

Effect of partially methylated β cyclodextrin on percutaneous absorption of metopimazine

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Abstract Metopimazine (MPZ) is an antiemetic drug used by oral and rectal administration. A transdermal delivery system of MPZ may present a great advantage for the treatment of nausea and vomiting to improve therapeutic adhesion. MPZ is a lipophilic drug with poor water solubility. Partially methylated β cyclodextrin (PM β -CD) was tested to enhance percutaneous absorption of MPZ. Complex MPZ/cyclodextrin was characterized by Higushi's phase solubility, Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) analyses and MPZ octanol partition coefficient was also determined. The permeation of free MPZ and inclusion complex through pig skin were investigated using Franz's cells. Four concentrations of cyclodextrins, 0, 5, 10 and 20% were tested. Partition coefficient was depending on pH of the solution. At pH 5.5, MPZ ionization increased the hydrophilicity (0.71) and at pH 10.3, non-ionized MPZ was the dominant form (591). The solubility of MPZ increased with the concentration of PM β -CD and the phase solubility diagram is an A_p type. The used

characterization analyses demonstrated the formation of an inclusion complex and this complex improved percutaneous absorption of MPZ. No MPZ flux was detected for a suspension of MPZ and it was more important with MPZ hydrochloride, $0.177 \pm 0.044 \mu\text{g}/\text{h}/\text{cm}^2$. Flux was increased to $0.570 \pm 0.058 \mu\text{g}/\text{h}/\text{cm}^2$ with a concentration of 20%. The use of cyclodextrin with MPZ hydrochloride increased also the percutaneous absorption with $0.549 \pm 0.175 \mu\text{g}/\text{h}/\text{cm}^2$ for a concentration of 5%, $0.435 \pm 0.031 \mu\text{g}/\text{h}/\text{cm}^2$ for a concentration of 10% and $0.474 \pm 0.054 \mu\text{g}/\text{h}/\text{cm}^2$ for a concentration of 20%. This study shows that PM β -CD improves percutaneous penetration of MPZ. But the absorption is not enough to allow a therapeutic effect. Cyclodextrin complex increases MPZ solubility and this bioavailability at the skin surface, and cyclodextrin may also modify the barrier propriety of skin.

Keywords Cyclodextrin · Metopimazine · Franz's cell · Percutaneous absorption

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Introduction

Metopimazine (MPZ) is a phenothiazine derivative with dopamine D₂-receptor antagonist propriety [1], which presents an antiemetic activity. This drug has a short elimination half-life [2] and requires frequent dosing [3, 4]. Oral administration of drugs is generally the route of choice [5], but in this case, oral absorption is often compromised by nausea and vomiting. The transdermal route has also a promising potential interest in those situations in which oral administration may be inadvisable. Calpena et al. have studied the MPZ 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 and the lag time of MPZ was too important to have an immediate therapeutically effect [6]. In this case, and as it often happens, the transdermal route is often compromised by the low bioavailability of the drug due to the skin barrier. Cyclodextrins (CDs) could be efficiently used as solubility enhancers of poorly water-soluble drugs by formation of inclusion complex between the host cyclodextrin molecule and the guest drug molecule. They act by increasing drug availability at the surface of the biological barrier [7] and, in particular, derivatized CDs (HP β -CD and PM β -CD) may extract lipids from the stratum corneum, facilitating permeation of many drugs across the skin [3, 8]. The purpose of the present paper was the study of the influence of PM β -CD, used as percutaneous penetration enhancer, on the MPZ transdermal absorption. Figure 1

Experimental

Materials

Schwartz Pharma AG (Boulogne Billancourt, France) provided MPZ hydrochloride (Vogalene[®]). Partially methylated β -cyclodextrin (PM β -CD) was a gift from Wacker (Lyon, France). HPLC solvents were from Carlo erba. All other chemicals were obtained from Acros.

