REVIEW

Biocatalytic solutions to cyclomethicones problem in cosmetics

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Silicones are polymers that have properties of great interest for cosmetic and personal care industry, especially D₄ (octamethylcyclotetrasiloxane) and D₅ (decamethylcyclopentasiloxane), generically named cyclomethicones. However, different studies show the hypothesis that the use of these products is harmful and, therefore, several countries have adopted legislative actions to limit their use in personal care and cosmetic products. Faced with this new situation, different cosmetic companies began to look for different alternatives to cyclomethicones, mainly: organomodified silicones or esters. The former are based on the addition of functional groups to the main chain of silicon and oxygen. The latter represent a totally different line, since their functional group is the ester, but they have properties similar to silicones. Esters, especially branched-chain ones are currently the more promising alternative to replace cyclomethicones in cosmetic formulations. Nowadays, most of them are obtained by chemical reactions that require high temperatures and non-selective /contaminant catalysts that lead to low-quality final products. As an alternative, biocatalytic synthesis occurs always at mild operation conditions supplying ultra-pure, odor, and colorless products with less wastes and side reactions. Therefore, biocatalysis is a valid and environmentally sustainable option for the synthesis of silicone-substitute esters used in cosmetic formulations.

KEYWORDS

bioprocesses, biotechnology, esterification, green chemistry, lipases

1 | INTRODUCTION

Silicones are polymers of high molecular weight, whose main chain is formed by atoms of silicon and oxygen that appear alternately. Among the great variety of polymers with this skeleton -Si-O-, methyl substituted siloxanes stand out and are known as polydimethylsiloxanes, PDMSs [1]. PDMSs have a very stable chemical structure and present some physical-chemical properties, such as hydrophobicity, thermal stability, electrical resistance, impermeability, or lubricating properties

that determine their uses. This type of silicones will be named D or L depending on whether it is a cyclic or linear compound, respectively, also indicating the length of the chain in the subscript.

Despite its great applicability and extraordinary physical and chemical properties, recent studies point out the possibility that these PDMSs are harmful to the health of living beings and cause damage to the environment. The most used are octamethylcyclotetrasiloxane (D₄) and decamethylcyclopentasiloxane (D₅), which appear in great amount in cosmetic and personal hygiene products under the name of cyclomethicones (Fig. 1).

Cyclomethicones are colorless, odorless, transparent, and nongreasy silicone fluids with a low viscosity and surface

Abbreviations: DMAP, 4-N,N-dimethylaminopyridine; HOPME, high oleic palm oil methyl ester; RAC, Risk Assessment Committee; SEAC, Socio-Economic Committee.

FIGURE 1 D₄ and D₅ chemical structures

tension, and a relatively high vapor pressure, which allows the vast majority of silicone to evaporate from the surface where it is applied. As cosmetic additives, they have emollient properties and improve in cosmetic formulations extensivity and lubricity, favoring the application of the cream, and providing a sensation of dry and velvety skin [2]. In addition, cyclomethicones are soluble in organic solvents such as ethanol (99%), isopropanol (99%), stearic acid and in other aliphatic, chlorinated, and fluorinated solvents. They are also highly insoluble in water, but hydrolytically stable to be emulsified in different cosmetic preparations [3].

Currently, cyclomethicones D₄ and D₅ are found in numerous products of personal care industry (shampoos, facial and body lotions, and hair conditioners). They are mainly used as emollient agents, providing sensory properties to the products and favoring the mixture of fragrances with the oils present in the formulation.

Silicones had an exponential development in the last century, since they provide interesting properties to cosmetic products, even at small concentrations. However, the use of cyclomethicones D₄ and D₅ has declined owing to recent studies showing some harmful effects associated with these silicones [4]. The aim of this review is look for an alternative product to silicones.

2 | D₄ AND D₅ CURRENT PROBLEMS

The possible harmful effects of cyclomethicones are supported by numerous scientific studies. Dermal application or inhalation exposures would be the most directly relevant to humans. Some examples are shown in Table 1.

As a consequence, different countries or supranational entities have been legislating over the years to face the problem.

From a legislative point of view, the Danish Environmental Protection Agency [15] was the first entity pointing the problem of cyclomethicones in 2005. In that first study, the Danish government describes some of the effects that cyclomethicones can cause. Some of the most relevant conclusions of the study are:

PRACTICAL APPLICATION

From 31st of January of 2020 the use of D₄ and D₅ cyclomethicones in cosmetic products will be restricted. Among the possible industrial solution highlights are cyclomethicone replacement by organomodified silicones or esters. Nowadays, the market demands silicone free products for this reason, branched-chain esters that offer similar sensory properties are preferred. Among different methods for obtaining branched-chain esters, biocatalytic ones present the clear advantage of being environmental friendly because they work with “solvent-free” processes and with sustainable synthesis. Besides, the final product can be labeled as “natural.”

- Liver is the main target organ for D₄, and primary target organ for D₅ exposure by inhalation is the lung.
- The critical effects of the siloxanes are impaired fertility (D₄) and potential carcinogenic effects (uterine tumors in females) (D₅).
- None of the investigated siloxanes shows any signs of genotoxic effects.

Other harmful effects of silicones exposure are a decrease in weight, cellular, or subcellular changes, and an increase in liver weight, ovarian atrophy, or vaginal mucification. Cyclomethicones not only have harmful effects on human health, but are also toxic to the environment.

Later, in 2008 the Canadian government carried out an evaluation of the toxicological risks associated with silicones D₄ based on criteria from the Article 74 of the Canadian Environmental Protection Law. It was concluded that D₄ fulfilled the criteria and consequently was considered a toxic. However, it could not be clearly stated to have a risk on human health [16]. Some of the most relevant conclusions of the study are:

- D₄ is entering the environment in a quantity that may have a harmful effect on the biological diversity.
- D₄ is not entering the environment in a quantity that constitutes a danger in Canada to human life or health.
- D₄ meets the criteria for persistence as set out in the *Persistence and Bioaccumulation Regulations*. However, it is not possible to conclude that D₄ meets the criterion for bioaccumulation.

