New Developments in Physiological Cooling Agents

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ABSTRACT: *This chapter focuses on the latest technologies in physiological coolings agents and possibility of future trends.*

Physiological cooling agents are ubiquitous ingredients in many consumer products, such as chewing gums, toothpastes, mouthwashes, lotions and shampoos. Based on numerous new patents and publications, research and development in the field continues at a fast pace.

The chemistry and use of physiological cooling agents—or coolants—have been reviewed in relatively recent articles that cover literature published before 2005.[1,2,3] Also, the Web site of Leffingwell & Associates (*www.leffingwell.com*) is frequently updated and continues to be a valuable source of information.[4] The present chapter, warranted by rapid development in the chemistry and use of cooling agents, will focus mostly on newer publications, patents and patent applications, with references to older sources when necessary. Current patent trends will be reviewed separately at the end of this chapter.

According to classification suggested in the review "Progress in Physiological Cooling Agents,"[1] commercially available cooling agents with FEMA GRAS status can be divided into two major

families: menthoxy and Wilkinson Sword (WS) coolants. Menthoxy coolants include menthyl esters, menthyl ethers, menthone ketals and menthol analogs. WS coolants include p-menthane-3-carboxamides and acyclic carboxamides.

Menthoxy Cooling Agents

l-Menthyl lactate (FEMA 3748) is one of the most important physiological cooling agents in this family. Although this compound has been on the market for a long time, uncertainty still exists in the literature regarding the configuration of the asymmetric center at the lactic C^2. The Household Product Database of the National Library of Medicine lists *l*-menthyl lactate under CAS 59259-38-0, which corresponds to the R-configuration.[5] The same R-configuration for the lactic center of *l*-menthyl lactate is shown in recent publications.[2,6] On the other hand, the *Sigma-Aldrich Catalog of Flavors & Fragrances (2003–2004)* lists *l*-menthyl lactate under CAS 61597-98-6, which corresponds to the S-configuration, and the S-configuration is mentioned elsewhere.[7] For clarification, we esterified menthol with S-(+)-lactic acid. The product obtained matched by GC, optical rotation, melting point and spectra the most typical samples of *l*-menthyl lactate from the market, including Frescolat ML produced by Symrise GmbH. Thus, the correct CAS number for commercial *l*-menthyl lactate is 61597-98-6, and configuration of the lactic center is "S" (see **Figure 7.1**).

Another "missing link" in the story of *l*-menthyl lactate has been, until now, the lack of published information on its efficient synthesis, as well as for synthesis of its isomers such as *d*-menthyl lactate, neomenthyl lactates, and isomeric mixtures such as *l*-menthyl-*d,l*-lactate. *l*-Menthyl-*d,l*-lactate was first synthesized over a century ago by esterifying racemic lactic acid with *l*-menthol, but neither experimental details nor yield were reported.[8] In a later study, esterification of S-(+)-lactic acid with a 1.75 molar excess of *l*-menthol in chloroform in the presence of an acid catalyst gave only a 39% yield of *l*-menthyl lactate.[9]

l-Menthyl lactate is usually made by reacting lactic acid with an excess of *l*-menthol.[9] Recently, Millennium Specialty Chemicals developed and patented an efficient process for obtaining *l*-menthyl

lactate in high yield (over 90%) using excess lactic acid.[10] According to this process, the esterification produces a mixture of 57–68% of *l*-menthyl lactate, 24–32% of previously unknown *l*-menthyl lactoyl lactate, and smaller amounts of higher condensation products. Further, the mixture is carefully hydrolyzed by an aqueous base to convert *l*-menthyl lactoyl lactate and higher condensation products into *l*-menthyl lactate, while minimizing hydrolysis of *l*-menthyl lactate back to *l*-menthol and lactic acid (**Figure 7.1**).

In the course of the work on this method, pure *l*-menthyl lactoyl lactate (m.p. 58–60°C) was isolated and its structure was confirmed by NMR spectroscopy.[11] Formation of *l*-menthyl lactoyl lactate can be explained by condensation of *l*-menthyl lactate with another molecule of lactic acid. Higher oligomers can be formed by further similar condensations. An alternative mechanism of formation of *l*-menthyl lactoyl lactate and higher oligomers is self-condensation of lactic acid to dimers, trimers, etc., followed by esterification of the oligomers with *l*-menthol. Most likely, these two mechanisms coexist under the reaction conditions. It is well known that *l*-menthyl lactate is somewhat unstable on storage. Usually, over the course of several weeks, it develops an acidic, pungent odor and becomes unusable for most intended applications.

