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To cite this version:

Valentin Goussard, Jean-Marie Aubry, Véronique Rataj. Bio-based alternatives to volatile silicones: Relationships between chemical structure, physicochemical properties and functional performances. Advances in Colloid and Interface Science, 2022, Advances in Colloid and Interface Science, 304, pp.102679. 10.1016/j.cis.2022.102679 . hal-04138294

Bio-Based Alternatives to Volatile Silicones: Relationships between Chemical Structure, Physicochemical Properties and Functional Performances

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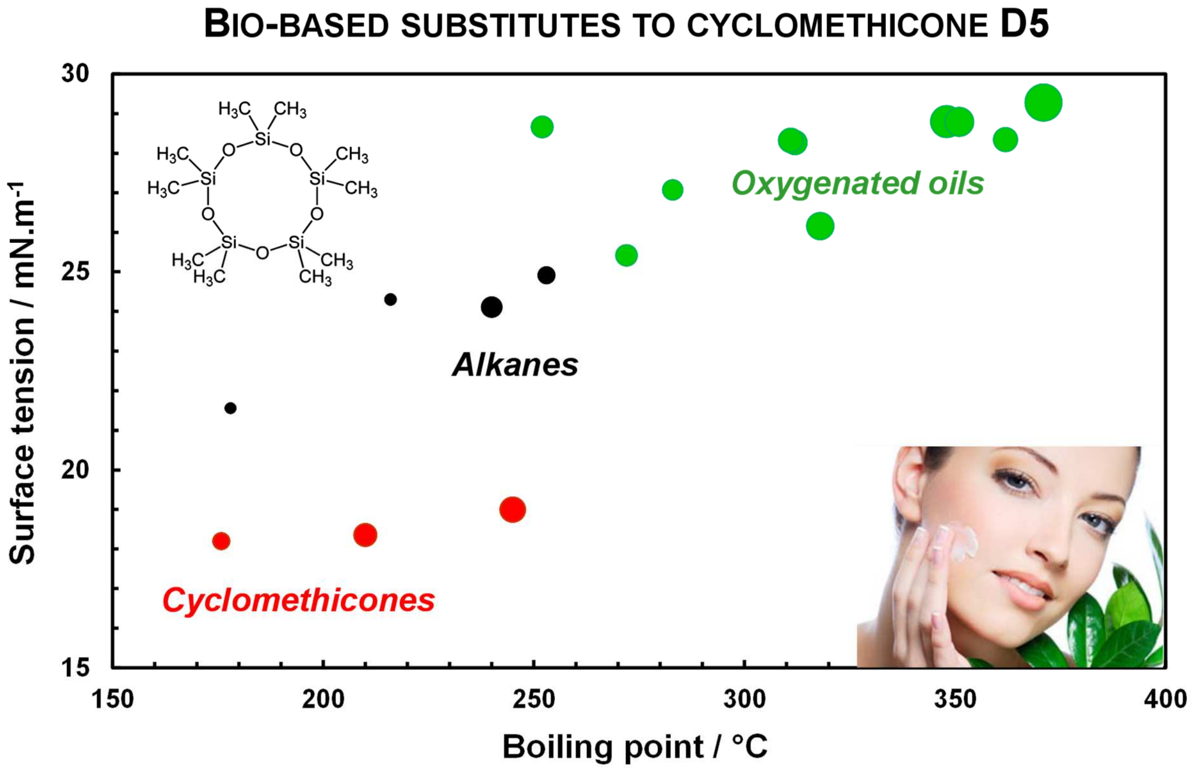
Abstract

Emollient oils are ubiquitous ingredients of personal care products, especially skin care and hair care formulations. They offer excellent spreading properties and give end-use products a soft, pleasant and non-sticky after-feel. Emollients belong to various petro- or bio-based chemical families among which silicone oils, hydrocarbons and esters are the most prominent. Silicones have exceptional physicochemical and sensory properties but their high chemical stability results in very low biodegradability and a high bioaccumulation potential. Nowadays, consumers are increasingly responsive to environmental issues and demand more environmentally friendly products. This awareness strongly encourages cosmetics industries to develop bio-based alternatives to silicone oils. Finding effective silicon-free emollients requires understanding the molecular origin of emollience. This review details the relationships between the molecular structures of emollients and their physicochemical properties as well as the resulting functional performances in order to facilitate the design of alternative oils with suitable physicochemical and sensory properties. The molecular profile of an ideal emollient in terms of chemical function (alkane, ether, ester, carbonate, alcohol), optimal number of carbons and branching is established to obtain an odourless oil with good spreading on the skin. Since none of the carbon-based emollients alone can imitate the non-sticky and dry feel of silicone oils, it is judicious to blend alkanes and esters to significantly improve both the sensory properties and the solubilizing properties of the synergistic mixture towards polar ingredients (sun filters, antioxidants, fragrances). Finally, it is shown how modelling tools (QSPR, COSMO-RS and neural networks) can predict *in silico* the key properties of hundreds of virtual candidate molecules in order to synthesize only the most promising-whose predicted properties are close to the specifications.

