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Dicarboxylic acid esters as transdermal permeation enhancers: Effects of chain number and geometric isomers

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ABSTRACT

A series of transdermal permeation enhancers based on dicarboxylic acid esters was studied. Single-chain amphiphiles were markedly more effective than the double-chain ones. Monododecyl maleate, that is a *cis* derivative, was a more potent enhancer than its *trans* isomer, while the activity of succinates strongly depended on the donor vehicle. No difference between diastereoisomeric tartaric and *meso*-tartaric acid derivatives was found.

Transdermal drug delivery offers numerous advantages over the conventional routes of administration; however, poor permeation of most drugs across the skin barrier constitutes a major limitation of this methodology. One of the approaches to promote drug permeation through the skin is the use of permeation enhancers.[1] The most promising enhancers, possessing high activity together with low toxicity, are amphiphilic compounds containing a polar head and a lipophilic chain. These molecules are capable of inserting themselves into the stratum corneum ceramide-rich lipid lamellae and disrupting their tight packing.[2]

The structure–activity relationships of the enhancer chain(s) are relatively well described.[3] For example, the optimum chain length is approximately 10-12C,[4] *cis*-unsaturation in the chain increases activity[5] and the effect of branching or cyclization is usually negative, dependent on its position and extent.[6–8] The properties of the polar head have been less studied. We have previously reported the structure–activity relationships of a series of permeation enhancers based on amino acid-based ceramide analogues suggesting that the hydrogen bonding ability is inversely related to the enhancing potency.[9,10] The most potent enhancer was a maleic acid derivative 12GM12 (Fig. 1).

The aim of this work was to prepare a series of structurally simplified single- and double-chain amphiphiles based on maleic, fumaric, succinic, tartaric, and *meso*-tartaric acids in order to study the role of geometric isomers, chain number and hydrogen-bonding groups in their transdermal permeation-enhancing activity. It should be noted that these compounds are not intended for potential clinical use, they serve as tools to study the structure-enhancing activity relationships.

The double- (M and S) and single-chain (MOH and SOH) enhancers derived from maleic and succinic acids were prepared from the corresponding anhydrides and dodecanol under acid catalysis in toluene[11] or without solvent[12] (Scheme 1). F was prepared by esterification of fumaric acid (Scheme 2).[13] The monododecyl ester FOH was obtained by iodine-catalyzed isomerization[14] of MOH since attempts to prepare it from fumaric acid resulted in a formation of a symmetrical diester F. The most convenient procedure for the synthesis of the unsymmetrical esters M1 and S1 employed partial re-esterification of the corresponding dimethyl esters (Schemes 1 and 2). This procedure was

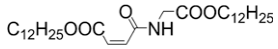
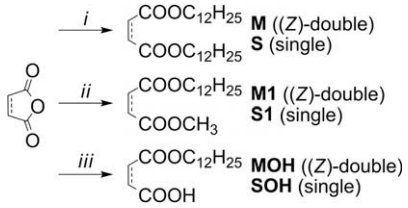


Figure 1. Transdermal permeation enhancer 12GM12.



Scheme 1. Reagents and conditions: (i) $C_{12}H_{25}OH$, H^+, toluene, reflux, 4 h; (ii) 1—MeOH, H^+, reflux, 3 h, 2—$C_{12}H_{25}OH$, H^+, reflux, 3 h; (iii) $C_{12}H_{25}OH$, H^+, 130–140 °C, 10 min.

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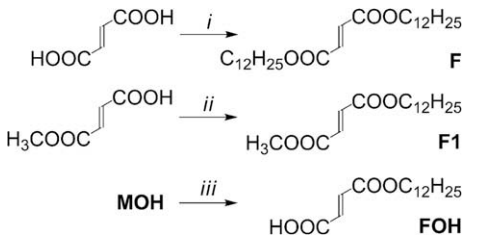


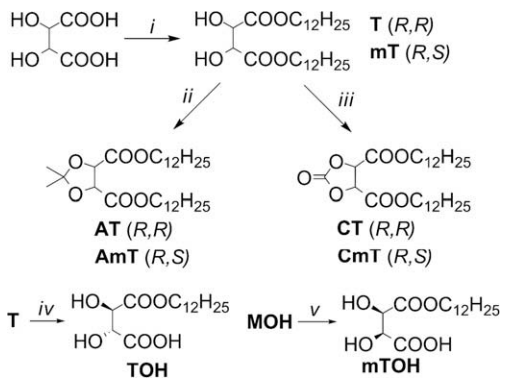
Scheme 2. Reagents and conditions: (i) $C_{12}H_{25}OH$, H^+, toluene, reflux, 4 h; (ii) $C_{12}H_{25}OH$, DCC, DMAP, 0 °C to rt, 24 h; (iii) I_2, 150 °C, 1 h.

not successful in case of F1, where a preferential formation of F was observed. Thus, the asymmetric diester F1 was prepared via carbodiimide coupling of methyl fumarate with dodecanol (Scheme 2).