D₄ in 2011, a new report was published about D₅ and its distribution and hazard index in human health and in the environment [17]. The “Canadian Cosmetic, Toiletry and Fragrance Association” and the “Ministry of the

Environment,” among others, were participants in the study, postulating a series of summary conclusions as:

- D₅ exceeds the regulatory threshold for persistence but it did not exceed the threshold established in the *Persistence and Bioaccumulation Regulations*. It cannot be classified as a bioaccumulative substance.
- D₅ cannot be considered as a biomagnifiable substance, its concentrations do not increase in predators relative to their prey. There is no evidence to demonstrate that D₅ is toxic to any organism tested up to the limit of solubility in any environmental matrix.

In 2009, the Environment Agency (public body of England and Wales) published the “Environmental Risk Assessment Report: Decamethylcyclopentasiloxane” [18]. The report is based on the methods outlined in the European Union Technical Guidance Document for the risk assessment of new and existing chemicals.

The most relevant report conclusions are:

- D₅ meets the screening criteria for very persistent (vP) and very bioaccumulative (vB) substances.
- D₅ is not readily biodegradable in aquatic systems. Due to its high volatility, D₅ is lost from water by volatilization to the air, where subsequent degradation occurs.
- Some studies with fish show only slow depuration of accumulated D₅ from the liver, and effects on liver weight occur in rats at relatively low doses of D₅. However, it is not clear if these effects are sufficient to warrant D₅ as toxic.

In 2010, according to the publication of the Government of the United Kingdom, the Scientific Committee on Consumer Safety (SCCS) of the European Union presented a report based on the content of D₄ and D₅ in cosmetic products, affirming that D₄ is a toxic product for reproduction, being classified as category III [19]. In 2011 (updated in 2015), the focus of attention was for D₅, studying in depth the characteristics and optimal concentrations in which it is found in cosmetic products. Different tests were carried out based on its toxicity, and how the human body assimilated silicone. Finally, a series of conclusions were issued regarding the use and recommendations related to silicone D₅ [20]:

- Its use can be safe at the concentrations currently reported, except for the use of lotions for hair styling, and sun care products, since in these products can produce toxic effects to the body.
- D₅ may contain D₄, although the latter is classified as toxic for reproduction by the EU. The content must be kept as low as possible (the level of purity must be greater than 99%).

As a consequence of the abundance of reports in which the use of silicones in personal care products is unfavorably evalu-

ated, and its problems with the environment, the Committee of Member States of the European Chemicals Agency (ECHA) met to regulate the persistence and bioaccumulation of D₄ and D₅, concluding that both substances fulfilled the requirements to be considered as very persistent and very bioaccumulative substances (vPvB). Additionally, D₄ was classified as toxic for the reproduction in category III, and with probability of being included within category I of persistent organic pollutants for different mammals and aquatic species [21,22].

On April 17, 2015 the United Kingdom submitted to ECHA a dossier proposing to restrict the use of D₄ and D₅ in cosmetic products that are washed off in normal conditions of use [23]. The dossier demonstrated that action is necessary to address the risk to the environment caused by the use of D₄ and D₅ when discharged into the waste water.

On April 22, 2015 the Member State Committee adopted an opinion that both D₄ and D₅ fulfil the criteria of the Regulation (EC) No. 1907/2006 for the identification of very persistent (vP) and very bioaccumulative (vB) substances. Later, on March 2016 the Agency's Risk Assessment Committee (RAC) concluded that D₄ meets the criteria of the above-mentioned regulation for the identification of a persistent, bioaccumulative, and toxic (PBT) substance.

In June 2016, the Agency's Socio-Economic Committee (SEAC) proposed that the restriction is the most appropriate measure to reduce the discharge of D₄ and D₅ to waste water and recommended a 2 years deferral of its application, to allow the stakeholders to take the necessary compliance measures. The opinions of RAC and SEAC were submitted to the Commission on August 10, 2016.

The Commission considered that risks derived from the use of D₄ and D₅ in certain cosmetic products should be addressed and on January 10, 2018 published the Regulation (EU) 2018/35 amending Regulation (EC) 1907/2006. After January 31, 2020, D₄ and D₅ “shall not be placed on the market in wash-off cosmetic products in a concentration equal to or greater than 0.1% by weight of either substance.”

The first studies of possible risks produced by cyclomethicones especially by D₄, began in 2005. Since then, as far as we know, these studies have only been transformed into new legislation by the European Commission. However, since these studies are widespread in the media, the environmental concern acquired by the population has forced to cosmetic products companies to advertise silicone-free products, even though they are not banned.

3 | ALTERNATIVES TO CYCLOMETHICONES

Because of this imminent limitation of D₄ and D₅ use in many cosmetic formulations, active ingredients manufacturers for cosmetics have adopted different positions.

TABLE 1 Possible cyclomethicones harmful effects

Effect	Reference
Estrogenic activity (D_4).	[5,6]
Liver and lung damage (D_4).	[7]
Weak estrogenic effect of (D_4).	[8]
D_4 was detected in plasma and blood of women who are or were exposed to silicone gel-filled implants (14-50 ng/mL and 79–92 ng/mL, respectively)	[9]
Effects on rats of inhalation of D_5 . Female rats are more sensitive. Increase of liver weight and pulmonary inflammatory response.	[10]
Uterine endometrial adenocarcinomas in rats provoked by D_5 exposure.	[11]
D_5 was determined to be not genotoxic.	[12]
D_5 inhalation causes a small but statistically significant increase in the incidence of uterine adenocarcinoma.	[12]
Slight increased incidence of pulmonary alveolar histiocytosis (D_5).	[13]
Inhalation of D_4 causes statically significant reductions in the mean live litter size and mean number of pups born in rats.	[14]

On the one hand, the most important manufacturers of silicones, as is the case of Dow Chemicals, have aimed for obtaining organomodified silicones lacking of D_4 and D_5 [24]. However, the great majority of cosmetic manufacturers are removing silicones from their products, and publicizing them as “silicone-free.” In fact in 2017, more than 3500 new products that claimed to be “silicone-free” were launched in Europe alone, according to the Mintel Global New Products Database (GNPD) [25] so that not make sense to substitute one “silicone” by another “silicone” if they are advertised as “silicone-free.”