A FT-IR (Perkin Elmer) equipped with an ATR-Ge crystal from Pike Technologies was used for the analysis in the frequency range between 4,000 and 600 cm^{-1} , at a 4 cm^{-1} resolution (50 scans). Thermal analysis was performed using a Perkin Elmer differential scanning calorimeter model DSC-4 equipped with a compensated power system. Heating rate was 10 $^{\circ}\text{C}/\text{min}$

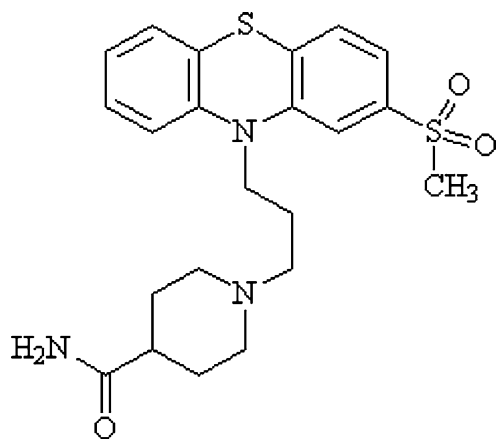


Fig. 1 MPZ formula

in a dynamic nitrogen environment between 30–250 $^{\circ}\text{C}$. HPLC method used a LC Module 1 from Waters coupled with a fluorimetric detector, Waters 474.

Partition coefficient determination

About 2 mL of n-octanol solution containing 100 μg MPZ/mL were mixed with 2 mL of a buffer solution, pH 5.5, 7.4 and 10.3. The obtained solutions were stirred for 24 h at 25 $^{\circ}\text{C}$ and concentration of MPZ, in aqueous phase was assayed by UV detection at 264 nm, after centrifugation at 4,000 rpm for 20 min. Each sample was triplicate.

Phase solubility studies

The phase solubility studies were performed according to the method of Higuchi and Connors [9]. After three days equilibrium, aliquots were withdrawn, centrifugated at 4,000 rpm during 30 min and supernatant was filtered on 0.22 μm cellulose nitrate membrane to eliminate possible aggregates. MPZ is assayed by UV spectrophotometry at 264 nm. The apparent binding capacity was calculated from the straight line portion of the phase solubility diagram according to Higuchi-Connors equation:

$$K_c = \frac{\text{slope}}{\text{intercept} (1 - \text{slope})} \quad (1)$$

Preparation of solid inclusion complexes (IC) and corresponding physical mixtures (PM)

PM β -CD was dissolved in distilled water. To these solutions MPZ was added in the 1:1 molar ratio. The whole solutions were stirred for three days, filtered and freeze-dried. The corresponding PM were obtained by thoroughly mixing the equivalent amount of reagents.

Skin preparation

Pig ears were obtained from a slaughterhouse. The skin was carefully removed leaving the fat tissue behind, then examined for damage conditions and any skin in which the barrier was disrupted was removed. The skin was cut into 2 cm \times 2 cm samples for permeation studies. Its thickness was lower than 1,300 μm .

In vitro skin permeation studies

The excised skin was mounted between the donor and the receptor chambers of Franz type diffusion cells

with epidermal side facing the donor fluid. The volume of donor and receptor chambers were respectively 2 ml and 13.5 ml and the effective surface area available for permeation of drug was 2 cm². About 2 ml of test solution was placed on the donor side. The receptor chamber was filled with 13.5 ml of acetate buffer solution (pH 5.5 ; 300 mOsm). Sink condition was obtained by the use of this buffer solution. The contents in the receiver compartment were stirred with magnetic bar. The diffusion cell was immersed in a water bath maintained at $37 \pm 0.5^\circ\text{C}$ on magnetic stirrer. At predetermined times, 0.5 ml samples were withdrawn from the receiver compartment and replaced with an equivalent amount of drug free solvent to maintain a constant volume. The samples were assayed for MPZ hydrochloride by HPLC and experiments repeated six times.