The tartaric and *meso*-tartaric acid esters, T and mT, respectively, were prepared by esterification of the pertinent dicarboxylic acid. For the preparation of the acetonides AT and AmT, either T or mT reacted with 2,2-dimethoxypropane under acid catalysis. The analogous carbonates CT and CmT were synthesized from T and mT, respectively, with dimethylcarbonate and sodium metal. The monoester TOH was prepared by partial hydrolysis of T. This procedure was not successful in case of mTOH; thus it was prepared by syn dihydroxy addition to MOH (Scheme 3).

The transdermal permeation-enhancing activity of the prepared compounds was evaluated in vitro using Franz diffusion cell and porcine skin. Theophylline was selected as a model permeant of medium lipophilicity and to allow for the comparison with our previous results. All the prepared enhancers were evaluated in three donor vehicles of different polarity: water, 60% propylene glycol (PG), and isopropyl myristate (IPM). Theophylline was present at its maximum thermodynamic activity in all the donor samples either with or without the enhancer. The potencies of the individual enhancers are reported as the enhancement ratio values (ER), that is a ratio of the flux of theophylline through the skin with and without the studied enhancer.

Double-chain compounds. The activity of the first series, that is maleic, fumaric, and succinic acid derivatives is outlined in Figure 2. The didodecyl esters M, F, and S, that is the double-chain enhancers, did not increase theophylline permeation from either vehicle. This finding was rather surprising as the previously described maleic acid derivative 12GM12 was a relatively potent enhancer.[10] The difference between M and 12GM12 is an absence of glycyl linker. This suggests that the permeation-enhancing activity is not simply inversely related to the polar head size and hydrogen



Scheme 3. Reagents and conditions: (i) $C_{12}H_{25}OH$, H^+, 100 °C, 2 h; (ii) $(CH_3O)_2C(CH_3)_2$, H^+, CH_2Cl_2, rt, 2 h; (iii) $(CH_3O)_2CO$, Na, toluene, 90 °C, 3 h; (iv) 1—OH^-/H_2O, 2—H^+; (v) 1—$KMnO_4$/acetone/H_2O, 2—Na_2SO_3, H^+.

bonding ability as observed previously[10] but requires a certain optimum.

Fumaric acid derivative F even decreased the skin permeability with ER = 0.6, 0.1, and 0.7 from an aqueous, PG, and IPM suspension, respectively (Fig. 2). Although the differences were not significant, similar *trans* double bond-containing amphiphiles may serve as a lead for designing potential permeation retardants. These compounds are currently widely discussed for their potential to prevent absorption of hazardous substances through the skin.[15]

Single-chain compounds. The removal of one dodecyl chain resulted in a markedly increased activity (Fig. 2). The most active compound was MOH, which increased the flux of theophylline 26 times from the PG vehicle. The higher activity of the monoesters compared to the double-chain compounds cannot only be caused by the free carboxyl group; for example, lauric acid enhanced theophylline permeation only twice under the same conditions.[7] Moreover, the dodecyl methyl ester M1 showed significant activities as well. To our knowledge, this is the first report of such an effect. The possible explanation is that these double-chain amphiphiles may incorporate into the stratum corneum lipid bilayers without causing any significant disturbance. On the other hand, their single-chain counterparts possess a polar head of the same size but only one chain, which may prevent tight association of the chains via hydrophobic interactions. Interestingly, the activity of the enhancers in lipophilic IPM was negligible except for MOH and FOH showing ER = 7.5 and 4.5, respectively.

Geometric isomers. The higher permeation-enhancing activity of the single-chain compounds allowed for a comparison of the *cis* (*Z*) and *trans* (*E*) derivatives. The activities of the dodecyl methyl esters M1 and F1 were comparable. However, monoester MOH, that is a *cis* derivative, was significantly more active than the corresponding *trans* isomer FOH in all of the evaluated donor vehicles (Fig. 2). These monoesters differ in acidity but not to such an extent as the parent maleic and fumaric acid—the dissociation constants of MOH and FOH are 4.87 and 4.40, respectively.[16] Moreover, the different acidity cannot fully explain the difference in activity of the monoesters, since the less acidic SOH is inactive in aqueous and IPM vehicle but its activity is similar to MOH in PG.

Thus, the most likely explanation for the observed difference in permeation-enhancing activity of MOH and FOH is a different packing of the geometric isomers. Such behavior was described in unsaturated fatty acids with a double bond situated approximately in the center of the hydrophobic chain. For example, oleic acid was much more effective enhancer than elaidic acid, its *trans* isomer.[5,17] This was attributed to the presence of a 'kink' in the chain caused by *cis* double bond[18] leading to disruption of the stratum corneum lipid packing or phase separation. Although the double bond in MOH and FOH was situated in their polar head and not in the hydrophobic chains where the influence on the lipid packing is obvious, the difference in spatial arrangement may explain the higher activity of the maleate as well. Generally, the straighter-shaped *trans* isomers pack better than the U-shaped *cis* isomers as reflected, for example by their higher melting points (for example, mp of FOH and MOH were 82 and 58 °C, respectively, see Supporting Information). The shape of the polar head of the *cis* isomer does not allow for close packing of its hydrophobic chain with those of the stratum corneum lipids. That means that the intermolecular forces between the hydrophobic chains are not as effective so the drug can cross the lipid matrix more easily. The lesser ability of *trans* isomers to promote skin permeability seen in this study is further supported by the fact that the natural skin barrier constituents, that is sphingosine and 6-hydroxysphingosine-type ceramides, contain *trans* double bond in close proximity to their polar head too. Moreover, this C4-*trans* double bond was found to promote closer packing of ceramide in monomolecular films at the argon–buffer interface relative to comparable saturated species.[19]