Keywords: Bio-based emollients; Volatile silicones; Top-down approach; Structure/properties relationships; Predictive tools

Graphical abstract



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1. Introduction

Oil is a general term used to define a substance, liquid at ambient temperature and water immiscible. Oils differ from fats which have higher melting points.[1] They are widely used in various application fields, as a consequence of their broad range of functional properties. For example, the nutritional properties of vegetal and animal oils and fats result in their large use in the food industry.[2,3] The technical properties of oils, in particular the wide range of their dynamic viscosity (from 1 to 1000 mPa.s) account for their use in engineering industries and especially as lubricants.[4–6] Their film-forming properties allow them to improve the spreading of cosmetic and pharmaceutical formulations on skin and hair.[7]

Oils, which can be synthetic or natural, are generally classified according to their composition. Vegetal and animal oils mainly contain triglycerides which are starting materials for obtaining a great diversity of fatty acids and alcohols.[8] For their part, mineral oils are mainly composed of hydrocarbons and silicone derivatives, whereas essential oils, with fragrant and biological properties,[9] are rich terpene compounds.

Oils are important ingredients in cosmetics. They are often termed "emollients" because they contribute to the formulation texture and make the skin soft, supple and comfortable. Beside mineral oils such as paraffin oil, silicone oils are the most frequently used. Silicones are prime ingredients in personal and hair care products because of specific properties difficult to match with hydrocarbon oils. Unlike very occlusive oils such as paraffin oil, they form a partially occlusive film leading to a physical protective barrier which slows down the loss of water and thus, ensures skin hydration.[10] In addition, they provide a smooth, light, dry, velvety and non-sticky after-feel.[11–13] Such properties result from their particular chemical structure. The numerous silicones on the market are usually ranged within two classes: the linear silicones, i.e. polydimethylsiloxanes (PDMS) or dimethicones and the cyclic silicones or cyclomethicones. The linear silicones constitute a large family of compounds, whose functional properties depend on their molecular weight. For instance, the light and pleasant touch is a specific characteristic of volatile silicones, i.e. cyclic or linear chemical structures of low molar mass. Their very low surface tension (< 20 $mN.m^{-1}$ for non-organo-modified PDMS)[14] associated with low viscosity also decreases the oily and tacky touch. The light after-feel results from the evanescent character of cyclomethicones. The strength of the Si-O bond gives the siloxane backbone a great thermal, chemical and biological stability but, it negatively impacts the biodegradability of silicone oils, resulting in a high bioaccumulation potential. Thus, the octamethylcyclotetrasiloxane (D4) has been listed as a PBT (Persistent, Bioaccumulative and Toxic) and a vPvB (very Persistent and very Bioaccumulative) substance and the decamethylcyclopentasiloxane (D5) is also a vPvB substance.[15,16] Such environmental issues have rendered the regulation in cosmetic field more stringent and have led the European Union to limit the use of D4 and D5 to 0.1 wt% in rinse-off products after January 2020 (Directive 76/769/EEC from appendix XVII).[17]

Besides these environmental considerations, consumers are increasingly demanding products formulated with bio-based raw materials, while keeping the same performances of the final product. This new tendency has forced industrials to search for alternatives to silicone oils. Nevertheless, replacing silicone oils and developing novel effective bio-based emollients is challenging as it requires considering performances, cost, safety and respect of the environment. This needs to meet several specifications in terms of sensory and physicochemical properties but also in terms of industrial constraints. Figure 1 gives the expected requirements to design ideal bio-based alternatives to volatile silicone oils.

Sensory requirements	Physicochemical properties	Industrial constraints
Easy spreading on skin/hair	Semi-volatile at 37°C	Safe (human & environment)
Neither sticky, nor greasy	Low viscosity	Cost-effective
Silky and light after-feel	Low surface tension	Biobased raw materials
Practically odorless	Solubilizer of cosmetic actives	Industrial scale-up

Figure 1 – Ideal profile of a bio-based volatile emollient for skin care formulations. The sensory properties of emollients are assessed by a panel of trained experts.