Data analysis and statistical

The cumulative amount of MPZ permeated per unit skin surface area was plotted against time. Slope of the linear portion of the plot was estimated as steady-state flux (J_{ss}). 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 of MPZ (445.6 g/mol, melting point between $170\text{--}171^\circ$) in n-octanol/water was evaluated at three different pH. Log P are represented Table 1 and are respectively equal to -0.15 , 1.12 and 2.77 for pH 5.5, 7.4 and 10.3. The log P value was of the same order as that of fentanyl (4,05) and of scopolamine (1,659), molecules already used by transdermal route and that have similar general features as MPZ. These latest results were encouraging for undertaking 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.

PM β -CD phase solubility diagram is represented Fig. 2 and shows a typical A_p curve. This may indicate the formation of 1:1 and 1:2 inclusion complexes stoichiometric ratios. Apparent binding capacity

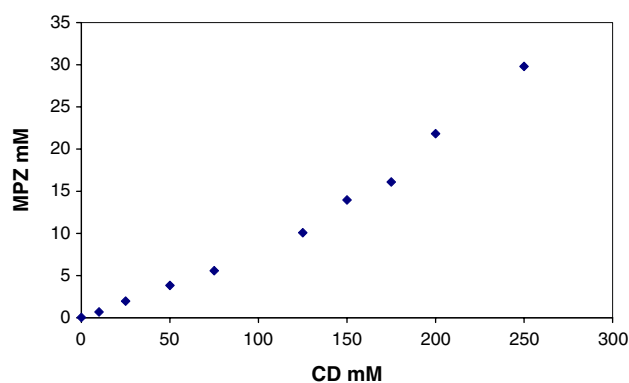


Fig. 2 MPZ solubility diagram with PM β -CD ($n = 3$)

obtained from the slope of the linear phase solubility diagram was evaluated to 925 M^{-1} , value observed currently for many drugs (celexocib : 214 M^{-1} [10] and nicotine : 194 M^{-1} [11]).

