm^{-1} are represented in Figure 6. PMβCD shows maximum reduction in peak area for symmetric C-H stretching vibration and for asymmetric C-H stretching vibration, and HPβCD presented a minor change of the pick area at 2920 cm^{-1} and 2840 cm^{-1}. PMβCD and HPβCD do not produce changes in the amide stretching peak corresponding to ceramides and proteins. These results are in agreement with the findings of Babu and coworkers (2004), which have shown that a pre-treatment of rat skin with a 10% (w/v) concentration of PMβCD during 3 h increased 1.7 fold the flux of bupranolol and a pre-treatment with HPβCD didn't modify the permeation of the drug. Vollmer and coworkers (1993) also have observed an increase of the liarozole permeation after pre-treatment of rat skin with PMβCD. These studies show that PMβCD reduces the barrier function of skin, whereas HPβCD has a limited specificity for stratum corneum structure.

CONCLUSION

Higuchi's phase solubility, infrared spectroscopy (IR), and differential scanning calorimetry (DSC) analyses demonstrate the formation of an inclusion complex between cyclodextrins and MPZ. HPβCD and PMβCD improve percutaneous penetration of MPZ with two mechanisms. Cyclodextrin complexes increase MPZ solubility and thus bioavailability at the skin surface. PMβCD also is able to change the structure of stratum corneum through the displacement of fatty acids. However the MPZ flux remains not significant enough to consider a clinical use. Other galenic solutions, as iontophoresis, must be tested to increase it.

REFERENCES

Ahmed, S. M., Naggi, A., Guerrini, M., & Focher, B. (1991). Inclusion complexes of bropirimine with B cyclodextrin in solution and in solid state. *Int. J. Pharm., 77*, 247–254.

Angelo, H. R., Herrstedt, J., & Jorgensen, M. (1989). High performance liquid chromatographic method with fluorescence detection for the simultaneous determination of metopimazine and its acid metabolite in serum. *J. of Chrom., 496*, 472–477.

Arellano, A., Santoyo, S., Martin, C., & Ygartua, P. (1998). Influence of propylene glycol as isopropryl myristate on the in vitro percutaneous penetration of diclofenac sodium from carbopol gels. *Eur. J. Pharm. Sci., 7*, 129–135.

Babu, R. J., & Pandit, J. K. (2004). Effect of cyclodextrins on the complexation and transdermal delivery of bupranolol through rat skin. *Int. J. Pharm., 271*, 155–165.

Bently, M. V. L. B., Vianna, R. F., Wilson, S., & Collett, J. H. (1997). Characterization of the influence of some cyclodextrins on the stratum corneum from the hairless mouse. *J. Pharm. Pharmacol., 49*, 397–402.

Bloch, J., Rixe, O., Meric, J. B., Delgado, A., & Khayat, D. (2005). Comparison of the efficacity and safety of combinations of metopimazine or ondansetron with methylprednisolone in the prevention of delayed emesis in patients receiving chemotherapy. *Curr. Med. Res. Opin., 21*, 1763–1771.

Calpena, A. C., Blanes, C., Moreno, J., Obach, R., & Domenech, J. A comparative in vitro study of transdermal absorption of antiemetics. *J. Pharm. Sci., 83*, 29–33.

Catz, P., & Friend, D. R. (1990). Transdermal delivery of levonorgestrel. Effect of enhancers on rat skin, hairless mouse skin, hairless guinea pig skin and human skin. *Int. J. Pharm., 58*, 93–102.

Felton, L. A., Wiley, C. J., & Godwin, D. A. (1993). In vivo skin pharmacokinetics of liarozole: Percutaneous absorption studies with different formulations of cyclodextrin derivatives in rats. *Int. J. Pharm., 99*, 51–59.

Herrstedt, J., Hyttel, J., & Pedersen, J. (1996). The interaction of the antiemetic metopimazine and anticancer agents with brain dopamine D2, 5-hydroxytryptamine3, histamine H1, muscation, cholinergic and a1-adrenergic receptors. *Cancer Chemother. Pharmacol., 33*, 53–56.

Higuchi, T., & Connors, K. A. (1965). Phase solubility techniques. *Adv. Anal. Chem. Instr., 4*, 117–212.

Levang, A. K., Zhao, K., & Singh, J. (1999). Effect of ethanol propylene glycol on the in vitro percutaneous absorption of aspirin—Biophysical changes and macroscopic barrier properties of the skin. *Int. J. Pharm., 181*(2), 255–263.

Loftsson, T., & Masson, M. (2001). Cyclodextrins in topical drug formulations: Theory and practice. *Int. J. Pharm., 225*, 15–30.

Lopez, R. F. V., Collett, J. H., & Bentley, V. L. B. (2000). Influence of cyclodextrin complexation on the in vitro permeation and skin metabolism of dexamethasone. *Int. J. Pharm., 200*, 127–132.

Masson, M., Loftsson, T., Masson, G., & Stefansson, E. (1999). Cyclodextrins as permeation enhancers: Some theoretical evaluations and in vitro testing. *J. Cont. Rel., 59*, 107–118.

Nathan, P. C., Tomlinson, G., Dupuis, L. L., Greenberg, M. L., Ota, S., Bartels, U., & Feldman, B. M. (2006). A pilot study of ondansetron plus metopimazine vs ondansetron monotherapy in children receiving highly emetogenic chemotherapy: A Bayesian randomized serial N of 1 trials design. *Supp. Care Cancer, 14*, 268–276.

Sato, K., Sugibayashi, K., & Morimoto, Y. (1991). Species differences in percutaneous absorption of nicorandil. *J. Pharm. Sci., 80*, 104–107.

Scott, R. C., Walker, M., & Dugard, P. H. (1989). In-vitro percutaneous absorption experiments: A technique for production of intact epidermal membranes from rat skin. *J. Soc. Cosmet. Chem.*, 37, 35–41.

Shaker, D. S., Ghanem, A. H., Li, S. K., & Warner, K. S. Mechanistic studies of the effect of hydropropryl β cyclodextrin on in vitro transdermal permeation of corticostreone through hairless mouse skin. *Int. J. Pharm., 253*, 1–11.

Sigsgaard, T., Herrsted, J., Handberg, J., Kjaer, M., & Dombernowsky, P. (2001). Ondansetron plus metopimazine compared with ondansetron plus metopimazine plus prednisolone as antiemetic prophylaxis in patients receiving multiple cycles of moderately emetogenic chemotherapy. *J. Clin. Onc., 19*, 2091–2097.

Simeoni, S., Scalia, S., & Benson, H. A. E. (2004). Influence of cyclodextrins on in vitro human skin absorption of the sunscreen, butyl-methoxydibenzoylmethane. *Int. J. Pharm., 280*, 163–171.

Vianna, R. F. L., Bently, M. V. L. B., & Ribeiro, G. (1998). Formulation of cyclodextrin inclusion complexes with corticosteroids: Their characterization and stability. *Int. J. Pharm., 167*, 205–213.

Vollmer, U., Muller, B. W., Mesens, J., Wiffert, B., & Peters, T. (1993). In vivo skin permeation kinetics of liarozole: Percutaneous absorption studies with different formulations of cyclodextrin derivatives in rats. *Int. J. Pharm., 99*, 51–58.

Williams, A. C., Shatri, S. R., & Barry, B. W. (1998). Transdermal permeation modulation by cyclodextrins: A mechanistic study. *Pharm. Dev. Tech., 3*, 283–296.