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Immobilised lipases in the cosmetics industry

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Commercial products for personal care, generally perceived as cosmetics, have an important impact on everyday life worldwide. Accordingly, the market for both consumer products and specialty chemicals comprising their ingredients is considerable. Lipases have started to play a minor role as active ingredients in so-called 'functional cosmetics' as well as a major role as catalysts for the industrial production of various specialty esters, aroma compounds and active agents. Interestingly, both applications almost always require preparation by appropriate immobilisation techniques. In addition, for catalytic use special reactor concepts often have to be employed due to the mostly limited stability of these preparations. Nevertheless, these processes show distinct advantages based on process simplification, product quality and environmental footprint and are therefore apt to more and more replace traditional chemical processes. Here, for the first time a review on the various aspects of using immobilised lipases in the cosmetics industry is given.

1. Cosmetics and its industry

Cosmetics are generally perceived as a class of products related to personal care and in particular skin care. As a matter of fact, however, the term (from the ancient Greek κοσμετικός *kosmetikós*, based on κοσμεω *kosméo*, 'arrange', 'decorate') comprises all human activities related to body care such as cleaning, softening, odouring and colouring. As such, cosmetics can most probably be considered as old as mankind. Distinct peculiarities in approaches to cosmetics developed according to cultures and ages, but a major focus has always been set on the preservation, restorage and improvement of beauty (the perception of which can be rather diverse, of course) as well as on the retardation of aging (or even rejuvenation).[1,2] Broad implementation of cosmetic products into everyday life started with the rise of synthetic organic chemistry enabling general access to desired ingredients and formulations with an acceptable effort.[1]

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Today cosmetics are of considerable and regarding the late 'wellness' movement still increasing importance.

The world market for cosmetics and toiletries accounts to about 200 billion € (value retail, source: Euromonitor International Database), excluding sales connected to cosmetic surgery or the 'wellness sector' (*e.g.* hotel business and provision of services). In 2010, the cosmetics market within the EU-27 alone was 67 bn €, while the US added 38 bn € and Japan another 30 bn € (source: Colipa Annual report 2010).[3] Most cosmetic products have a lifespan of less than five years and manufacturers reformulate 25% of their products every year. They need to improve products constantly in order to stay ahead in a highly competitive market where more choice and ever greater efficacy are expected by the consumer. Particular market drivers are innovations such as new colour pallets, treatments targeted to specific skin types and unique formulae concentrating on individual requirements.

The market for cosmetic chemicals (*i.e.* ingredients for cosmetics) in the EU-27, US and Japan was estimated to be about 6.8 bn US$ in 2008 (source: SRI Consulting), excluding natural soaps (*i.e.* salts of tallow and coconut fatty acids), fragrances, solvents and most fillers or bulking materials. The worldwide market for flavours and fragrances in 2008 (for all fields of application including food, beverages, cosmetics and pharmaceuticals) was 20.3 bn US$.[4] Thus, cosmetic chemicals represent an important market for the chemical industry, which accordingly is served mainly by chemical companies such as BASF, Evonik Industries, Clariant or Rhodia. Cosmetic products as a whole are predominantly marketed by international enterprises like Procter&Gamble, L'Oreal, Unilever, Beiersdorf or Colgate-Palmolive.[5]

According to application, cosmetics are categorised into fragrances and perfumes (*e.g.* eau de toilette, deodorant and perfumes), decorative cosmetics (*e.g.* face make-up, lip care, nail varnish and self-tanning lotion), skin care (*e.g.* body milk, lotion, shaving foam, sunscreen and insect repellents), hair care (*e.g.* shampoo, conditioners and colouring) and toiletries (*e.g.* soaps, shower gel, bath additives, tooth paste and mouth wash).[5]

The concrete composition of cosmetic products strongly depends on the product type and manufacturer and a multitude of cosmetic chemicals can therefore be distinguished. Liquid skin cleaners, for instance, typically comprise surfactants (*e.g.* cocamidopropyl betaine, sulfosuccinate, alkylpolyglycoside), refatting agents (*e.g.* fatty acid poly(glycolesters), fatty acids and alcohols, lecithin derivatives), thickeners (*e.g.* ethoxylated glycoesters, xanthan gum), skin conditioners (*e.g.* protein hydrolysates, poly(dimethyl siloxane), polyquaternium), moisturizers (*e.g.* amino acids, glycerin, lactic acid, sorbitol), fragrances, colours, organic acids (*e.g.* tartaric or citric acid), preservatives (*e.g.* benzyl and salicylic acid, parabens, Bronopol), antioxidants (*e.g.* α-tocopherol, butyl hydroxytoluene) and complexing agents (*e.g.* sodium salts of ethylene diaminotetraacetic acid or iminosuccinic acid). In addition, components with specific activities, such as plant extracts, vitamin derivatives, skin calming or stimulating additives, cooling agents, abrasive additives or essential oils, are frequently included.[6]

As illustrated by this example, many products and their ingredients are characterised by an overall fatty composition or low solubility in water, respectively, which in view of biocatalytic production specifically implies use of lipases.

2. Lipase-derived cosmetic products

Lipases (triacylglyceride hydrolases; EC 3.1.1.3) are an enzyme family which under natural conditions catalyse the hydrolysis of carboxylic ester bonds in hydrophobic compounds such as triglycerides. Under non-aqueous conditions, their function can be redirected towards alcoholysis, esterification, interesterification and transfer of acyl groups from esters to other nucleophiles like amines or thiols involving long- to short-chain carboxylic acids.[7] Importantly, they are further characterised by a particularly good compatibility with fatty, non-aqueous media and emulsions as required for use in the production of cosmetics, a broad substrate acceptance, including many non-natural compounds, a high chemo- and stereoselectivity, activity without requirement of expensive cofactors and comparably high process stability.[8] Lipases are currently considered the most important enzymes for biotechnological applications.[9–12] In the production of cosmetics they can function as both active ingredients in a cosmetic formulation and biocatalysts in the synthesis of specific cosmetic chemicals.

2.1 Lipases in functional cosmetics

As all biological processes are based upon the activity of enzymes, these biocatalysts are also essential for body care. *In* the skin enzymes are responsible for uncoupling complex inactive molecules and transforming them into simpler and often more active molecules. Proteases, for example, decouple or hydrolyse proteins, glycosidases promote the enrichment of the epidermis with ceramides and tyrosinase facilitates the synthesis of melanin. *On* the skin and the *stratum corneum*, enzymatic reactions modulate keratinisation processes, ensure inter-corneocytar cohesion, encourage tanning and auto-photoprotection, act on the metabolism of sebaceous glands and adipocytes, have a whitening activity on age spots, stimulate the natural defense mechanisms of the skin or protect collagen and elastin fibers.[13] Accordingly, enzymes obviously make promising natural active agents for specified personal care products belonging to the so-called 'functional cosmetics', 'cosmeceuticals' or 'treatment products'.[14]

Active lipases can mainly be found in cosmetics for surfacial cleansing[15] (*e.g.* 'Facial Cleanser' by Juju Cosmetics, 'Revue Sebum Soap' by Kanebo Cosmetics), anti-cellulite treatment[16–18] (*e.g.* 'Silhouette Sculptant Exfoliating Mousse 402' by Maria Galland, 'Double Minceur Ciblée' by Guinot) or overall body slimming (*e.g.* 'Bath Additive with Fat Dissolving Enzymes' by Ishizawa Laboratories),[19,20] where they are responsible for the mild loosening and removal of dirt and/or small flakes of dead corneous skin (*i.e.* peeling) and/or assist in breaking down fat deposits, often in combination with further enzymes such as proteases. Further applications have been described for nose cleansing,[19,21] makeups,[22] beauty masks,[23] and hair care.[20,24,25]

In a different approach lipases are included in cosmetic formulations for controlled *in situ* release of an active ingredient (*e.g.* hydroxy acids) from an inactive precursor (*e.g.* hydroxy acid ester),[26] an application type that has become of particular interest in the field of functional perfumery for an even development of odour over time. Increasingly, however, enzymes already present in the skin instead of added enzymes are addressed by such cosmetics,[27] as exemplified for the ''on demand released'' deodorant active polyglycerol-3 caprylate.[28]

2.2 Lipases for catalysis

Based on the broad variety of compounds derived from (or *via* use of) fats and (fatty) carboxylic acids in cosmetic products (see Section 1), lipases and their hydrolytic, esterifying and acylating activities show enormous potential for implementation in the production of cosmetic ingredients. In fact, a multitude of possible lipase-catalysed syntheses have been described to date, and a variety of products have actually been commercialised. For classification, specialty esters, aroma compounds and functional actives can essentially be distinguished.