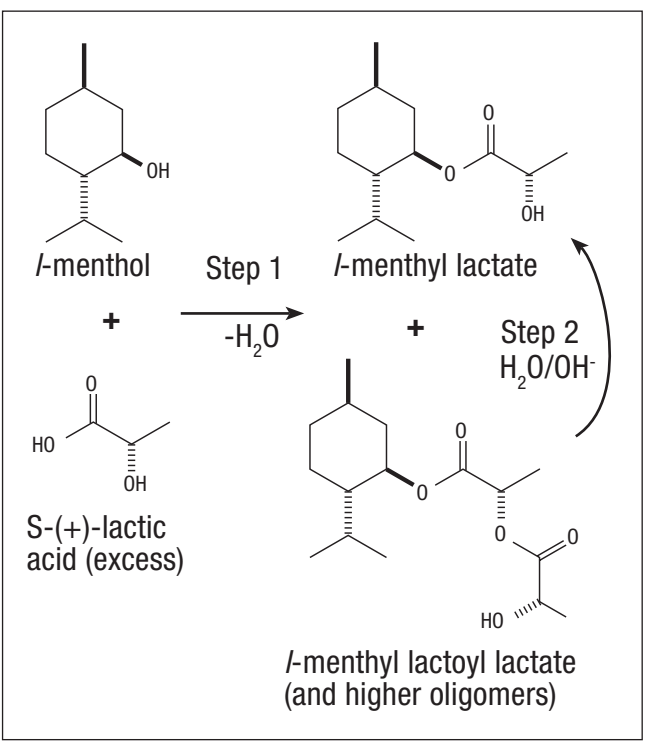

Figure 7.1. Millennium Specialty Chemicals process for l-menthyl lactate

This loss in quality is frequently accompanied by a rise in the acid number. The shelf life of *l*-menthyl lactate can be improved by adding small amounts of a base, for example $NaHCO_3$.[12] The mixture of *l*-menthyl lactate and inorganic salt obtainable by this method is, however, disadvantageous for some applications, especially if the presence of inorganic salt results in turbidities or precipitates in the consumer products. Recently it was found that the product can be stabilized without the addition of inorganic salts: *l*-menthyl lactate compacted under pressure is stable for a long period (at least six months), does not change from the sensory standpoint, and maintains a low acid number.[13]

Last, but not least, *l*-menthyl lactate has been detected and rigorously identified in natural cornmint oil (*Mentha arvensis*) of Indian origin, which may significantly improve its regulatory status in a number of countries.[7]

l-Monomenthyl succinate (FEMA 3810) and its closest homolog ***l-monomenthyl glutarate*** (FEMA 4006) have also been found in natural products.[6] Thus, *l*-monomenthyl succinate was identified in extracts of dry leaves of peppermint (*Mentha piperita*) and dry fruit of wolfberry (*Lycium barbarum*). *l*-Monomenthyl glutarate and *l*-dimenthyl glutarate were identified in an extract of dry fruit of *Litchi chinensis*. In the latter case, the concentrations of mono- and diester in the extract were 0.9 and 0.2 PPM, respectively, as determined by external standard quantification (monoester/diester ratio = 4.5).[6]

Certain uses of *l*-monomenthyl succinate as a physiological coolant have been patented by V. Mane Fils SA, and it is available from this supplier as a component of flavor blends sold under the trade name Physcool.[14] *l*-Monomenthyl succinate is essentially tasteless and provides a good balance of cooling onset and length of cooling.[6]

Interestingly, many uses of *l*-monomenthyl glutarate have not been patented, probably due to an early publication that gives multiple examples of consumer goods with suggested use levels of *l*-monomenthyl glutarate.[15] According to M.L. Dewis in the article "Molecules of Taste and Sensation,"[2] International Flavors & Fragrances (IFF) sells *l*-monomenthyl glutarate as "Cooler 2." The sensory profile of this product is similar to the succinate, but the onset is slower at about 40 s and the cooling is tenaciously long.