On the other hand, more and more suppliers of ingredients include in their catalogs certain substances that can replace the silicones of the formulations, as is the case of oils and esters, which act as substitutes for cyclomethicones due to their low viscosity, high capacity of extension, great compatibility with the skin due to its biodegradability and low aquatic toxicity [26]. The use of these compounds meets with consumer desires for renewable-based and biodegradable ingredients instead of the non-biodegradable and potentially toxic silicones.

3.1 | Modified silicones

The organomodified silicones have been used in many applications such as personal and health care or compositions in agriculture. In addition, the presence of organic groups in the modified silicones changes and improves the properties of the naked silicones, maintaining always silicone as the main element of the structure. Thus, different properties are obtained based on what the functional group provides. Organic groups can be attached to one or both of the main chain ends, or they can appear along the silicone skeleton. Alkyl groups increase the velvety sensation and the firmness in the creams; aryl and phenyl groups provide brightness; glycoside groups provide emulsifying properties to the product and perfluoro groups increase diffusion [27].

The current trend in the evolution of silicones is the combination of basic silicone structures with organic residues, with the aim of creating new hybrid materials, which flow into silicone resin gels, silicone polyethers, or new hyper-branched structures [28,29].

A few examples of these modified silicones, proposed by the different companies, are listed in Table 2.

3.2 | Branched-chain esters

As previously mentioned, another alternative to silicones are esters, mainly branched-chain esters [30].

Branching in fatty acids hydrocarbon chain causes the molecule to lose its ability to easily crystallize, because it hinders the close association of molecules, preventing crystallization. The effects caused by branching of the alcohol versus branching of the acid are similar. So, branched-chain esters remain fluid over a much greater temperature range than linear ones. The melting point and the boiling point are reduced. In consequence, these esters are more fluid, less oily-feeling and have a higher spreading factor on skin [31]. As an example, the melting temperature of 2-ethylhexyl acetate (branched-chain) and octyl acetate (straight-chain) are -93 and -38.5°C respectively. Moreover, secondary alcohols esters, i.e. isopropyl alcohol (branched-chain), are more hardly hydrolyzed than the esters of primary alcohols. This is an essential property that should also be taken into consideration when the ester is a constituent of a cosmetic formula that should maintain its properties until the date of preferential consumption.

Although short-chain esters exhibit lower melting and boiling temperatures, they are also more irritating to the skin, so it is preferable to use high molecular weight esters whose fluidity is reduced by branching.

Ester fluidity can also be increased by introducing a double bond in either the acid moiety or the alcohol moiety of the ester. This solution compromises formulation stability since the double bonds are easily oxidized under the normal

TABLE 2 Some modified silicones used in cosmetic formulations

Supplier	Cosmetic ingredient	INCI name
Jeen International	JEELUX® VHIPIS ⁽¹⁾	Isopropyl isostearate, isododecane, bis-vinyl dimethicone/dimethicone copolymer
	JEELUX® DMIPIIS ⁽¹⁾	Isopropyl isostearate, dimethicone, bis-vinyl dimethicone/dimethicone copolymer
Siltech	Silwax DO2 ⁽¹⁾	Ethyl methicone
Dow	DC CB 1502 Gum Organic Blend ⁽¹⁾	C11-13 isoparaffin/isohehexadecane/dimethiconol/dimethicone
	DC ES-5226 DM	Dimethicone (and) PEG/PPG-18/18 dimethicone
	DOWSIL™ MQ-1640 FLAKE RESIN	PEG-7 Dimethicone (and) laureth-7 (and) polysorbate 20
	DOWSIL™ CE-8411 Smooth Plus Emulsion	Dimethicone/bis isobutyl PEG-14 copolymer (and) polysorbate 20 (and) butyloctanol
Exsymol	Capillasil®	Silanediol salicylate
	D.S.H. C N® and D.S.H. C®	Dimethylsilanol hyaluronate
	G.P.S.®	Silaneetriol trehalose ether
	Methiosil C+	Polysilicone 3
Biosil Technologies	Biosil Basics® Amino DL-30 CE	Dimethiconol panthenol
	Biosil Basics® A-30	Dimethiconol arginine
	Biosil Basics® DL-Methionine-30	Dimethiconol methionine
	Biosil Basics® L-Cysteine CE	Dimethiconol cysteine
	Biosil Basics® I-90	Cetyl PEG/PPG-10/1 dimethicone
Momentive Performance Materials	Silsoft* Tone	Polysilicone-18 cetyl phosphate
Clariant	SilCare® Silicone WSI	Amodimethicone glicerocarbamate
	SilCare® Silicone SEA	Trideceth-9 PG-amodimethicone, trideceth-12
Grant Industries	Gransurf 67	PEG-10 dimethicone
	Gransurf 90	Cetyl PEG/PPG-10/1 dimethicone
Evonik	Abil® UV Quat 50	Polysilicone-19
	Abil® WE 09	Polyglyceryl-4 isostearate, cetyl PEG/PPG-10/1 dimethicone, hexyl laurate
	Abil® T Quat 60	Silicone Quaternium-22
Chemsil	Emulsil® S-391	PEG-3 dimethicone
	Microsil HAF-HV	Propoxytetramethyl piperidiny dimethicone (and) C11-15 pareth-7 (and) trideceth-6

⁽¹⁾Declared by the supplier as a replacement for cyclomethicones.

conditions of cosmetics use. Therefore, branching is the best option to obtain esters with a suitable stability and fluidity [32].

The last aspect to be highlighted of the branched esters as opposed to the linear ones is that branching can affect the skin feel of the ester, providing a sensation named as “cushiony.” This effect can be described as the fact that the skin does not immediately absorb the ester applied on it, but it remains forming a film on the skin [31].