2.2.1 Specialty esters. Specialty esters are fatty acid derivatives with an important role as emulsifiers (functioning to form emulsion), emollients (functioning as an oil phase in emulsions), detergents, thickeners and pearlizing agents (*i.e.* additives that give the final formulation a pearl like shine). Tailoring of ester functionalities to specific requirements is easily possible due to the availability of fatty acids in numerous different chain lengths.[29] Therefore specialty esters are the most frequently used components in cosmetic products next to water.[30,31]

Emollient esters derived from long-chain fatty acids and fatty alcohols more and more replace simple oils (*e.g.* mineral oil or vaseline) as an oil phase in cosmetic emulsions due to their ability to keep the skin smooth, soft and elastic through prevention of dehydration.[12,32] Most of these esters are produced by conventional methods, but a couple are also synthesised *via* lipase catalysis on a commercial scale (see Fig. 1).[32] The first lipase-derived emollient esters were launched by Evonik Industries AG. Today the portfolio of such esters comprises myristyl myristate,† decyl cocoate, cetyl ricinoleate, oleyl erucate and isoamyl cocoate.

An early process yielding isopropyl esters such as isopropyl myristate and isopropyl palmitate (with widespread uses in skin and sun-tan creams, bath oils, *etc.*) was developed by Unichema,[10,33] but to our knowledge never commercialised. This might be explained by the difficulties usually encountered with the separation of isopropanol–water mixtures and the resulting complex reactor setup demanding additional investment. Enzymatically produced 2-ethylhexylpalmitate was lately launched by the US based company Eastman.

Structured triglycerides containing long chain fatty acids are an important class of raw materials for emulsions since their sensory properties vary with the fatty acid composition (content, position and saturation degree of fatty acids).

† All cosmetic products mentioned in this text are named according to their official INCI registration (CTFA name).

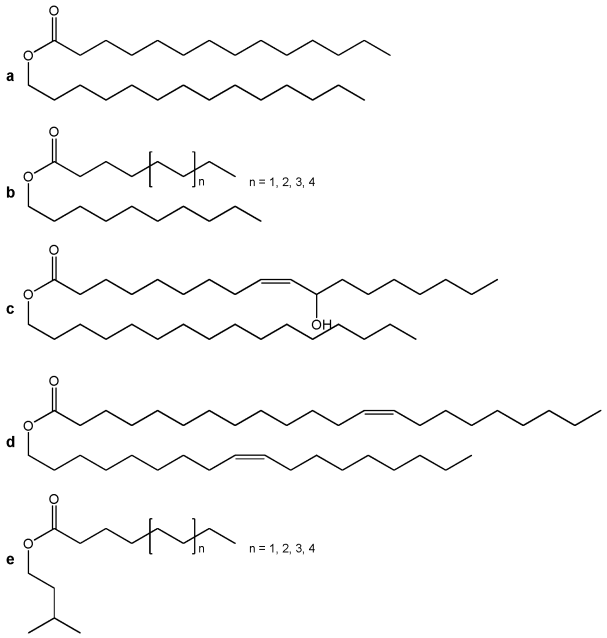

Fig. 1 Emollient esters commercialised by Evonik Industries AG. (a) myristyl myristate; (b) decyl cocoate; (c) cetyl ricinoleate; (d) oleyl erucate and (e) isoamyl cocoate.

Tailoring of fats and oils from natural resources to specific needs (*e.g.* shifting the melting point of margarine towards the surface temperature of the human tongue) can easily be performed *via* lipase catalysis (see Fig. 2). While this approach follows the same rational as that of the above mentioned emollient esters, structured triglycerides are nowadays rather used in the food than in the cosmetics industry. This is mainly due to the fact that in cosmetics consumers today prefer more ''light'' formulations that usually require the use of oil components with low molecular weight. As a result, triglycerides used in cosmetics are mostly based on short fatty acids, such as caprylic/capric triglycerides, which are synthesised by esterification

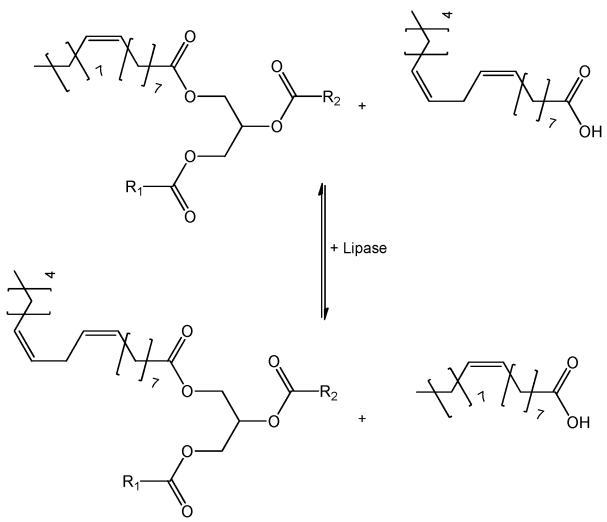

Fig. 2 Representative reaction scheme for the preparation of structured triglycerides. Here, an oleic acid moiety is replaced by a linoleic acid moiety.

of glycerol with the corresponding fatty acids rather than starting with natural oils.[34–38]

Surfactants (*i.e.* surface-active agents with an amphiphilic structure) are mandatory ingredients of almost all cosmetic products for emulsification and alteration of foaming properties. Ester-based surfactants, consisting of a medium to long chain fatty acid and a hydrophilic head group, play a particularly important role,[39] which might in future be further enhanced by the finding of specific antimicrobial activity of some of these compounds.[40] Depending on the length and saturation degree of the fatty tail and the choice and size of the hydrophilic head (typically glycerol, sorbitol or glucosides) employment for stabilisation of water-in-oil (W/O) lotions or oil-in-water (O/W) emulsions is possible. The specific performance in this regard is described as the hydrophile–lipophile balance (HLB) value.[41] Surfactants with HLB values of 3–8 produce W/O lotions whereas those with HLB values of 8–18 are suitable for producing O/W emulsions.[42] Of particular importance are *partial glycerol esters* (*e.g.* glycerol mono- or dilaurate, which represents one of the oldest industrially produced emulsifiers for cosmetic application[43]), *inter alia* because of their unique property of interacting with polysaccharides and polypeptides changing the rheological properties of the emulsion,[42] and *sugar esters*, (*e.g.* sorbitan monostearate) due to their excellent surface-active properties. Both types are mainly produced by chemical means, but are also accessible by lipase-catalysed synthesis.[39,44–46]