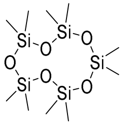
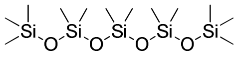
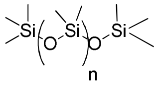
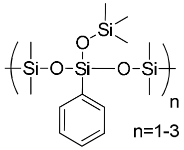
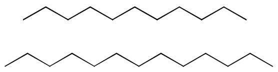
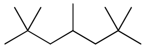
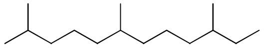
Despite their ubiquity in cosmetic and pharmaceutical formulations, emollients have rarely been the subject of specifically dedicated reviews. Actually, they are generally considered by galenists and dermatologists as simple vehicles for giving texture to formulations and for dissolving the active ingredients and facilitating their penetration into the skin.[18] In contrast, in the cosmetic field, they play a major role in providing a pleasant feel to the formulations, in preventing dryness of the skin and in making the hair shinier and easier to comb. The mistrust of consumers and authorities for silicones has focused the attention of academic and industrial scientists towards the search for less problematic alternatives. The objective of this review is to rationalize the emollient properties in order to facilitate the design of new bio-based alternatives to the petro-based cyclomethicones. Our strategy initially consisted in identifying in patents in particular and among raw material suppliers the emollients claimed as alternatives to silicones, using keywords such as « silicone-free » or « silicone-like ». Then, we carried out a more detailed analysis of the scientific literature (SciFinder and Web of Science) to understand and link the emollient properties to real physicochemical parameters and descriptors in order to identify a strategy allowing the development of new emollients with properties approaching those of silicones. A recent publication deals with the sustainability of all cosmetic ingredients[19] but, to the best of our knowledge, no review focuses on the relationship between the physicochemical properties and the sensory properties of cyclomethicones substitutes.

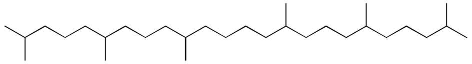
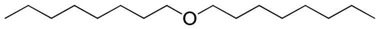
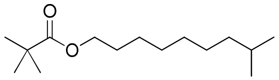
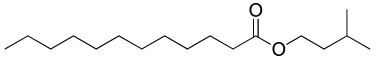
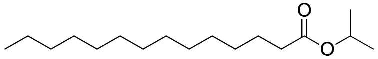
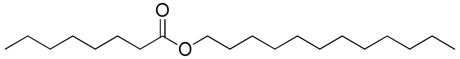
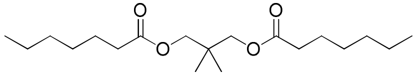
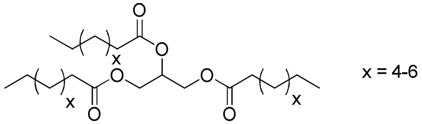
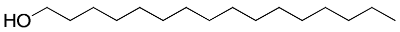
Thus, the first part describes the main chemical families of emollients as well as the specific properties of silicone oils. In a second part, correlations between physicochemical and functional properties of volatile emollients are established and the influence of structural modifications is discussed. Finally, available predictive tools able to estimate the physicochemical properties of emollients are presented. Such modelling approach turns out to be very useful to point out the most promising candidates among a series of virtual compounds, for which experimental characterization is not possible.

2. Diversity of oils on the cosmetic market

The use of oils and fats in skin care is found throughout the ages and across all cultures. For example, emollients and moisturizers from vegetal and animal origins can be traced back to the ancient Egyptians, Greeks and Romans[20,21]. Nowadays, the emollient market is mainly divided into three main chemical families: the silicone derivatives, the hydrocarbons and the esters. However, other chemical families are also claimed for their emollient properties, in particular ethers, carbonates or fatty alcohols. Table 1 reflects the great diversity of the chemical families within the emollient ingredients and gives significant examples of oils currently available on the cosmetic market as well as the claims given by the suppliers. Essential oils, although called "oils", do not possess emollient properties by themselves. However, they can be incorporated at low concentration in cosmetic formulations (massage oils, moisturizers) to provide a pleasant odour appreciated by consumers and other beneficial biological effects such as antioxidant, anti-microbial or anti-inflammatory.[22,23] However, their choice must be made with care because many essential oils are irritating and/or allergenic[24].

Table 1 – Typical emollient oils used for cosmetic applications.

N°	INCI name	Examples of suppliers	Emollient types/Origin	Chemical structures	Volatility	Claims
			CYCLIC, LINEAR & POLYMERIC SILICONE OILS			
1	Cyclopentasiloxane D5	Dow Corning	Cyclomethicone/ Inorg		✓	Excellent spreading properties Light, dry, soft and velvety after-feel
2	Dodecamethylpentasiloxane	Dow Corning	Volatile dime thicone / Inorg		✓	Good spreading properties Reduce the stickiness and greasiness
3	Dimethicone	Dow Corning	Polydimethylsiloxane/ Inorg			Soluble in organic solvents Good spreading properties
4	Phenyl Trimethicone	Dow Corning	Polydimethylsiloxane/ Inorg			Provide brightness Decrease the whitish effect
			LINEAR & BRANCHED HYDROCARBONS			
5	Cetiol® Ultimate	BASF	Hydrocarbon / Agro		✓	Excellent spreading properties Light, soft and dry after-feel,
6	Isododecane	The Innovation Company	Hydrocarbon / Petro or Agro		✓	Volatile emollient No residual film and light feeling
7	Hemisqualane	Amyris	Hydrocarbon / Agro		✓	Bio-based alternative to silicone & paraffin oils - Light and soft after-feel
8	Paraffinum liquidum	Cooper	Hydrocarbon / Petro	Saturated hydrocarbons mixture		Occlusive properties - Wide range of applications (body, hair care, make-up)