Currently, many suppliers of cosmetic components are including in their catalogs branched-chain esters as cyclomethicones substituent's, because of their excellent properties to be used as cosmetic formulations ingredients. There is a great variety of branched-chain esters with different applications, but this review is focused on cosmetic uses exclusively.

Therefore, in Table 3 only commercialized branched-chain esters as alternative to D₄ and D₅ are summarized by INCI name, supplier and commercial name. Esters from Table 3 have been described at least for one supplier as cyclomethicones alternatives. When the commercial product is a mixture of different esters, it appears associated to each ester (i.e. PARYOL EMOLL, commercialized by A&A Fratelli Parodi, which contains ethylhexyl palmitate and ethylhexyl stearate). The information showed in Table 3 has been obtained from suppliers' website and platform Special Chem (www.specialchem.com).

As we can observe from Table 3 there are twelve branched-chain esters commercialized as D₄ and D₅ alternatives, although other possible compounds of this type could have suitable properties (low surface tension, high lubricity,

TABLE 3 Commercialized branched-chain esters as alternative to D₄ and D₅ in cosmetic formulations

Ester (INCI name)	Supplier	Cosmetic product
Cetyl ethylhexanoate	A&A Fratelli Parodi	PARYOL COT
Alzo International	Bernel Ester CO
		Dermol 168
		Trivent OC-16
	Berg & Schmidt	Bergacare EM-CO
	Bionest	NeSol HO
	Blue Sun International	Cetyl Ethylhexanoate
	Dow	DOWSIL™ CE8401 emulsion
	Evonik	TEGOSOFT® CO
	Jeen International	Jeechem CO
	KCI	CEH 100KC
	Kokyu Alcohol Kogyo	CEH
	Lonza	Lonzest® CO
	Lubrizol	Scherzemol™ CO ester
	Miwon	Mipearl CO
	Natura Tec	Natura-tec Ultrafeel CEH
	Nikkol	Nikkol CIO
	SMA Collaboratives	SILK CO
	The Nisshin OilliO Group	SALACOS 8161
	AQIA	Polymol® ADI
Diisopropyl adipate
Asko	AakoEmo DIIPA
	Alzo International	Dermol DIA
	Ashland Specialty Chemical	Ceraphyl™ 230 ester
	Cosmetochem	Spread Oil 146-B
	Croda	Crodamol™ DA
	Georges Walther	DIISOPROPYL ADIPATE
	Hallstar	Hallstar® DIPA
	Jeen International	JeeChem DIA
	Lipotec	Pollushield™ functional ingredient
	Lubrizol	Fixate™ Keratin Activator
		Schercemol™ DIA ester
	Mamta Polycoats	Diisopropyl Adipate (DIPA)
	Momentive Performance Materials	SilForm® 60-A Emulsifier (D)
	Nikkol	Nikkol DID
	Phoenix Chemical	Pelemol® DIA

(Continues)

TABLE 3 (Continued)

Ester (INCI name)	Supplier	Cosmetic product
Diisopropyl sebacate	Protameen Chemicals	Protachem™ DIPA
		Protamide™ DIPA
	Sino Lion	Sunzerse™ ZN
	Southern Chemical Textiles	Techmide 470
	Stearinerie Dubois	DUB DOPA
	Tivent	Trivent DIA
	AE Chemie	AE Sunboost 1033B
	Alzo International	Dermol DIPS
	Jeen International	JeeChem DIS
Ethylhexyl ethylhexanoate	Lubrizol	Sherzemol™ DIS ester
	Nikkol	Nikkol DIS
	Phoenix Chemical	Pelemol® DIPS
	Stearinerie Dubois	DUB DIS
		DUB SYNERSOL
	Berg & Schmidt	BergaCare 88
Ethylhexyl isononanoate	Sabo	Saboderm OO
	Uniproma Chemical	Sunsafe® Complex A9
	Hallstar	Halstar® Octyl Isononanoate
	Alzo International	Dermol 334
		Dermol 866
		Dermol 89
	Berg & Schmidt	BergaCare 89
	Blue Sun International	Ethylhexyl Isononanoate
	Domus Chemicals	DomusCare EEIS
	Italmarch Chemicals	Dapracare® EHN
	KCI	EHIN 100KC
	Kokyu Alcohol Kogyo	ES 108109
	Lubrizol	Schercemo™ OISN
	Phoenix Chemical	Pelemol® 89
		Pelemol® 899
		PhenoMulse™ 100
	Stearinerie Dubous	DUB INO

(Continues)

TABLE 3 (Continued)

Ester (INCI name)	Supplier	Cosmetic product
Ethylhexyl palmitate	Symrise	Dragoxat® 89
	A&A Fratelli Parodi	PARYOL EMOLL
		PARYOL NEODERM OP
	AQIA	Polymol® OP
	Akott	Biogenico UVSpense T40/OS
	Alzo International	Dermol 816
		Wickenol 155
		Wikenol 161
		Wikenol 163
	Ashland Specialty Chemical	Ceraphyl™ 368 M ester
	BASF	Cegosoft® C 24
		Cetiol® EHP
	Berg & Schmidt	BergaCare EM-OP
		BergaCare FG5
	Borica	Hylube™ A2616C
	CISME Italy	OLOROL OP
	CREMER OLEO	CremerCOOR® EHP
	Chemir	Labial CH
	Comercial Química Massó	MASSOCARE EMO SUN1
		MASSOCARE EP
	Croda	Tioveil™ TGOP (D)
		Crodamol™ OP
		Maxi-lip™
		Spectraveil™ OP
		Tioveil™ 50 OP
	Domus Chemicals	DomusCare® OP
	Eastman Chemical Company	Eastman GEM™ 2-Ethylhexyl palmitate
	Elementis	Bentone Gel® OPV
	ErcaWilmar	ERCAREL OP V
	Evonik	Tegosoft® OP
	Exsymol	PRO-D.S.B.
	Fine Organics	Octyl Palmitate
	Georges Walther	ETHYLHEXYL PALMITATE
	Granula	GranLux® OP1-50
	Hallstar	Hallstar® OP
	INOLEX	Lexol® EHP
	Italmatch Chemicals	Dapracare® OP
	KLK Oleo	PALMASTER® 1543
	KahlWax	Khalbase 6397-Lipstick base

