Synthesis of a Nicotinol DHA Ester for Prevention and Treatment of Cardiovascular Diseases: Enzyme and Process Optimization

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Polyunsaturated fatty acids (PUFA) of the Omega-3 family, like *cis*-4, 7, 10, 13, 16, 19-docosahexaenoic acid (DHA) and *cis*-5, 8, 11, 14, 17-eicosapentaenoic acid (EPA) are essential during development and they reduce risk factors of arthritis, cancer and cardiovascular diseases. Nicotinol (3-hydroxymethylpyridine) is an alcohol from the group B pro-vitamin. After absorption, nicotinol is rapidly converted into nicotinic acid (Vitamin B3), which can substantially decrease plasma free fatty acid, triglyceride, VLDL and LDL (very low and low density lipoproteins) levels and raise the plasma concentration of protective HDL (high density lipoproteins). Nicotinol is recommended in the treatment of dyslipidemia, hypercholesterolemia and hyperlipidemia.

It was hypothesized that EPA, DHA and nicotinol positive effects would be additional and even synergistic. The transesterification reaction of highly concentrated Omega-3 PUFAs ethyl esters with nicotinol was optimized using triacylglycerol lipases (EC.3.1.1.3) in a solvent-free-system (SFS). Commercially immobilized lipase B from *Candida antarctica*, Novozyme 435, at a temperature of 60°C, was demonstrated to be the best catalyst for the transesterification reaction between concentrated Omega-3 PUFAs ethyl esters and nicotinol. An eco-compatible SFS enabled enzyme activity, conversion at thermodynamic equilibrium and volumetric productivity to be maximized. From both kinetic and thermodynamic points of view, it was demonstrated crucial to evacuate ethanol co-product from the reaction medium. Using nitrogen bubbling, a conversion of DHA ethyl ester to nicotinyl-DHA superior to 97% was obtained in 4 hours using 45g/L of enzyme. In these conditions, a productivity of 4.2 g of product/(h.g of enzyme) was obtained.