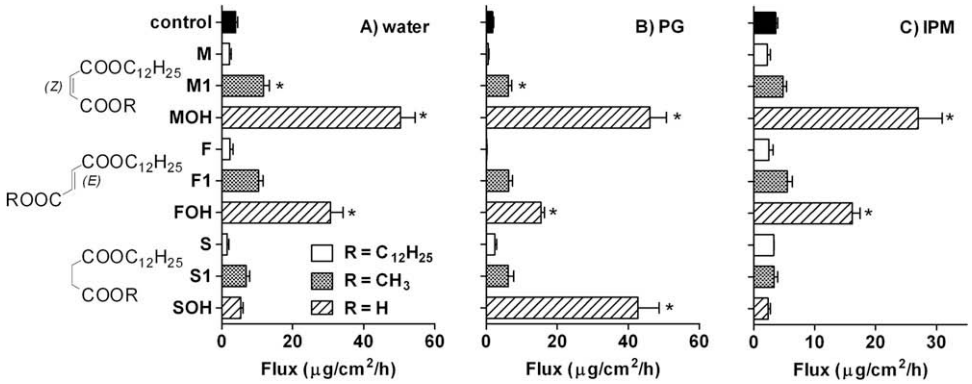


Figure 2. Transdermal permeation-enhancing activity of the maleates, fumarates, and succinates in (A) aqueous, (B) PG, and (C) IPM donor vehicle. Data are presented as the mean ± SEM (n = 4–12, 2–6 donors), * indicates statistically significant difference against control (p < 0.5).

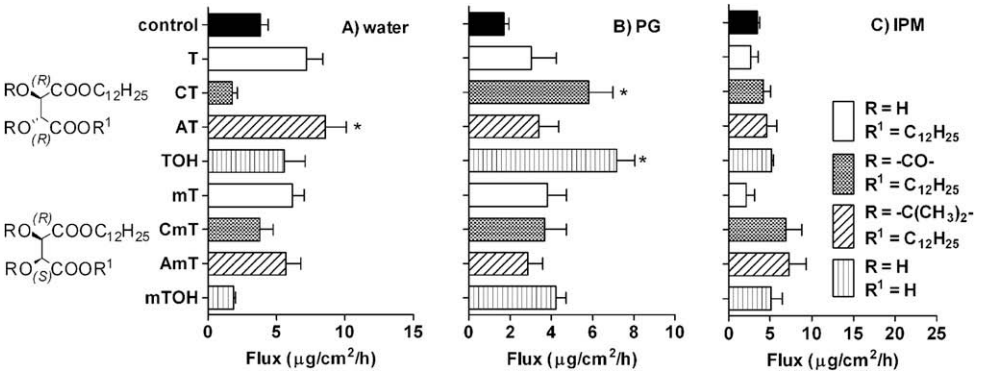


Figure 3. Enhancing activity of the tartaric and *meso*-tartaric acid derivatives in (A) aqueous, (B) PG, and (C) IPM donor vehicle. Data are presented as the mean ± SEM (n = 4–11, 2–4 donors), * indicates statistically significant difference against control (p < 0.5).

Double vs. single bond. The activity of the succinate SOH, that is the single bond counterpart of the above compounds with unrestricted rotation about the C2–C3 bond, was highly dependent on the donor vehicle. While its behavior was close to that of MOH in PG (ER of SOH = 24), it was inactive in the aqueous and IPM vehicle (Fig. 2). Such synergic action of solvent-type permeation enhancers such as PG with the amphiphilic ones has been observed previously[20,21] and may be explained by a combination of different mechanisms of action, for example increased partitioning plus lipid fluidization.

Tartrates. The activity of the tartaric and *meso*-tartaric acid derivatives is outlined in Figure 3. Some of these compounds showed significant enhancement but the activity of this series was generally low. Furthermore, no modification of the structure including masking the hydroxyls by acetonide or a cyclic carbonate or removal of one chain resulted in a significant improvement.

Furthermore, no significant difference was found between diastereomeric tartarates T, CT, AT, and TOH and the corresponding *meso*-tartaric acid derivatives mT, CmT, AmT, and mTOH. This is consistent with our previous studies showing no stereoselectivity in the action of amino acid-based enhancers.[22,23]

In conclusion, this study showed novel structure–activity relationships, which will be useful in designing future transdermal permeation enhancers.

Acknowledgments

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Supplementary data

Synthetic procedures, compounds characterization, skin permeation experiments, HPLC analysis, and data treatment. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.11.083.

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