Partial glycerides are classically synthesised *via* base-catalysed glycerolysis (excess of glycerol) of native plant oils at 210–240 °C and under a nitrogen atmosphere. However, the resulting mixtures are inhomogeneous consisting of free fatty acids, practically all positional isomers of mono- and diglycerides and unreacted triglycerides. Diacylglycerols can exist in three isomeric forms, a symmetrical (*sn*-1,3-) derivative and two enantiomers (*sn*-1,2- and *sn*-2,3-). These are thermodynamically less stable than the symmetrical molecules and can undergo acyl group migrations, resulting in equilibrium mixtures in favour of the symmetrical, achiral *sn*-1,3-isomer, which are overall interesting as building blocks for structured lipids.[36,47] Likewise, monoglycerides can exist as three positional isomers, two being enantiomers and one an achiral molecule. Monoglycerides of higher chemical, but not isomeric, purity (>90%) can be obtained by cost- and energy-intensive molecular distillation.[47]

In contrast, isomerically pure *sn-1,3-diglycerides* and *specific monoglycerides* are obtained under mild conditions *via* lipase-catalysed esterification of glycerol with a variety of acyl donors such as free fatty acids, free fatty esters or the corresponding vinyl esters (see Fig. 3).[48–55] Various processes describing technical realisation of these reactions can be found in the literature.[56,57] The major problem encountered here is the immiscibility of the participating compounds. Approaches to overcome this problem include adsorption of glycerol onto silica gel as a solid support before reaction,[58–60] and use of sophisticated solvent systems such as supercritical CO_2 and ionic liquids (ILs).[61,62] A widespread use of ionic liquids in the production of cosmetics, however, has been so far limited as

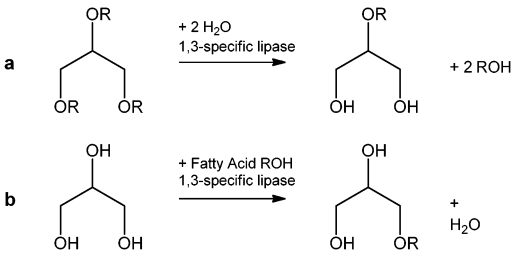

Fig. 3 Scheme for the enzymatic synthesis of monoglycerides either by selective hydrolysis of triglycerides (a) or monoesterification (b); R = acyl chain of fatty acids.

the recovery and recyclability is difficult. Some common ILs such as BF_4^--based ILs might also not be accepted in cosmetic applications due to the general ban of specific compounds (*e.g.* borate) for use in cosmetics. In addition to the miscibility problems encountered with the enzymatic production of partial glycerides, by-products such as water or low-boiling alcohols frequently have to be removed in order to drive conversions to completion (*e.g.* by addition of molecular sieves, application of vacuum, azeotropic removal by distillation and reactions in solid phase),[54] which particularly in the case of highly viscous reaction mixtures is rather difficult to achieve.

Sugar esters based on short chain alkyl glucosides and fatty acids have been intensively investigated as targets for lipase catalysis due to the overall low (regio-)selectivity of chemical methods towards the numerous hydroxy groups in sugars (see Fig. 4).[63]

Mainly two strategies for the lipase-catalysed synthesis of sugar esters can be distinguished. The first was based on the use of organic solvents suitable for the solubilisation of both substrates (typically dimethylsulphoxide, dimethyl formamide or pyridine),[64–69] while the second relied on modification of the sugar moiety followed by solvent-free esterification with molten fatty acids.[70–74] Although the first procedure is more straightforward, the reaction kinetics are such that the overall productivity is poor.[50] Furthermore, use of solvents is highly unwanted in the cosmetics industry. For these reasons, the second methodology is more attractive. Adelhorst *et al.*[70] described a method for regioselective esterification of simple alkyl glycosides using a small molar excess of molten fatty acids. The esterification rate was considerably dependent on the length of the alkyl chain. With ethyl-, *n*- and iso-propyl or butyl glycosides the reaction is complete in a few hours. A process for preparation of 6-*O*-acylglucopyranosides (see Fig. 5) was put to a pilot-scale by Novo-Nordisk.[50] However, while the obtained products show

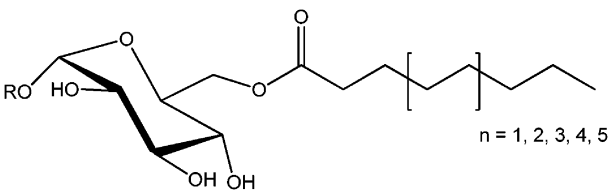

Fig. 4 Schematic of glycoside esters described by Björkling *et al.*;[63] R = short alkyl chain.

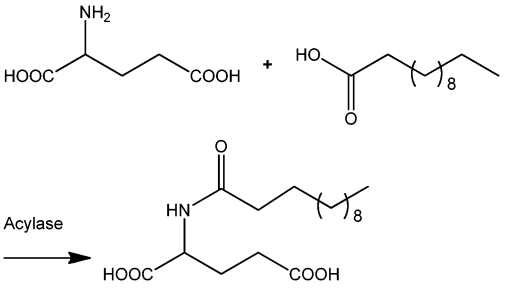

Fig. 5 Direct amidation of glutamate to yield *N*-lauroyl glutamate according to Wada *et al.*[99]

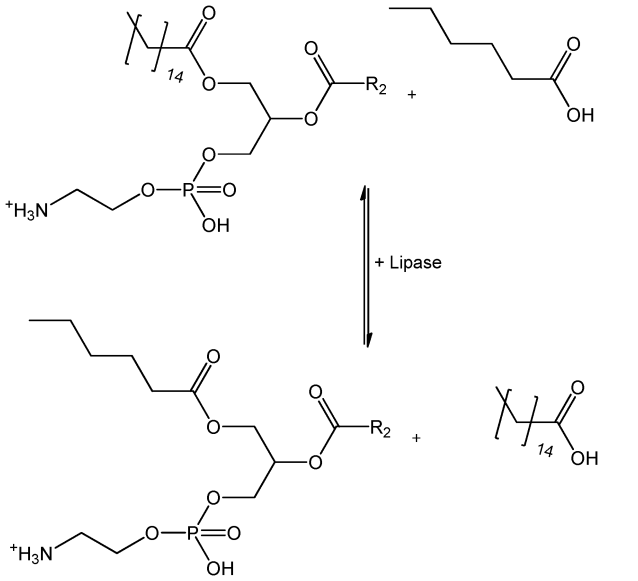

Fig. 6 Synthesis of structured phospholipids according to Svensson *et al.*[107]

good application behaviour, the process still needs further optimization to reduce overall costs as due to the high difference in polarity of glucose and fatty acids only the rather expensive propyl or even butyl glycosides can be converted with reasonable efforts. A possible strategy would be to improve mixing of the reactants in order to allow esterification of the cheap methyl glycosides. The additional impact of water production on the outcome of glycosylmyristate synthesis was reviewed by Cauglia and Canepa,[75] and available measures for improvement such as use of membrane reactors, azeotropic mixtures, pervaporation systems and water adsorbent systems were discussed. Approaches to overcome miscibility problems include use of detergents,[76] temporary protection groups,[68] heterogeneous reaction systems (suspension of substrates),[77,78] microwave/ultrasound assisted syntheses,[79] and, again, use of specific ionic liquids.[80–82]

Alternatively, sugar acetals were used as starting materials to facilitate miscibility of the reactants.[71,72,83] The final products, mono- and disaccharide fatty acid esters, were obtained in good yields after mild acid hydrolysis of sugar acetal esters following lipase-catalysed esterification. This also provides a route to the synthesis of various (oligo)saccharide fatty acid esters.[50] However, although large-scale acetalization and subsequent deprotection do not impart serious technological difficulties,[50] the overall production sequence is complicated and was never commercialised.