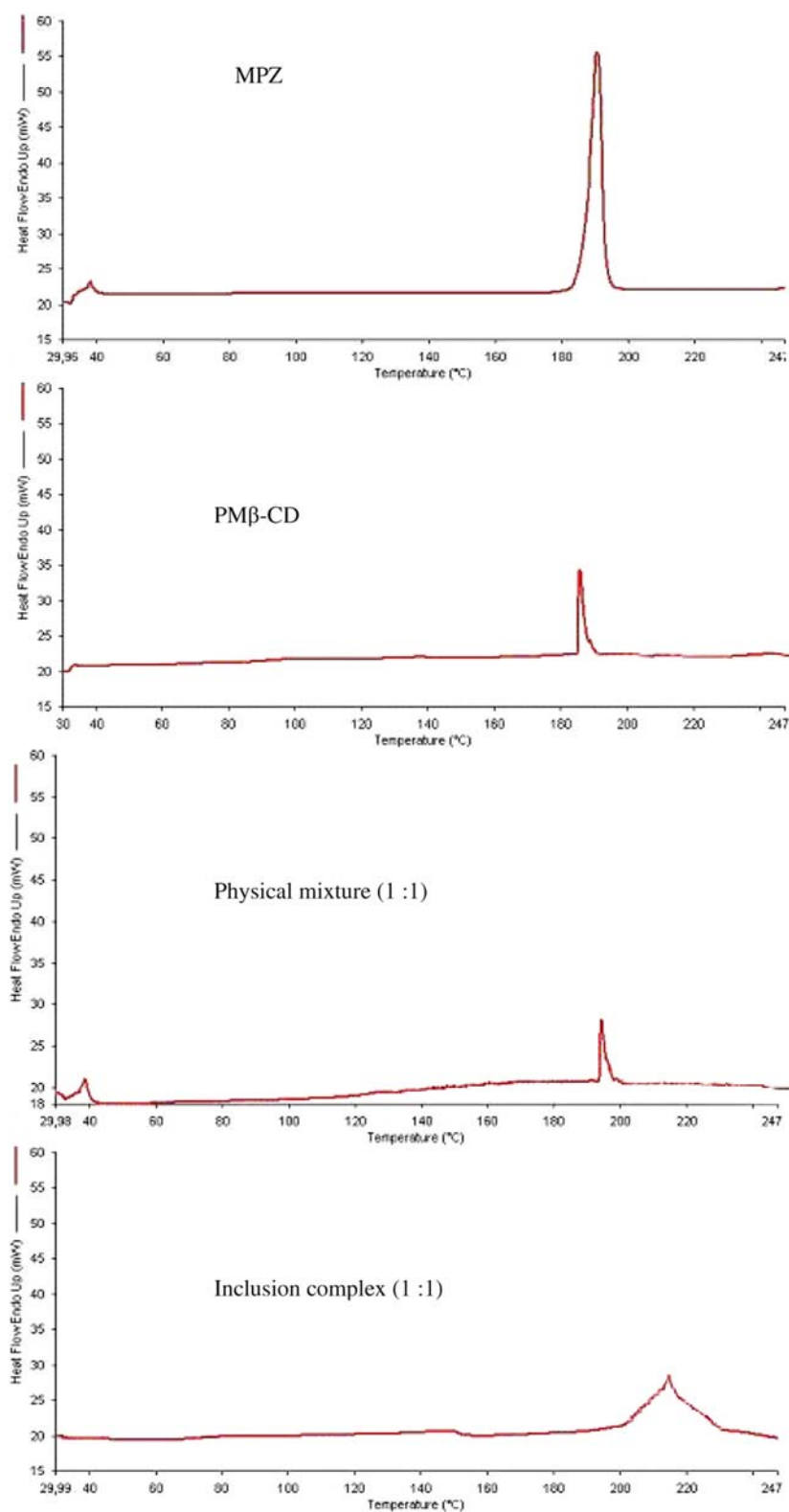
MPZ complex was characterized by DSC and IR spectroscopy. The results are represented Fig. 3 and Fig. 4. DSC thermogram of MPZ presented a melting point between 185 and 190°C and PM β -CD had also this melting point with the same temperature. In case of inclusion complex (1:1), this melting point was highly increased to $210\text{--}230^\circ\text{C}$ and any melting point corresponding to PM β -CD or MPZ was observed. These results suggest that an interaction between MPZ and PM β -CD was consistent with the great stability of the complex. In case of physical mixture (1:1), the spectrum presented a single melting point at $185\text{--}190^\circ\text{C}$ that seemed to result to the superposition of MPZ and PM β -CD signal. IR spectra confirmed also the formation of inclusion complexes: all IR bands characteristics of MPZ (S = O function at $1,307 \text{ cm}^{-1}$ and at $1,144 \text{ cm}^{-1}$, C = O function at $1,700 \text{ cm}^{-1}$ and N–H function at $3,431 \text{ cm}^{-1}$) disappeared in case of complex formation whereas IR spectrum from physical mixture showed no significant differences with the respective spectra from MPZ and PM β -CD.

Permeation profile of a 2 mg/mL MPZ hydrochloride solution with or without PM β -CD are depicted on Fig. 5. MPZ flux, on the base form, was null but MPZ hydrochloride flux was increased to $0.177 \pm 0.044 \mu\text{g/h/cm}^2$ being smaller to that reported by Calpena et al. ($5.01 \mu\text{g/h/cm}^2$ with hairless rat skin in the first 24 h [6]). But the difference may be explained by the use of another skin and of ethanol in the donor and receiver solution to improve the solubility of MPZ. This relatively low flux was explained by the low MPZ dissolved present in the donor chamber. Addition of 20% PM β -CD, complexed to MPZ, enhanced the amount of MPZ permeated to $0.570 \pm 0.058 \mu\text{g/h/cm}^2$ and simple

Table 1 Log P of MPZ between n-octanol and buffer at different pH ($n = 3$)

PH	5.5	7.4	10.3
Log Poct	-0.15	1.12	2.77

Fig. 3 Differential scanning calorimetric thermogram of MPZ, PM β -CD, physical mixture between MPZ and PM β CD in 1:1 molar ratio and inclusion complex between MPZ and PM β CD in 1:1 molar ratio (25–250°C, 10°C/min)



addition of PM β -CD to MPZ hydrochloride increased the percutaneous absorption with $0.549 \pm 0.175 \mu\text{g/h/cm}^2$, $0.435 \pm 0.031 \mu\text{g/h/cm}^2$, $0.474 \pm 0.054 \mu\text{g/h/cm}^2$ in case of 5%, 10% and 20% PM β -CD respectively.

