Improved Terbinafine Formulations, Based on Third Generation Deformable Vesicles, for Noninvasive Topical Application and Superficial Mycoses Therapy

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ABSTRACT SUMMARY
To improve topical therapy of superficial mycoses, esp. onychomycosis, we studied locally targetable antimycotic agent carriers. Good candidates are deformable and superficially hydrophilic vesicles, which can be loaded well with terbinafine, as an antimycotic agent. The most modern kind of such carrier vesicles is chemically more robust and can accommodate more drug than the previously used vesicle kind, that is more challenged by the low effective dissociation constant and solubility of the drug. Novel and judicious choice of the carrier lipid, buffer, and pH value improves the resulting drug-carrier dispersion, which we exemplify with several dozen illustrative formulations.

INTRODUCTION
Superficial fungal infections affect up to 25% of the global population, and prominently include onychomycosis. Six-month oral use of an antimycotic drug is needed to treat successfully the latter, owing to inefficiency of the conventional topical antimycotic products. The chief reason is nail barrier, which might be conquered by local applications of suitable antimycotic drug carriers.

Antimycotic drug incorporation into deformable and superficially hydrophilic vesicular carriers promises to meet the goal.¹ Association of an antimycotic drug, terbinafine (TRB), with such carriers of the 1ˢᵗ/2ⁿᵈ generation remarkably ensures ~15-22% clear nail growth, according to an open label clinical study that tested daily topical application of such carrier dispersion on infected toes for 12 weeks.² In vitro studies confirmed importance of the carrier adaptability, achieved by adding a surfactant (polysorbate 80) to the chief vesicle building substance (phosphatidylcholine, PC).³ Unfortunately, chemical stability of phosphatidylcholine based vesicles reportedly decreases exponentially with a pH deviation from the optimum value, which for the tested vesicles loaded with cationic TRB is around 5.5 (−pKₐ,app ≡ pKₐ,mem → Results) and depends on the carrier, drug, and ion concentration.⁴ In turn, TRB solubility and carrier deformability increases with solution or dispersion acidity, esp. if pH ≤ pKₐ,app(TRB).

To face such and other problems, the published PC-based vesicles contain ethanol;⁵ quick disappearance of alcohol from skin surface prevents a lasting solution, however. We consequently addressed this and other issues by using PC-free vesicles of the 3ʳᵈ generation, to which pharmacologically inactive, water soluble ingredients (e.g. buffers) are a key.⁶ The final result are new dispersions of TRB in adaptable and superficially hydrophilic vesicles with an excellent prospect of locally treating superficial fungal infections, including onychomycosis.

EXPERIMENTAL METHODS
The reference, 1ˢᵗ generation, deformable carriers were made as published previously.¹,³,⁵ Their main components were soybean phosphatidylcholine (SPC, as membrane builder) and polysorbate 80 (Tw80, as membrane softener and even solubiliser,⁷ enabled by its large area per molecule and chain⁴) dispersed in an acetate buffer. TRB concentration in the resulting vesicles is 15 relative wt-%. We now prepared and tested different drug-carrier weight ratios and buffers to gain refined SPC-based, TRB loaded, and highly deformable vesicles without changing total SPC/Tw80 ratio (2/1 mol/mol). We also tested several types of the newest, 3ʳᵈ generation, deformable, TRB-loaded vesicles, here including polysorbates but no phospholipid or alcohol. The used polysorbates (mainly poly-
sorbate 21, Tw21) were moreover of non-solubilising kind, owing to their area per hydrophobic chain that is lower than for Tw80.6

We visually monitored TRB carrier dispersions as a function of time, simultaneously checking for drug precipitation, if any. We moreover determined the average vesicle size and size distribution using photon correlation spectroscopy. To gauge average vesicle adaptability in each dispersion, we utilised the enforced vesicle fragmentation method, described in full detail in ref. 8. Ref. 4 provides details of the potentiometric method that we used to assess TRB dissociation and partition coefficients.

RESULTS AND DISCUSSION

TRB association with a carrier lowers its apparent dissociation constant, expressed as \( pK_a \) to \( pK_{a,app} \equiv pK_{a,mem} \).4 The shift amounts to 1-2 pH units, depends on the carrier forming lipids and highlights importance of the carrier-water interface, and its relatively low dielectric constant, for drug dissociation in and loading to the studied carriers.

Partition coefficient, \( P^+ \) (or more precisely binding constant) of the cationic TRB form, pertaining to SPC and Tw21 based vesicles, corroborates the conclusion. The neutral form \( P^- \)-value is quite similar for both lipids, reflecting differential interfacial polarity / dielectric constant effects (see the following table).

<table>
<thead>
<tr>
<th></th>
<th>( \log P^+ )</th>
<th>( \log P^- )</th>
<th>( pK_{a,app} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td></td>
<td>7.05</td>
<td></td>
</tr>
<tr>
<td>SPC</td>
<td>3.87</td>
<td>2.69</td>
<td>5.84</td>
</tr>
<tr>
<td>Tw 21</td>
<td>4.40</td>
<td>2.46</td>
<td>5.09</td>
</tr>
</tbody>
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Results determined by potentiometric method allowing for the Coulombic, electrostatic effects (cf. ref. 4).

Despite broadly similar affinity of SPC and Tw21 based carriers for uncharged TRB, the latter kind of vesicles can accommodate more of the drug if water is supplemented with a well-chosen organic buffer. This can also improve the carrier vesicle adaptability, which is moreover drug ionisation and pH dependent (see the following figure) at low pH <\( pK_{a,app} \). In vitro antimycotic activity of TRB associated with the carrier is promising too. The related aggregates formed by amphipats having a similar hydrophobic chain and longer headgroup (Tw20) and amphipats having a similar polar headgroup and longer hydrophobic chain (Tw81) do not yield good TRB carriers, but some other, better matched, polysorbates do.

CONCLUSIONS

To improve deformable vesicles dispersion loaded with TRB, reported to treat effectively onychomycosis, we developed and characterised new TRB carriers containing no alcohol and no phospholipids. The new vesicles presented herein are based on a non-solubilising polysorbates exemplified by Tw21. They are highly adaptable and stable at low pH~3.5.

REFERENCES