Another interesting target for enzymatic processes are *N-acylated amino acids*,[84,85] an important class of surfactants for cosmetic products due to excellent emulsifying properties, attractive skin tolerance, good biodegradability, low toxicity and strong antimicrobial activity.[86,87] In addition, the chemical linkage between the hydrophilic and hydrophobic parts of the molecules is highly stable under alkaline conditions, which is of key interest for many surfactant applications.[88] Conventional production is based on fatty acid chlorides and uses the Schotten–Baumann or Einhorn type of amidation.[89–91] However, besides the use of undesired chlorine chemistry, this multistep process usually yields significant side products and a lot of salt, which can significantly interfere with the final formulation. Enzymatically synthesis of such surfactants (*e.g.* lauroyl glutamate (see Fig. 5), oleyl homoserine) can be achieved by use of lipases[92–97] and acylases.[98,99]

Lipase-catalysed reactions usually employ amino acid esters or amides since direct acylation of the α-amino function with free acids leads to only low product concentrations. This results from the thermodynamic equilibrium which in aqueous environment favours the free amine and acid, respectively.[99] The processes have not been commercialized yet due to the unavailability of enzymes with sufficient activity and selectivity to allow economically feasible production. However, first efforts to improve the activity of such enzymes to come closer to potential commercialization have recently been published.[100]

A natural and therefore environmentally benign emulsifier used in cosmetic products is *lecithin*, a complex mixture of individual phospholipids (mainly phosphatidyl choline and phosphatidyl ethanolamine) recovered from plant oils such as soy bean oil.[101] However, due to emerging negative issues with crude soy lecithin (*e.g.* potential allergenicity of trace amounts of soy protein and scarcity of non-GM-soy beans as raw materials) and specific surface-active properties required for use in personal care a wide range of '*special lecithins*' have also been developed.[102] On an industrial scale, these are currently derived from the crude material by chemical and physical methods,[103,104] but there is a clear scope for application of enzymes due to the presence of numerous functional groups in phospholipid molecules requiring control over regioselectivity and/or the degree of modification (see Fig. 6).[38,104–107]

Special phospholipids with beneficial properties, which in crude lecithin occur only in minor quantities (*e.g.* phosphatidylserine, phosphatidylglycerol), can be obtained in good yield from phosphatidylcholine and serine or glycerol using phospholipase D.[102,108] Enrichment of the desired phospholipid in natural lecithin can also be achieved with this enzyme catalysing transphosphatidylation under low water conditions.[109] For specific commercial applications such phospholipase D mediated syntheses are performed on a multi-kilogram scale.[50] Another class of industrially important lecithin-derived surfactants currently prepared on a large scale are lysophospholipids.[50] Their synthesis is achieved in a continuously run process using

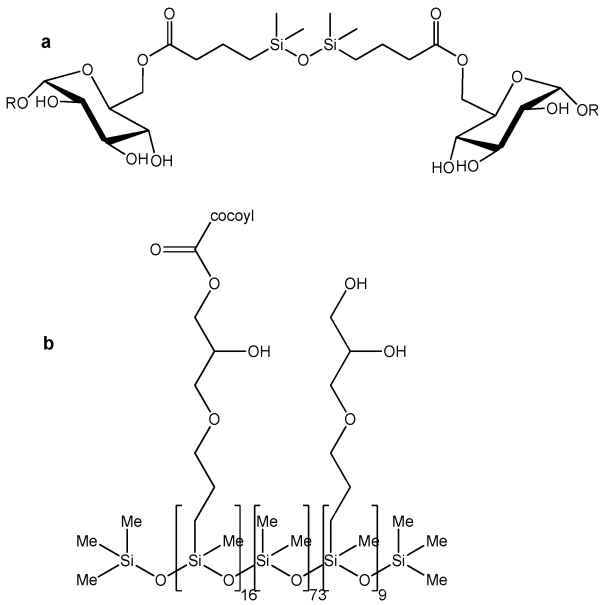

Fig. 7 Exemplified structures of enzymatically obtained siloxanes according to Brandstadt *et al.*[113] (a) and Ferenz *et al.*[118] (b).

a fungal lipase that catalyses transesterification of lecithin in alcohols. The lipase displays strict regioselectivity towards the *sn*-1 fatty acid in the phospholipid molecule, exclusively yielding *sn*-1 lysophospholipid as the final product. *sn*-2 Lysophospholipids have been obtained from this starting material *via* acyl migration catalysed by ammonia vapour.[110]

Siloxanes: a couple of years ago researchers from Ciba[111] on the one hand and Dow Corning (see Fig. 7a)[112,113] on the other hand for the first time described the enzymatic modification of silicone derivatives. Like fatty acids, siloxanes play an important role as raw materials for cosmetic products.[114–116] They are chemically highly stable and by choosing among the numerous available chain lengths and topologies they are also ideal hydrophobic building blocks. While these results showed the possibility of modifying siloxanes the actual process trials showed the limitations of that approach: due to the immiscibility of the reagents additional solvents have to be applied (which is usually to be avoided in the cosmetics industry, see above) and only rather short siloxane chains were successfully converted. By changing the order of reaction steps it was possible to develop a process in which also highly hydrophobic long chain siloxanes could be enzymatically converted.[117] This process gives access to novel structures with interesting properties and potential new emulsifiers and thickeners (see Fig. 7b).[118]

Thickeners play an important role for the appropriate adjustment of rheological properties in cosmetic formulations. Frequently used examples are PEG-55-propylene glycol oleate (see Fig. 8) or PEG-120 methyl glycoside dioleate. While the enzymatic synthesis of such compounds is possible,[119] it requires novel reactors to transfer the process to the production scale (see Section 4) and novel enzyme immobilisates to achieve sufficient long-term stability (see Section 3.2).

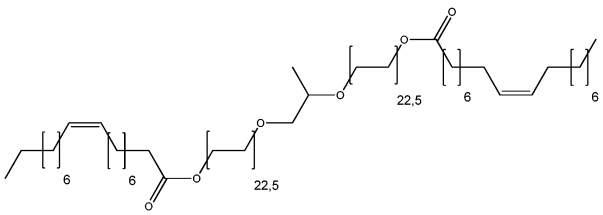

Fig. 8 Structure of the rheological additive PEG-55-propylene glycol oleate according to Hilterhaus *et al.*[119]

The same applies to *pearlizing agents* such as ethylene glycol distearate. It can be easily made by lipase catalysis,[29] but the formation of the surfactant-like intermediate monoester causes significant enzyme loss and thus also requires more stable enzyme preparations (see Section 3.2).

Oligomers: not directly linked to cosmetic applications but nevertheless of potential interest is the work on enzyme-catalysed polymerization reactions. While the obtained polymers are usually of limited interest for cosmetic applications, the shorter oligomers formed that way could have interesting properties such as film forming or sensorial quality. Biodegradable oligomers formed by lipase catalysis are polyesters derived by ring-opening polymerisation (see Fig. 9),[120] or by polycondensation of diols and diacids.[121]

2.2.2 Aroma compounds. *Flavour and fragrance compounds* are important chemical ingredients of cosmetic products, with further applications in the food, feed, chemical and pharmaceutical industries. Distinct chirality and high purity of the structurally diverse compounds are usually required to achieve the required odour impact. This is due to the different organoleptic properties that isomeric structures of the same compound frequently encounter. Menthol, for instance, is one of the most important flavouring agents for many applications and is the major compound in natural peppermint oil. The characteristic peppermint odour and the typical cooling/refreshing effect, however, are limited to 1-(−)-**menthol**, which is only one of eight possible isomers. Isomerically pure production can hardly be achieved by chemical synthesis and many flavours and fragrances for commercial use are therefore still obtained by extraction from the natural product. Lipases with