(Continues)

TABLE 3 (Continued)

Ester (INCI name)	Supplier	Cosmetic product
	Kalichem	KEMIDERM MICROSOMIC KMF
	Kobo Products	OPP60ZSI
	Kokyu Alcohol Kogyo	IOP
	Lakeland Chemicals	LAKLAS EHP
	Lonza	Gel Base 2 (D)
	McKinley Resources	McKinley Octyl Palmitate
	Natura-Tec	Natura-tec Ultrafeel OP
	Nikkol	Nikkol IOP
	Norfox	Norfox 163
	Oleon (Avril Group)	Radia [®] 7779
	Pilot Chemical	Macare [®] OP
	Protameen Chemicals	Protachem TM OP
	RITA	Gblock TM DT102 (D)
		Gblock TM DT104 (D)
		Rita OP (D)
	Res Pharma	Emulpharma [®] CM
		Emulpharma [®] CM Preservative Free
		Emulpharma [®] PGF E
	Sabo	Saboderm OP
	Stearinerie Dubois	DUB PO
	The Nisshin OilI/O Group	SALACOS P-8
	Thornley Company	Thorcoest OP
	Vantage Specialty Ingredients	Liponate [®] EHP
		Liponate [®] GC
	Zschimmer & Schwartz	HelioPro OP 50H
Ethylhexyl stearate	A&A Fratelli Parodi	PARYOL EMOLL
PARYOL NEODERM OS
	AQIA	Polymol [®] OS
	Alzo International	Dermol 818
		Wickenol 156
		Wickenol 161
		Wickenol 163
	B.C. Cosmetic and Food s.r.l	Beautyderm WW
	BASF	Cetiol [®] 868
		Cosmedia [®] ATH
		Rheocare [®] ATH
	BK Giuliani	Gilugel [®] OS
	Berg & Schmidt	Bergacare EM-OS
		Bergacare FG 5
	Bionest	NeSol OS

(Continues)

TABLE 3 (Continued)

Ester (INCI name)	Supplier	Cosmetic product
	Blue Sun International	Bluevisc AH
	Borica	Hilube™ A2618C
	CISME Italy	DERMAROL OST
	CREMER OLEO	CremerCOOR® EHS
	Chongqing Star-Tech Specialty Products	PVP K90 20% solution
	Clariant	Hostacerin® EWO
	Comercial Química Massó	MASSOCARE EMO SUN2
		MASSOCARE ES
	Croda	Estol 1545 (D)
		Crodamol™ OS
	Domus Chemicals	DomusCare® OS
	Ecogreen Oleochemicals	Rofetan® 188
	ErcaWilmar	ERCAQUAT HRC V/FD
		ERCAREL OS V
	Evonik	ABIL® Filler CL
		HyaCare® Filler C
		TEGO® Wipe Flex
		TEGO® Wipe Lux
		TEGOSOFT® OS
	Fine Organics	Octyl Stearate
	GfN-Selco	Natursol A100
	INOLEX	Lexol® EHS
	Kolb	Synpatens ES
	Lakeland Chemicals	LAKLAS EHS
	NAYAKEM ORGANICS	NAYAKEM-Octyl Stearate
	Natura-Tec	Natura-tec Ultrafeel OS
	Nikkol	Nikkol STO
	Norfox	Norfox 161
		Norfox 163
	Oleon (Avril Group)	Radia® 7770
		Radia® 7772
	Protameen Chemicals	Protachem™ OS
	Rheolab	NATURSOL HYDRA A
		NATURSOL ION A
		NATURSOL AVH
	Sabo	Saboderm OS
		Saboquat HRC
	Stearinerie Dubois	DUB SO
	Thornley Company	Thorcoest EHS
Isodecyl ethylhexanoate	Alzo International	Dermol 108

(Continues)

TABLE 3 (Continued)

Ester (INCI name)	Supplier	Cosmetic product
Isodecyl isononanoate	Stearinerie Dubois	Dermol 334 DUB INID
	Kokyu Alcohol Kogyo	Kak 109
	Alzo International	Dermol 109
Isononil isononanoate	A&A Fratelli Parodi	Wickenol 152 PARYOL BIOS 99
	AE Chemie	AE Ester 99
	Alzo International	Dermol 99
		Wickenol 151
	Berg & Schmidt	BergaCare IN 2
	Bionest	NeSol ININ
	Blue Sun International	Isononyl Isononanoate
	Calumet Lubricants	Versagel [®] MN1600
		Versagel [®] MN750
	Comercial Química Massó	MASSOCARE ININ
	Domus Chemicals	DomusCare [®] ISIS
	Georges Walther	Georges Walther ISONONYL ISONONANOATE
	Grant Industries	Gransil ININ
	Granula	GranLux [®] GAI-45
		GranLux [®] GAI-45 TC
		GranLux [®] GAI-50TMBBT
		GranLux [®] GAI2-45TZ
		GranLux [®] GTI-45TMBBT
		GranLux [®] GTI2-45
		GranLux [®] GTI2-45TZ
		GranLux [®] LECISUN-45
	KCI	ININ 100KC
		ISIS 100KC
		ITIN 100KC
	Kobo Products	IN45R7C (D)
		IN50R6B (D)
		IN50TZ (D)
		IN50Y5A (D)
		IN50Y6A (D)
		IN70UB (D)
		INH80LZ (D)

(Continues)

TABLE 3 (Continued)

