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*Abstract*

# Biocatalytic Acylation of Menthol with Fatty Acids in Deep Eutectic Solvent as Reaction Environment †

**Florentina Olanescu and Madalina Tudorache ***

Faculty of Chemistry, University of Bucharest, 4-12 Regina Elisabeta Av., 030018 Bucharest, Romania; floriolanescu@gmail.com

* Correspondence: madalina.sandulescu@g.unibuc.ro

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For decades, the administration of transdermal drugs has been accepted as a possible route of noninvasive administration, with advantages of prolonged therapeutic action, low side effects, easy use, and better patient compliance. With all however, the major limitation of the transdermal drug delivery system is the skin itself. Terpenes can provide advantages over these enhancers due to their natural origin. A protective feature of terpenes is hydrophobicity (water repellent characteristic), which allows them to easily pass through the membrane of invading cells. When crossing cell membranes, these compounds can increase the fluidity of the membrane, so that the cell no longer has the ability to maintain a balanced internal environment.

In this context, we developed a biocatalytic method for the fatty acid methylesters (FAME) transesterification with menthol in the deep-eutectic solvent (DES) medium. In the literature, the fatty acid menthol esters have an accepted hydrophobicity, to be able to diffuse easily through the cell membrane. Lipase enzymes were proposed as biocatalysts of the transesterification process. Additionally, the use of DES combining menthol and fatty acids exhibited a proper reaction environment for an efficient transesterification process. The deep eutectic solvent (DES) contains (-)—menthol:fatty acid (3:1, *v*/*v*). The mixture was homogenized in thermoshaker for 24 h, 250 rpm, at a temperature of 40 °C. Biocatalytic tests for the transesterification reaction of fatty acid esters with menthol were performed according to a typical procedure, as follows: in 1.5 mL Eppendorf tube, DES (menthol:fatty acid = 3:1 (*v*/*v*)), lipase (1 mg or 10 mg/mL distilled $H_2O$), and fatty acid methyl ester (methyl laurate, methyl palmitate, methyl oleate) were mixed together. The final mixture was vortexed for 10 min, and incubated for 24 h, under 1000 rpm stirring and at 40 °C temperature. After the reaction, the samples were centrifuged for 15 min at 1500 rpm; the supernatant was filtered (0.2 µm porosity) directly in the HPLC vials. A sample analysis has been performed based on HPLC-DAD/RID method.

The transesterification of FAME with L-menthol catalysed by lipase enzyme was performed. The reagents were mixed previously in order to provide a DES environment for the reaction. The enzymatic screening of lipases from different biological sources was performed in order to establish the enzymewith high catalytic activity for the transesterification process. The experimental study demonstrated that the tested lipase did not have catalytic activity in the esterification process. Therefore, the DES content did not react in the set-up chemical context. The optimization process has been considered. Different FAME were used, demonstrating that the carbon chain of the fatty acid residue influenced the biocatalytic process. Furthermore, both components of DES will affect the performance of the transesterification of FAME with menthol. As an example, lipozyme RM 1M novozyme biocatalyst exhibited a maximum ester conversion of 93% for DES1.

Different conversion values were recorded in different DES environments for Lypozyme RM Novozyme. RM Novo preferred C12 type structures to the C16 and C18 type structures. At the same time, RM Novo preferred to catalyze the transesterification of FAME with saturated chains (methyl laurate) compared to those unsaturated (methyl oleate). Novozyme 435 novozymes exhibited catalytic affinity for methyl laurate. The maximum conversion value for Novo was reached in DES 1, amounting to 96%. A biocatalytic method for the transesterification of FAME with menthol was developed. The process was set up in the DES environment. Maximum conversion of 53% has been achieved for optimum experimental conditions. The developed process is a promising alternative for the efficient derivatization of FAME/menthol, in order to improve their organoleptic properties.

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