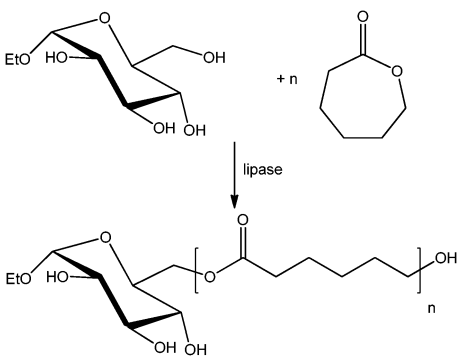

Fig. 9 Reaction scheme for the formation of biodegradable oligomers according to Bisht *et al.*[120]

their usually high stereoselectivity can be, and partly are, involved in the synthesis of flavours and fragrances in two principal ways: direct synthesis from appropriate precursors and resolution of racemic mixtures.[122,123]

Aroma esters consisting of short chain fatty acids (including acetic acid to hexanoic acid and branched-chain fatty acids such as 4-methyloctanoic acid) and alcohols (including methanol to hexanol, geraniol and citronellol) have been obtained by direct synthesis with lipases.[124–134] They are often characterised by a fruity flavour (*e.g.* methyl butanoates, methyl butyl esters, isoamyl isovalerate) and/or a green note (*e.g.* (*Z*)-3-hexenyl acetate),[122] but lack specific stereochemistry. Lipase catalysis in that case is mainly performed, because the products can be labelled as natural.[134] Large-scale synthesis of (*Z*)-3-hexenyl acetate with lipase in hexane has been described by several authors.[135–137] Methyl benzoate which is part of the aroma of some exotic fruits and berries was produced from benzoic acid with methanol by Leszczak and Tran-Minh.[138] In 2001, Gatfield *et al.* reported a method to produce natural ethyl (*E*,*Z*)-2,4-decadienoate, the impact compound of pear, by transesterification of *Stillingia* oil with ethanol.[139] A stereoselective enzymatic synthesis of *cis*-pellitorine ((2*E*,4*Z*)-*N*-isobutyldeca-2,4-dienamide), a taste-active alkamide naturally occurring in tarragon, was then reported in 2004 using ethyl (2*E*,4*Z*)-2,4-decadienoate as a precursor (see Fig. 10).[140]

Aroma lactones such as (*S*)-γ-lactones with varying chain lengths and γ-butyrolactone can be produced by lipase-catalysed intramolecular transesterification of 4-hydroxycarboxylic esters.[141,142] The preparation of optically active δ-lactones is more difficult as most lipases lack selectivity towards these compounds.[122]

Isomerically pure **(−)-menthol** can be obtained *via* lipase-catalysed stereoselective hydrolysis of various methyl esters in satisfying purity.[143] The enantioselective hydrolysis of racemic menthyl benzoate (see Fig. 11) leads to optically almost pure **(−)-menthol**,[144] which was claimed as a process by the company Haarmann & Reimer (nowadays known as Symrise AG) in 2002.[145] A related approach by AECI Ltd. starts directly from the mixture of the eight isomers of menthol.[146] The enantio- and diastereoselective acylation of this mixture *via* lipase yields menthyl acetate in a 96% enantiomeric excess. The ester is separated from the unreacted isomers by distillation and then hydrolysed to yield **(−)-menthol**. In both processes the undesired isomers are recycled by isomerisation. None of them have been commercialised yet,[27] but being supported by well-established routes will most probably be the subject of further development.

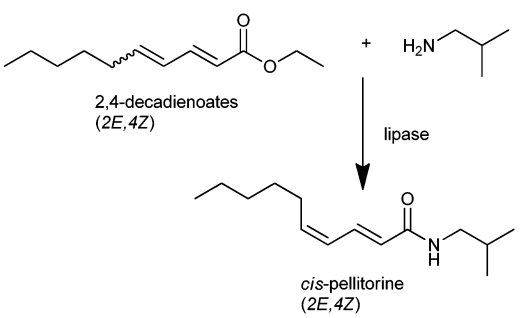

Fig. 10 Lipase-catalysed high-yield synthesis of *cis*-pellitorine according to Ley *et al.*[140]

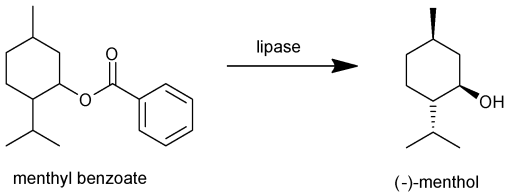

Fig. 11 Lipase-catalysed synthesis of enantiopure **(−)-menthol** according to Vorlova *et al.*[144]

The *p*-menthane monoterpene (−)-isopulegol, an odourless compound useful as a cooling agent or intermediate for **(−)-menthol** production,[27,147] was prepared *via* lipase-catalysed enantio- and diastereoselective acetylation of the commercial mixture of its eight isomers.[148]

Further racemic resolutions using lipases with impact for the cosmetics industry have been described for the production of (−)-*trans*-jasmonate (a relevant component of jasmine oil fragrance),[149,150] (+)-mesifuran [2,5-dimethyl-4-methoxy-3(2*H*)-furanone] (an important flavour compound in arctic bramble, also occurring in strawberry and pineapple),[151] *ionone and irone derivatives* (components of the commercially extremely important Iris essential oil),[152,153] *damascone* (rose odorants),[154] and *dehydrotheaspirone* (nectarine flavour).[155]

Many more examples exist, where lipase catalysed resolutions yield the isomeric forms of synthetic aroma compounds with a yet unclear role in odour development (*e.g.* the alcohols muguesia®, pamplefleur® and mugetanol®) and intermediates for the synthesis of important flavour and fragrance compounds[27] such as (−)-ambrox, (a key compound of the complex odour ambergris) which are then further converted by chemical steps.[156,157]

2.2.3 Functional actives. Cosmetic ingredients with a more distinct function, usually related to the specific effect and target of a cosmetic product, are numerous. Accordingly, many reports on structures which are actually or can possibly be synthesised *via* lipase catalysis can be found. These include many antioxidants such as retinyl (vitamin A),[158,159] vitamin C and polyhydroxyphenol,[131,160] idebenone, kojic acid and dimethylaminoethanol esters,[42] UV filters such as ferulic acid derivatives,[161] anti-aging specialties such as sphingolipids,[162,163] special moisturizers such as pyroglutamic acid esters,[164] tyrosinase inhibitors such as 4-hydroxybenzyl alcohol esters,[165] and natural dyes such as indigo derivatives.[88]

Vitamin A (retinol), *vitamin C* (ascorbic acid), *idebenone*, *kojic acid* and *dimethylaminoethanol* are valuable ingredients for cosmetics and pharmaceuticals due to their ability to scavenge free radicals that could otherwise cause DNA mutations.[166–168] Thus, they are employed to combat skin disorders such as cancer, photo-aging, psoriasis, ichtyose or acne.[42,169–171] All of them, however, can hardly be applied directly due to low stability, irritative effects on the skin and/or low solubility in water.[42,88] Synthetic derivatives, particularly esters, have therefore been developed, which overcome these

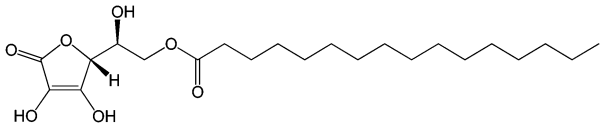

Fig. 12 Structure of 6-*O*-ascorbyl palmitate, accessible by lipase catalysis.

problems without negative effects on the anti-oxidative properties. In the case of vitamin C, esterification with fatty acids (see Fig. 12) even seems to enhance the radical scavenging performance,[88] thus preventing peroxidation of low density lipoproteins more effectively.[172] Additionally, esters of vitamin C and hydroxyl acids such as kojic acid are unusually effective as skin conditioners.[42,88] Fatty acid esters of dimethylaminoethanol on the other hand have been developed as odourless derivatives,[173] which have also been reported to contribute to anti-microbial activity in cosmetic formulations.[174]

In lipase catalysis, retinyl esters can best be derived using fatty acid esters as the acyl donor (see Fig. 13)[175] while for ascorbic acid effective synthesis of 6-*O*-ascorbyl palmitate and 6-*O*-ascorbyl oleate,[81,176–179] or vitamin C hydroxy acid esters such as ascorbyl lactate and ascorbyl salicylate[180,181] has been described.