Ester (INCI name)	Supplier	Cosmetic product
Neopentyl glycol diethylhexanoate		INX55EY (D)
		INX70EB (D)
		INX70ER (D)
	Kokyu Alcohol Kogyo	Kak 99
	Natura-Tec	Natura-tec Ultrafeel ININ
	Phoenix Chemical	Pelemol® 899
		Pelemol® IN-2
		PhenoMulse™ 100
	RITA	Ritamollient ININ
	SEIWA KASEI	Promois EK-118(IN)
	Sabo	Saboderm ISN
	Sensient Cosmetic Technologies	COVAMER®
		LIPSHINE
	Seppic	LANOL™ 99
	Stearinerie Dubois	Dub Heliocrystal
		Dub ININ
	The Innovation Company	Creage1® EZ IN
	The Nisshin OilliO Group	SALACOS 99
	Alzo International	Dermol NGDO
Neopentyl glycol diheptanoate		Minno 21
		Minno 41
	Blue Sun International	Neopentyl Glycol Diethylhexanoate
	ExxonMobil	Puresyn™ 2E7
	Kokyu Alcohol Kogyo	KAK NDO
	Lubrizol	Fixate™ Keratin Activator
		Sherzemol® NGDO ester
	Stearinerie Dubois	DUB DONPG
	The Nisshin OilliO Group	COSMOL 525
	Advance Nanotec	ZinClear IM® 55L7
	ExxonMobil	Puresyn™ 2E5
	Grant Industries	Granosil DML
	INOLEX	Lexfeel® 7
		Lexfeel® D4

(Continues)

TABLE 3 (Continued)

Ester (INCI name)	Supplier	Cosmetic product
		Lexfeel® D ₅
		LexFilm® Sun
		LexSolv® A
	Stearinerie Dubois	DUB DNPG

enhanced softness, chemical stability) to be used in cosmetic formulations.

4 | CHEMICAL METHODS FOR ESTER PRODUCTION

4.1 | General methods

Most esters can be obtained by esterification between acids and alcohols [33], but also by transesterification, alcoholysis, or acidolysis reactions. The classic methods are well known, but the catalysts used have been changing and improving over time in order to develop yielder, more efficient and environmental friendly processes.

Fischer or Fischer–Speier esterification is a special type of esterification by refluxing a carboxylic acid and an alcohol in the presence of a Lewis or Brønsted acid catalyst, in which the products and reactants are in equilibrium. The equilibrium may be influenced by either removing one product from the reaction mixture (e.g., removal of the water by azeotropic distillation or absorption by molecular sieves) or by employing an excess of one reactant [34–36].

Other alternatives to esters synthesis include using different substrates and catalysts. Steglich esterification involves the use of coupling reagents such as DCC (dicyclohexylcarbodiimide) to activate the carboxylic acid and DMAP (4-N,N-dimethylaminopyridine) as catalyst. The reaction is carried out at mild conditions, which allows the conversion of sterically demanding and acid labile substrates. It is one of the convenient methods for the formation of *tert*-butyl esters, with the additional advantage that no water is produced [37].

Another pathway for the production of esters is the formation of a carboxylate anion, which reacts as a nucleophile with an electrophile. For example, the Mitsunobu reaction allows the conversion of primary and secondary alcohols to esters, phenyl ethers, thioethers, and various other compounds. The nucleophile employed should be acidic, since one of the reagents (DEAD, diethylazodicarboxylate) must be protonated during the course of the reaction to prevent from side reactions [38].

The Yamaguchi esterification allows the mild synthesis of highly functionalized esters after the formation of

a mixed anhydride between the Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) and the carboxylic acid. The volatiles are removed and the reaction of the anhydride with an alcohol in presence of a stoichiometric amount of DMAP generates the desired ester [39].

The Baeyer–Villiger oxidation is the oxidative cleavage of a carbon–carbon bond adjacent to a carbonyl, which converts ketones to esters. The reaction can be carried out with peracids, such as MCPBA (3-chloroperoxybenzoic acid), or with hydrogenperoxide and a Lewis acid [40–42].

4.2 | Branched-chain esters synthesis

Different synthesis methods for branched-chain esters methods can be found in the available literature.

Branched-chain esters from alkyl dicarboxylic acids, mainly adipic and sebacic acids, have been widely studied. They are easily esterified with the appropriate branched-chain alcohol, with or without acid or metal catalyst, by Fischer esterification. For example, diisopropyl adipate is produced by esterification of adipic acid with an excess of isopropanol. The alcohol excess is removed by vacuum stripping and the ester is then alkali-refined and filtered [43]. High yields have been reached by using pervaporation membranes to continuous water removal from reaction mixture because of equilibrium shift to product conversion [44].

Diethylhexyl adipate can be prepared by the reaction of adipic acid and 2-ethylhexanol in the presence of an esterification catalyst such as sulfuric acid or *p*-toluenesulfonic acid [45]. Purification of the reaction product includes removal of the catalyst, alkali refining, and stripping [43].

Neopentyl glycol is a very versatile substrate to obtain branched-chain esters, because it can yield mono or diesters by reacting with linear or branched carboxylic acids. For example, esterification with propionic acid is carried out by using a commercial, heterogeneous gellular type resin (Dowex 50 WX 2) as catalyst and preheated N₂ flowing at temperatures up to 100°C. The aim of the research is to maximize the monoester production but diester is also synthesised [46].

Neopentyl glycol has also been esterified with hexanoic acid, and investigated as a potential additive for improving the cold flow properties of vegetable oil esters used as biodiesel. The synthesis is carried out in toluene, with a slight excess of acid, using *p*-toluenesulfonic acid as catalyst [47]. When sulfuric acid is used as catalyst, conversions of 99%

are reached by operating under optimal conditions: 150°C, 0.5 kPa, catalyst 0.5% w/w and a molar ratio hexanoic acid:neopentyl glycol 3:1 [48].

Synthesis of neopentyl glycol diheptanoate has been developed as well, by using toluene as solvent. When 1:3 neopentyl glycol:heptanoic acid molar ratio is used, in presence of acid ion exchange resin catalyst (polystyrendivinylbenzensulfated, 2.2 % w/w) at elevated temperature (120–220°C) during five hours, a reaction yield of 87% is reached [49]. The process of synthetic fatty esters preparation comprises continuously removing water formed as by-product by distillation. Addition of an azeotroping agent facilitates the removal of water from the reaction mixture. Preferably, the water is removed in the form of a binary mixture (water and toluene). Using similar procedures, in this study it has also been obtained neopentyl glycol dipentanoate, neopentyl glycol dihexanoate (dicaproate), and neopentyl glycol dioctanoate with yields of 88, 90 and 82% respectively, at temperatures between 100 and 220°C.