PM β -CD improved the percutaneous flux of MPZ but this increase was insufficient to reach the therapeutic flux estimated between 7 and 21 $\mu\text{g/h/cm}^2$ for an IV dose of 10–30 mg/d.

Fig. 4 Infrared absorption spectra of MPZ, PM β -CD, physical mixture between MPZ and PM β -CD in 1:1 molar ratio and inclusion complex between MPZ and PM β -CD in 1:1 molar ratio (600–4,000 cm^{-1} , 50 scans, resolution of 4 cm^{-1})

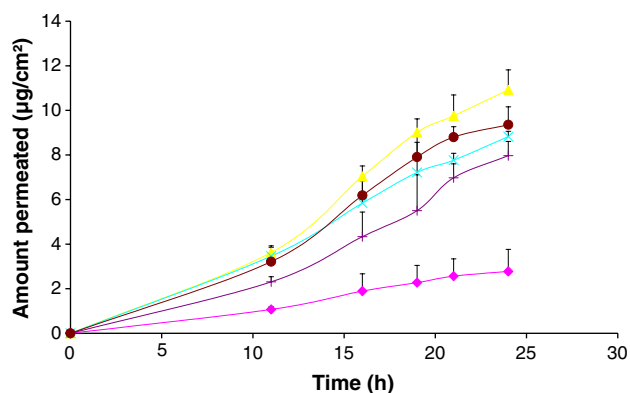
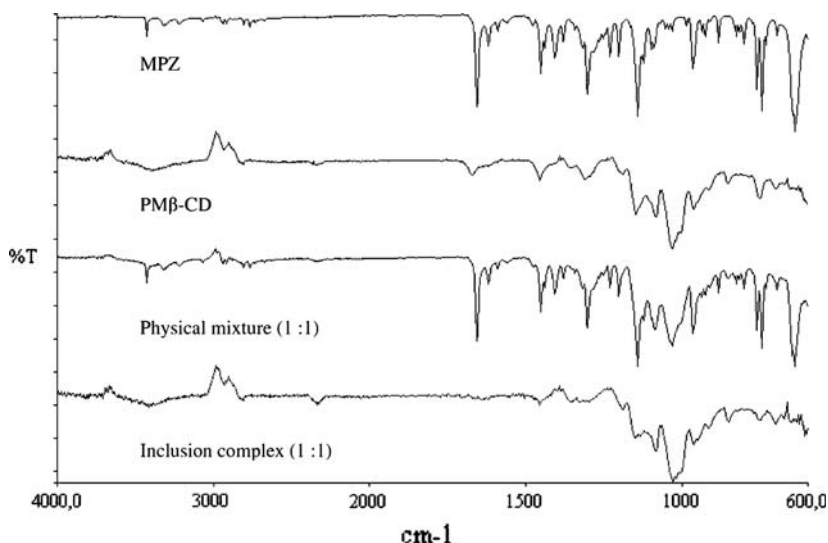


Fig. 5 Effect of PM β -CD on the permeation of MPZ at concentration of 2mg/ml ($n = 6$), \blacklozenge : MPZ hydrochloride \times : MPZ hydrochloride + PM β -CD 5% $+$: MPZ hydrochloride + PM β -CD 10% \circ : MPZ hydrochloride + PM β -CD 20% \triangle : MPZ at 2 mg/ml + PM β -CD 20% (solution)

Conclusion

Consequently, CDs increased MPZ apparent solubility, facilitating its availability and delivery through the cutaneous barrier. This study showed that PM β -CD improved penetration of MPZ. But the absorption was not enough to allow a therapeutic effect.

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