UV filters are individual compounds or mixtures absorbing ultraviolet light and therefore are key ingredients in sunscreen products. Among the various compositions, feruloyl glycerides derived *via* lipase catalysis specifically qualify as a 'green' suncreen or sunscreen booster. Due to their special absorption spectrum they additionally exhibit anti-aging benefits.[182]

Sphingolipids such as ceramides (see Fig. 14) are naturally occurring membrane lipids derived from the unsaturated aminoalcohol sphingosine and fatty acids *via* peptide bonding. Their natural function is within the nerve tissue, but in cosmetic products anti-aging activity is achieved[183] and several more beneficial effects on human skin can be found.[184,185] Recently, a lipase catalysed process has been described providing a more eco-efficient synthesis route,[162] as well as a process yielding new ceramide structures based on natural oils.[163]

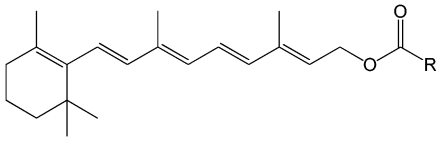

Fig. 13 Structure of enzymatically prepared retinyl esters; R = alkyl moiety of fatty acids.

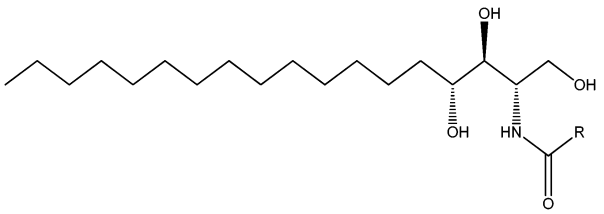

Fig. 14 Structure of ceramide III (R = alkyl chain of stearic acid) according to Hollmann *et al.*[162]

Natural dyes, which were originally derived from plants, animals or certain minerals, have in many application fields been replaced by synthetic dyes, but have maintained or regained considerable importance in cosmetics due to regulatory pressure. This is exemplified by indigo, which was originally extracted from various plant species such as *Indigofera*, *Isatis tinctoria* or *Polygonum tinctorium*, but at the end of the 19th century it was almost completely replaced by synthetic indigo. More recently, considerable research has been performed to replace chemical synthesis of indigo by biotechnological production systems such as plant cell cultures,[186–188] microorganisms,[189,190] or isolated enzymes.[88] Enzyme catalysis using lipase or glycosidase releases indoxyl from the natural indigo precursors isatan B and isatan C and can then be further processed to indigo as well as various natural derivatives, which are responsible for the more pleasing tinge of natural indigo compared to the synthetic compound.[191,192]

3. Lipase preparations for use in cosmetics

Upon application of lipases as both active ingredients in cosmetic formulations or biocatalysts in the synthesis of cosmetic chemicals appropriate preparation of the enzyme is a particularly important task. A general problem encountered with the use of active enzymes in cosmetic formulations is maintenance of activity without affecting further ingredients.[14] In view of the lipolytic function of lipases and the general importance of lipid-derived compounds in cosmetic products, it can easily be imagined that this is a particularly severe problem when using lipases. In the case of enzyme-catalysed syntheses of cosmetic chemicals, on the other hand, the final product usually needs to be free of residual enzymes either because of regulations on cosmetics forbidding certain types of enzymes (*e.g.* catalase), incompatibility with specific ingredients (*e.g.* lipases might react with lipid-derived compounds) or health issues as there is a general concern regarding the danger of possible allergies or skin irritation.[31] For large scale production processes, in addition, enzyme preparations with appropriate activity and long-term stability are generally mandatory since this has a dramatic effect on the process economics.[32] The longer the biocatalyst is active and stable – and can at best be used in repeated production cycles – the lower are the biocatalyst costs per kilogram of product.[31,42] Interestingly, all challenges can best be overcome by appropriate immobilisation of the involved lipases.[26,193] Actually, in the production of cosmetic chemicals only immobilised enzymes have gained industrial importance to date,[10,29,50,122,133,202,228] no processes based on free enzymes have to our knowledge been commercialized so far.

3.1 Immobilised lipases as active ingredients

Lipases destined for use as active ingredients in a cosmetic product are most frequently encapsulated in micro- or nanoparticles,[194] although storage as dry powder until use has also been reported as a strategy to maintain enzyme activity and product composition.[195,196] Particles for lipase encapsulation often consist of a core material in which the enzymes are dispersed in an oily dissipating medium (stabilised by aluminium distearate

or aluminium tristearate) and a peripheral material including agar.[197] More recently, hollow spheres from inorganic silica have also been reported as promising materials for lipase encapsulation because of advantageous properties such as a pleasant hand feeling of the resulting cosmetic formulations.[198]

3.2 Immobilised lipases for biocatalytic production

For immobilisation of enzymes destined to biocatalytic use, many immobilisation techniques have already been reported.[199,200] Unfortunately, most do not fulfil all the requirements for industrial use. In fact, only few off-the-shelf biocatalysts with appropriate features for implementation in technical production processes are currently available.

A particularly often used catalyst for synthesis of specialty esters is the commercial preparation Novozym 435® (Novozymes A/S, Denmark),[29,201,202] consisting of lipase B from *Candida antarctica* (CALB) adsorbed on the polymethacrylate carrier Lewatit VP OC 1600 (Lanxess, Germany).[203–205] This preparation is characterised by high protein loads (1–10%),[206] thermal stability up to 110 °C in solvent-free systems,[207] and often excellent regioselectivity and stereoselectivity in esterification and transesterification reactions.[203,208] Thus, even sensitive and highly functionalised raw materials such as linoleic acid or sugar derivatives can be processed almost without side reactions.[29] Alternatively, the immobilised lipase from *Rhizomucor miehei* can be used for emollient ester production,[10] an enzyme that also plays an important role in flavour and fragrance syntheses.[27,122]

However, even these preparations experience severe problems with a limited mechanical strength of the employed carriers.[209] Additionally, leaching of enzymes from the carriers in the presence of surface-active compounds frequently occurs due to only adsorptive binding.[210] This is a serious problem in the production of many cosmetic esters,[119] since these increasingly gain surface-active character with increasing product complexity. The leaching has a distinctly negative impact on production costs due to the mere loss of enzymatic activity. Additionally, however, it can entail necessity for processing steps to remove residual enzyme from the product. Thus, even if the problem of carrier destruction can be solved by use of appropriate reactor technology (see Section 4), applicability of the lipase preparations remains limited.

Most probably, the simplest way for improvement of immobilised enzymes with regard to both mechanical strength and leaching stability is the search for new carrier materials or immobilisation methods. However, success has been very limited to date. SiO_2 carriers, such as Sipernate based materials,[211,212] are cheap and have been successfully used for enzymatic synthesis, but do not show the required mechanical stability. Formation of carrier-free cross-linked enzyme aggregates (CLEA), which is one of the oldest approaches for improvement of enzyme properties,[213] yields highly active preparations, but only rather small particles which are difficult to recycle from the reaction mixture. Another technology called LENTIKATS uses polymeric matrices based on poly(vinyl alcohol) for enzyme entrapment yielding immobilisates of considerable mechanical strength. However, due to the hydrophilic character of the employed polymer these impart considerable restriction of mass transfer on hydrophobic substrates, and are therefore mainly suitable for aqueous applications, such as waste water treatment.