Raof et al. [50,51] have produced neopentyl glycol esters with high molecular weight by using not benched acids. For that purpose, they have carried out the high oleic palm oil methyl ester (HOPME) transesterification with neopentyl glycol at 180°C, under vacuum and using sodium methoxide as catalyst. Methanol formed is collected in a vacuum trap. The optimal conditions are established as molar ratio 2:1.3 HOPME:neopentyl glycol, 182°C, 0.6 mbar, and catalyst concentration of 1.2%. The maximum diester yield reached is 87% after 1 hour.

On the other hand, neopentyl glycol benched acids esters have also been synthesized. Inayama et al. [52] have described the production of different neopentyl glycol diesters that may be used in an industrial lubricant (e.g. refrigerating oil). Esterification of neopentyl glycol with isobutyric acid, 2-ethylhexanoic acid, and 3,5,5-trimethylhexanoic acid is performed at 180–220°C, bubbling nitrogen, under a reduced pressure of 2.4 kPa and using tetrabutoxytitanium as catalyst.

2-Ethylhexanoic acid esters are another group of branched-chain esters with important applications in cosmetic industry, standing out cetyl and 2-ethylhexyl 2-ethylhexanoate. However, their innocuity has recently been put into question. The Cosmetic Ingredients Reviewer's (CIR) Expert Panel of the Department of Health of the Australian Government [53] assessed the safety of 16 alkyl ethylhexanoates used in cosmetics, concluding that these ingredients are safe and non-irritating if they are used in cosmetic formulations in lower concentration than those reported. For instance: 77.3 % of cetyl ethylhexanoate in rinse-off formulations used near the eye, and 52% in leave-on use in lipstick formulations.

However, in 2005, the Australian Government Department of Health attended the proposal of limiting 2-ethylhexanoic acid and its derivatives concentration in cosmetic preparations containing esters that hydrolyse to 2-ethylhexanoic acid.

2-Ethylhexyl 2-ethylhexanoate is one of these compounds and currently, in Australia, it is limited in cosmetics at 10 % (which is broadly equivalent to 5% of 2-ethylhexanoic acid). There are no labeling requirements for others ethylhexanoates [54].

Several ethylhexanoates chemical synthesis procedures have been described in the literature, for example, 2-ethylhexanoic acid esterification with ethanol in a flow through catalytic membrane reactor in which reactants are forced to pass through the membrane pores, where catalyst is placed [55]. In this sense, the modified membrane was prepared by polymerization grafting of sulfonic groups on a polyethersulfone membrane.

Futhermore, 2-ethylhexyl 2-ethylhexanoate production via chemical esterification requires very severe reaction conditions and efforts have been conducted to develop alternative processes more efficient and environmentally friendly. In this sense, the ester is continuously synthesized in supercritical carbon dioxide with 100% selectivity and 40% conversion using zirconium oxide as catalyst [56].

Although cetyl 2-ethylhexanoate is also widely applied in cosmetic industry, its chemical synthesis is not described in the available literature.

Finally, another relevant group of branched-chain esters with cosmetic applications are the one derived from isononanoic acid: ethylhexyl isononanoate, isononil isononanoate, and isodecyl isononanoate. Only isononil isononanoate synthesis has been described in a 2010 Chinese patent [57], in which esterification is conducted in a cyclohexane or xylene medium, at 90°C and with *p*-toluenesulfonic acid (or amidosulfonic acid or sodium hydrogen sulfate) as catalyst.

Chemical methods are well studied and have been traditionally used, but they have a number of drawbacks. In one hand their environmental implications, as they are not “green processes,” because they require the use of high temperatures with the consequent energy consumption and they generate undesirable by-products with expensive operations to separate the desired product. On the other hand, the nature of the obtained product, since these esters are used in the cosmetic industry that requires high purity and if they are obtained by biocatalytic reactions can be labelled as “natural.”

5 | ENZYMATIC SYNTHESIS OF BRANCHED-CHAIN ESTERS. THE BIOTECHNOLOGICAL ALTERNATIVE TO CYCLOMETHICONES

After an exhaustive literature review, it can be affirmed that papers published related to branched-chain esters enzymatic synthesis are still quite limited. In this chapter, a revision of these few documents is presented.

The most frequently obtained is 2-ethylhexyl palmitate, whose synthesis has been approached by different researchers with a wide variety of results. In all cases, the catalyst used is a free or immobilized lipase from different sources. Reaction media tested were petroleum ether, *n*-heptane, water, or solvent-free. In Table 4, the most relevant reaction conditions and results in the esterification of palmitic acid and 2-ethyl hexanol are summarized.

Most processes are carried out with immobilized lipases in water-free medium to shift equilibrium towards ester production. An exception is esters synthesis with free *Candida antarctica* lipase A in aqueous medium, reaching 100% conversion in 18 hours [62]. Processes conducted in petroleum ether require also long times (10–24 h) and moderate conversions were obtained (90–91%) [58,59]. Richetti et al. [60, 61] have tested different commercial lipases and higher conversion and shorter operation times are obtained when Lipozyme® RM IM is used, although high enzyme concentration 10% is required. Unfortunately, this biocatalyst is not commercialized at present by Novozymes and has been replaced by Novozym® 40086, a lipase from the same enzymatic source (*Rhizomucor miehei*) but immobilized in different support, so the performance of the biocatalyst may not be the same.

Recently other researchers [63,64] have obtained product conversions up to 98 and 97% in 60 and 90 minutes respectively by using commercial lipases (Novozym® 435 and Novozym® 40086) in solvent-free systems. These results were slightly improved when heptane, thermophilic lipase, and microwave activation were employed [65], although longer operation time and higher alcohol excess were required (1:2) compared with those previous works (1:1.33) [63,64].

2-Ethylhexyl estearate is a similar branched ester that is also used in cosmetic formulations, pure or mixed with other esters, such as 2-ethylhexyl palmitate in the commercial product BergaCare FG5 [66]. The ester has been obtained by stearic acid and 2-ethyl hexanol enzymatic esterification in a solvent-free system, using immobilized commercial lipases: Novozym® 435 [67] and Novozym® 40086 [68], with slightly alcohol excess (1:1.33) and lipase concentration of 3.75%. Conversions of 98.94% in 60 minutes and 97.30% in 90 minutes were reached when Novozym® 435 and Novozym® 40086 are respectively used.

The biocatalytic synthesis of different neopentyl glycol esters have been described in the available literature. Using fatty acids obtained from natural sources: hydrolyzed soybean-oil [69], microbial oil [70], and palm fatty acid distillate [71]. In all the cases, over 87% conversion values are obtained with *Candida rugosa* lipase.

However, the enzymatic synthesis becomes more difficult when the branched substrate is the acid. Cetyl 2-ethylhexanoate is widely used in cosmetics as a base oil because of its lubricity, moisture retention and nontoxic

TABLE 4 Comparison of different lipase catalyzed 2-ethylhexyl palmitate synthesis processes

Lipase source	Immobilization support	Reaction medium	Molar ratio acid:alcohol	Enzyme concentration (%)	Reaction time (h)	Conversion (%)	Reference
<i>Candida</i> sp. 99–125	Celite	Petroleum ether	5:1	10	24	91	[58]
	Fabric membrane		1.3:1	—	10	90	[59]
<i>Candida antarctica</i> lipase B Novozym® 435	Macroporous acrylic resin	Solvent free	1:5.5	10.5	6	93	[60]
<i>Rhizomucor miehei</i> lipase Lipozyme® RM IM	Cationic silicate	Solvent free	1:3	10	1	95.22	[61]
<i>Candida antarctica</i> CAL-A	Native lipase	Water-abundant system	1:1.25	—	18	100	[62]
<i>Candida antarctica</i> lipase B Novozym® 435	Macroporous acrylic resin	Solvent free	1:1.33	3.75	1	98.39	[63]
<i>Rhizomucor miehei</i> lipase Novozym® 40086	Macroporous acrylic resin	Solvent free	1:1.33	3.75	1	98.34	[64]
Thermophilic lipase QLM (<i>Alcaligenes</i> sp. lipase)	Silica mesoporous SBA-15	Anhydrous <i>n</i> -heptane	1:2	2	3 microwave	99	[65]

properties. Its production by direct esterification of cetyl alcohol with 2-ethylhexanoic acid using an immobilized lipase Novozym® 435 as a catalyst in hexane has been published [72]. To reach conversion of 90%, 2.65 days and an enzyme amount of 251.39% are necessary, which makes clear the complexity of the process. Other researchers [73] have tried to synthesize 2-ethylhexyl 2-ethylhexanoate carrying out the reaction in hexane with Novozym® 435 as catalyst (2 g/L), reaching 83% of conversion in 40 hours. A more environmental friendly process has been developed using supercritical carbon dioxide (SC-CO₂) with the same lipase, but yielding not so good results [56].

However, other authors suggest than *Candida antarctica* lipase, which is widely used due to its high activity for a large number of primary and secondary alcohols, has some difficulties in accepting branched carboxylic acids, because its binding pocket close to the active center is rather restricted. Some attempts have been made in order to create more space for the substrates in the binding pocket and to establish a biochemical environment favorable for the substrates, but the specific activity of CalB wild type and the mutant towards 2-ethyl hexanoic acid ester was similar [74]. Therefore, until today, it seems impossible to obtain 2-ethyl hexanoic acid esters by enzymatic catalysis at least using *Candida antarctica* lipase.

6 | CONCLUDING REMARKS

Since 2005, many studies have been carried out in several countries (European and Americans) about the possible damages that D₄ and D₅ cyclomethicones can cause in living beings as well as in the environment. In the European Union from 31st of January of 2020 these compounds may not be present in cosmetic products that can be removed with water in concentrations equal to or greater than 0.1% by weight. In recent years also, ecological awareness and consumer's perception of using safe and not harmful to the environment products have also intensified. All these factors together with the great economic importance of cosmetics market has led to many cosmetic formulators to need viable alternatives to cyclomethicone and, to serve this growing demand, manufacturers are striving to enhance their raw material portfolio.

Although many companies have opted for changing cyclomethicones by organomodified silicones, the importance of “silicone free” marketing has led to an increase in the number of esters that are capable of offering the pleasant sensory properties that cyclomethicones provide. Most of the esters postulated as silicones alternatives are branched-chain esters that are currently obtained by classical methods using high temperatures and inorganic catalysts.

Faced to this production system, biocatalytic synthesis using immobilized lipases is an evident advance, both from the point of view of final product quality and the synthesis

processes sustainability, since they are carried out at mild temperature conditions achieving energy savings, in the absence of pollutant catalysts and even in “solvent-free” processes. Products obtained under these conditions are of high purity, expensive separation, and purification steps are avoided and they can be labeled as “natural” as well.

It would be desirable for the next years that the number of cosmetic ingredients biocatalytically obtained increases significantly, being this a study field continuously growing in order to improve environmental protection.

ACKNOWLEDGMENT

This work has been funded by Spanish MINECO the Spanish Ministerio de Ciencia e Innovación (CTQ2015-66723-R) and the European Commission (FEDER/ERDF) (CTQ2015-66723-R). M.D. Murcia and S. Ortega are beneficiaries RYC-2016-20211 contract and PTQ-15-08015 grant.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

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How to cite this article: Montiel MC, Máximo F, Serrano-Arnaldos M, Ortega-Requena S, Murcia MD, Bastida J. Biocatalytic solutions to cyclomethicones problem in cosmetics. *Eng Life Sci* 2019;19:370–388. <https://doi.org/10.1002/elsc.201800194>