The latest and probably most promising technology development for provision of improved lipase preparations is that of the so-called *silCoat*-enzymes,[214–216] which is based on the entrapment of carrier-bound enzymes in a silicone matrix,[209] forming a composite material.[217] By fine-tuning the used siloxane precursors, the mesh size of the polymer matrix can be tailored to allow the diffusion of small raw materials and products into and out of the immobilisates, while keeping the large enzyme in the particle.[217,218] Thereby enzyme desorption is prohibited without the need for covalent fixation (which usually results in significant loss of enzymatic activity).[200] Siloxane tuning also enables adjustment of the hydrophilicity degree providing applicability of the method to more or less hydrophobic reaction systems.[218] Diffusion limitation is overall minimised by employment of solid particles for surfacial enzyme adsorption in the outer sphere of the particle (*e.g.* in Novozym 435) prior to entrapment, resulting in considerably higher residual activities[209,217] than with immobilisates based on only silicone.[219] Thus, appropriate catalytic activity at excellent mechanical stability and stability towards desorption can be obtained with this technology favouring industrial production of emollient esters and surface-active compounds.[214,220]

Nevertheless, only those products are accessible today that are targets of commercially available and intrinsically stable enzyme preparations. Thus, although the workhorse among the lipases, immobilised CALB, shows a tremendous substrate spectrum,[206,221] many interesting classes of raw materials are not accessible. This is especially true for acids other than simple fatty acids. It is well known that, for example, aromatic, sterically hindered and other acids with a pK_a of lower than about 4.8 are converted several orders of magnitude slower than the natural substrates.[222] The many approaches for lipase engineering reported in the literature are mainly targeted towards stereoselectivity which is highly interesting for synthesis of fine chemicals but not for production of specialty chemicals such as cosmetic ingredients. Only lately one example providing a proof-of-principle for improvement of CALB activity towards sterically hindered acids was reported.[223] Alternatively, of course, new enzymes filling the activity gaps of commercial preparations could be provided. Despite the many reports in the literature in this regard,[224,225] however, no candidates apt to commercialisation have yet been identified.

4. Production set-up for lipase-catalysed synthesis of cosmetic chemicals

In the chemical industry the stirred tank reactor (STR) is still the benchmark for multi-purpose reactors. However, due to the limited mechanical stability of many commercially available enzyme preparations, alternative concepts often have to be employed. For production of compounds where low viscous

educts are involved, such as the above mentioned emollient esters, the packed bed reactor is such an alternative allowing for a sufficiently high reuse frequency of the biocatalyst.[29,226,227] Therefore, commercial processes for lipase-catalysed production of emollient esters typically involve a reactor packed with immobilised enzyme,[10,29,133,228] as exemplified in Fig. 15.

In this set-up, the packed bed is connected to a vessel *via* a loop and the reaction mixture is recycled through the bed until the target conversion has been obtained. The packed bed reactor is connected to a stirred-tank containing the solvent-free reactants in an optimised composition,[229] which allows the highest possible concentration of substrates (between 1.5 and 3.5 M at maximum productivity).[31] Water built during esterification (or alcohol during transesterification, respectively) is continuously extracted *via* a vacuum. Thus, full conversion of reactants is enabled without the need for addition of molecular sieves or salt anhydrates. The obtained products fulfil all necessary specifications without further purification steps.[31] Depending on the catalyst amount and turnover rate, process times between four and eight hours are possible.[228]

However, as solvents are usually omitted (for use on human skin or hair the final product must be free of any residual solvent) the conversion of substrates with high viscosity or high melting temperature such as sorbitol, glucose, fructose, xylitol, diglycerin or polyglycerin is impossible even in a fixed bed reactor.[119]

A promising new approach to overcome this problem is the use of a bubble column reactor (BCR, see Fig. 16) which uses a gas stream for mixing instead of a stirrer, thus imparting considerably less mechanical stress on the enzyme carriers. Additionally, the gas stream removes reaction water, which favourably influences conversion. Cosmetic emulsifiers such as polyglycerol-3-laurate have already been obtained with this technology.[119]

The BCR can be worked as a one stage reactor[231] as well as a multi-step setup,[230] and control can be gathered *via* addition of several sophisticated inline analytics.[232,233] Other interesting reactor concepts are based on the use of microreactors[234] and emulsion based reaction systems.[235] Synthesis of specialty monoglycerides by direct condensation of glycerol and fatty acid has been performed continuously in membrane-based

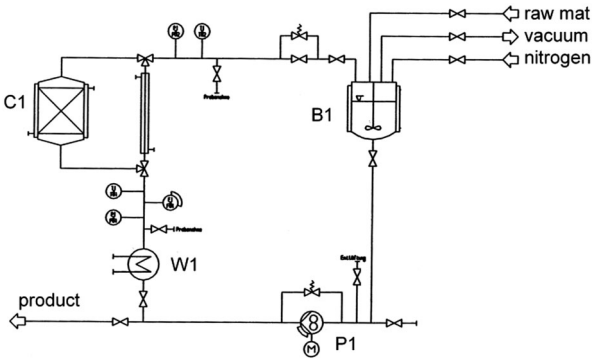

Fig. 15 Flow sheet of a packed bed reactor for enzymatic esterification. B1 = stirred tank; P1 = pump; W1 = heat exchanger; C1 = fixed bed filled with immobilised enzymes.

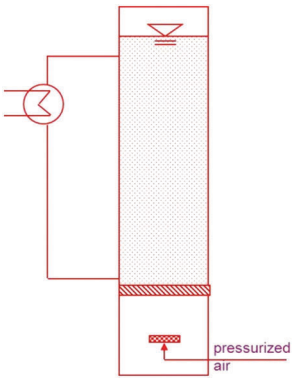

Fig. 16 Schematic of the bubble column reactor used for esterification reactions according to Thum *et al.*[230]

hollow-fibre reactors.[48] High conversion has also been achieved in batch experiments that were conducted under vacuum to shift the equilibrium towards the final product by evaporation of process water.[49] Similarly, polyglycerol esters of polyunsaturated fatty acids have been enzymatically synthesised in high yields at ambient temperatures in a solvent-free mixture of substrates.[50]

5. Benefits of lipase-catalysed production in the cosmetics industry

The framework for manufacture and marketing of cosmetic products is strictly regulated by official authorities. In the EU, the European Cosmetics Directive from 1976 (adapted by various amendments and adaptations)[236] has long set the standard. In July 2013 it will be replaced by a novel overall regulation (1223/2009 from 30th November 2009)[237] enabling consideration of the latest technological developments (*e.g.* the possible use of nanomaterials). Consequently, processes concerned with the provision of chemicals targeted to cosmetic products must consider both these regulations and the overall standards and developments in chemical production. On this background implementation of enzymes and particularly lipases has become of profound interest.

With increasing importance of eco-balances for individual products, considering the complete life cycles from resources to discharge, modern process development increasingly focuses on sustainable production routes. In adoption of the 'Twelve principles of green chemistry'[238] as a set of guidelines, these must integrate consideration of general economic aspects (*e.g.* overall demand, prices for raw materials) with the implementation of fewer and more efficient processing steps to save material and energy at reduced waste. A comprehensive assessment of 'greenness', however, is rather complex and must consider the overall ecological impact of a production process by including diverse parameters such as the geographical source of raw materials, annual renewability, competition with food supply, processes and solvents for manufacture, manufacturing energy and its source, processes for cleaning and maintaining equipment, packaging, shipping mode as well as

shelf-life and biodegradability of compounds.[42] Thus, the estimation of 'greenness' considerably depends on the mode of determination. Official certification is offered by various organisations like the Global Ecolabelling Network (GEN) and its various members.

A key technology in green chemistry provides the use of biocatalysts, such as enzymes, due to their highly selective initiation, acceleration and control of reactions at moderate temperature and pressure. This is increasingly recognised in the production of fine and pharmaceutical chemicals, but is not generally perceived for the manufacture of specialty chemicals such as ingredients for cosmetics[31] or commodities.

Nevertheless, particularly the production of cosmetic chemicals benefits from enzymatic production because of specific demands on product quality and the intensifying consumer trend to seek and preferentially purchase so-called natural care products, whether motivated by a sense of environmental or social responsibility or by the supposition that such products are better, safer and healthier.[39,239] Although 'natural' typically refers to the source of raw materials rather than to the production process,[42] both items are closely connected in the perception of the consumer.

5.1 Sustainability and economy

Based on an informal survey of cosmetic manufacturers, most sources agree that biocatalytic processes to cosmetic chemicals can be considered green as long as the process is free of petroleum based organic solvents,[42] probably since they are well suited to the use of renewable raw materials from plants or microbial fermentation and produce inferior amounts of dangerous waste. Mild reaction conditions save energy, reduce by-product formation and lower the time for heating and cooling cycles. The biocatalyst itself is biodegradable and does not show the toxic features of metal-based catalysts.

Advantages of enzymatic production, however, are both environmental and economic, as demonstrated for the provision of cosmetic fatty acid esters. Such esters are typically obtained from natural fatty acids and (poly)hydroxyl compounds. Conventional chemical synthesis involves esterification by use of metal catalysts such as tin or zinc salts (*e.g.* tin oxalate) or strong acids (*e.g.* sulphuric acid or *p*-toluene sulfonic acid) at temperatures between 160 °C and 240 °C (depending on the applied catalyst).[29] For high conversion, process water must be eliminated *via* distillation, molecular sieves, salt hydrates or specific process design.[240,241] Products in sufficient quality can only be obtained after substantial post-processing due to thermally induced side reactions of raw materials and catalysts. This is particularly significant when unsaturated fatty acids such as oleic acid or linoleic acid are involved since their double bonds are susceptible to many reactions including polymerisation, rearrangement and oxidation. Consequently, dark and sometimes even malodorous mixtures requiring further refining can be obtained. Refinement typically involves deodorisation by steam-stripping of water-soluble and volatile contaminations, bleaching with reagents like hydrogen peroxide, removal of residual water by drying and filtration for removal of catalysts, solid by-products and bleaching agents (see Fig. 17, left part).[29]

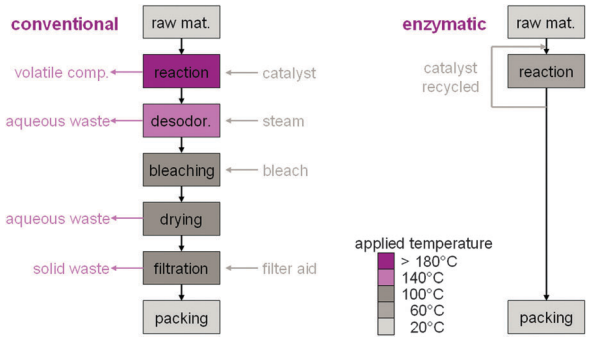

Fig. 17 Process steps of conventional (left) and enzymatic (right) esterification for production of cosmetic fatty acid esters.[29,31]

In contrast, the high selectivity and mild temperature (usually not succeeding 80 °C) of the enzyme-catalysed esterification (Fig. 17, right part) avoids by-product formation almost completely. Accordingly, deodorisation and bleaching are unnecessary, no additional reagents are required and almost no waste is obtained. If the enzyme is sufficiently stable and can be reused several times, the costs for the enzyme are equal or maybe even lower than that for these refinement steps (including materials, reactor time and waste disposal). Additionally, energy costs are decreased and investment costs can be dramatically reduced by applying cheap steam-based heating instead of thermal oil and by avoiding equipment adapted to high temperature. Thus, production costs are overall reduced.[29,227]

For the model product myristyl myristate (see Fig. 1a) which is assessable by both chemical and enzymatic synthesis, life cycle assessment (according to ISO 14040)[242] demonstrated energy savings of over 60% and a reduction of waste of up to 90% for enzymatic production.[201] Thus, introduction of enzyme catalysis is a prime example for improving the sustainability of production processes.

5.2 Effects on product quality and product range

The absence of by-product formation in enzymatic synthesis, whether due to increased selectivity or reduction of spontaneous side reactions, has beneficial effects not only on the production process, but also on the quality of cosmetic products.[227] For some chemicals, in fact, enzyme catalysis provides the only means to achieve the quality mandatory for cosmetic use.

Cetyl ricinoleate (see Fig. 1c), for example, is a wax ester derived from the vegetable based unsaturated hydroxy fatty acid ricinoleic acid and cetyl alcohol. In conventional chemical synthesis the non-specificity of the applied chemical catalyst and the lack of kinetic control in the esterification reaction at elevated temperatures (thus shifting towards esterification at the secondary hydroxyl function of ricin oleic acid) leads to oxidation of double bonds, formation of *trans* fatty acids through intramolecular rearrangement as well as dimerization and polymerisation through intermolecular esterification. For reduction of by-product formation, the chemical production is run at an excess of cetyl alcohol. As this can hardly be removed from the final product cetyl ricinoleate derived this way

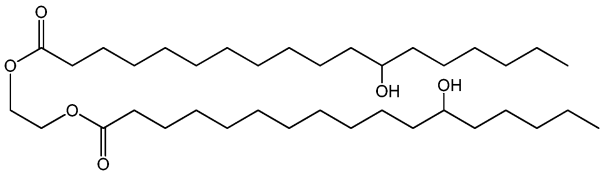

Fig. 18 Chemical structure of the thickener EGDHS.

contains between 10% and 30% of cetyl alcohol even after purification. An undefined amount of cetyl alcohol in cetyl ricinoleate, however, poses considerable formulation problems in cosmetic products such as creams due to viscosity enhancement (cetyl alcohol itself is used as a co-emulsifier or viscosity enhancer in many formulations). In contrast, cetyl ricinoleate derived from an enzymatic process contains 83% less residual cetyl alcohol and 75% less ricityl dimers, whereas the product content increases from 61% to 93%. Thus, the rheological effects of cetyl alcohol can be better controlled allowing the development of new formulations.[31]

Quality enhancements such as higher content of the active ingredient, better colour, less unreacted alcohol and less unidentified side compounds can also be observed for simple fatty acid esters like myristyl myristate, although educts of this compound are not known to undergo thermal side reactions.[10,29]

For the 12-hydroxy stearic acid derivative ethylene glycol dihydroxystearate (EGDHS, see Fig. 18, a novel rheological additive) the advantages of biocatalytic production go that far that enzyme derived EGDHS can easily be incorporated in cosmetic or household care formulations, whereas EGDHS produced in the conventional way (using catalysts like lead soaps)[243] shows no thickening activity.[29]

Similarly, surface-active sugar esters derived from chemical synthesis comprise so many by-products (*e.g.* at least 65 individual compounds from sorbitan esters including various isomers of sorbitan, isosorbide and their mono-, di- and tri-esters)[244] that their cosmetic application can be critical due to the low content of the actually desired active ingredient and thereby reduced performance. The more so as concern over allergenicity and carcinogenicity of some of the by-products arises.[50]

6. Conclusions

Lipases are currently used in both cosmetic products and synthesis of ingredients thereof, whereas the latter plays a particularly important role with regard to the increasing demand for 'green' chemical processes and 'natural' products. Nevertheless, only few processes have been commercialised to date, mainly due to the lack of appropriate enzyme preparations with regard to substrate acceptance and process stability, which considerably reduces the cost-effectiveness. Research and development in that direction, however, are very active both in academics and industry and some limitations have actually already been overcome. Thus, a broader implementation of lipase catalysis in the production of cosmetic chemicals can in future be expected.

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