9	Squalane	Clariant	Hydrocarbon / Agro			Non greasy after-feel Skin and hair moisturizing
				OXYGENATED OILS: ETHER, MONO- & POLY- ESTERS, FATTY ALCOHOL		
10	Dicaprylyl ether	BASF	Ether / Agro		✓	Light and silky after-feel similar volatile silicone oils
11	Isodecyl neopentanoate	Stéarinerie Dubois	Monoester / Petro		✓	Light and low viscous Excellent spreading properties
12	Isoamyl laurate	Oleon	Monoester / Agro		✓	Natural alternative to cyclomethicones
13	Isopropyl myristate	Croda	Monoester / Agro		✓	Excellent spreading properties Soft, silky and non-greasy after-feel
14	Coco-caprylate	BASF	Monoester / Agro		✓	Natural emollient - Similar sensory profile to cyclomethicones
15	Neopentyl glycol diheptanoate	Stéarinerie Dubois	Diester / Agro-Petro			Sensory profile similar to D5 Solubilising agent for UV-filters
16	Caprylic / Capric Triglyceride	Evonik	Triglyceride / Agro			Moisturizer Medium spreading
17	Cetyl alcohol	Berg & Schmidt	Fatty alcohol / Agro			Rheological modifiers Surfactant properties

2.1 Silicone oils, a major innovation of the 20th century

2.1.1 From the singularities of the siloxane backbone to a unique sensory profile[10,12,25–27]

Silicone oils appear on the cosmetic market in the second half of the 20th century and they were increasingly introduced in personal care formulations since the 1970s. Their ability to wet a wide range of surfaces and the smooth, light and dry after-feel they provide account for their ubiquity in cosmetics.[10,12]

This highly appreciated sensoriality results from their particular chemical structure. Starting from silicon and methyl chloride, silicon derivatives are obtained from the Müller-Rochow process, after steps of hydrolysis, condensation and polymerization. The resulting polydimethylsiloxane (PDMS) are ranked according to their chemical structures, i.e. linear, cyclic, grafted or cross-linked or to their physiochemical properties, i.e. fluids, elastomers or resins.[28] The diversity of chemical structures explains their use in a wide range of applications, including aeronautics, transports, constructions, electronics, food or pharmaceuticals and cosmetics.[12,29] In cosmetics, two types of silicone oils are mainly used: *i)* the volatile silicones, either linear or cyclic (cyclomethicones) like the D4, D5 and D6, and *ii)* the linear non-volatile PDMS with higher molar mass. Their viscosity varies from 1 to 10 000 mPa.s and increases with the polymerization degree. PDMS with higher viscosity constitute the family of rubbers. The less viscous decreases the tackiness of the formulations whereas the more viscous highlights a high substantivity and are mainly used as hair conditioners.[30] The properties of silicone oils can be modified by grafting lateral organic groups on the siloxane backbone. For instance, amine groups increase the antistatic character of the oil while phenyl groups increase the refractive index and consequently the brightness of the oil, which is required for conditioner applications in hair care products.[28,30,31] Table 2 summarizes the properties of four common cosmetic silicone oils. It highlights their very low surface tension (ST) values (17 – 22 $mN.m^{-1}$) and the wide range of viscosity.

Table 2 – Relevant physicochemical properties (boiling point BP, kinematic viscosity ν, surface tension γ) and cosmetic uses of four silicone oils used in cosmetics.[12]

N°	INCI name	BP (°C)	ν (cSt)	γ (mN.m^{-1})	Cosmetic use
1	Cyclopenta-siloxane, D5	211	3.7	18.4	Lotions, creams, deodorants
2	Dodecamethyl-pentasiloxane	229	2.1	18.7	Creams, hair care deodorants,
3	Dimethicone 350	> 230	350	20.3	Hair care, sun care, make-up
4	Phenyl trimethicone	315	15-30	20-22	Conditioner, sun care, make-up

Silicone oils are claimed for their excellent spreading properties on a wide range of surfaces due to very low surface tension values (17 – 22 mN.m^{-1}) compared to other benchmark emollients (23 – 35 mN.m^{-1}). In contact with a polar surface, as skin surface or hair, the polar siloxane backbone shifts towards the surface whereas the methyl apolar groups point outwards, playing a shield effect, which gives the PDMS an overall hydrophobic surface (Figure 2). This hydrophilic/hydrophobic dual behaviour imparts the silicon oils their high spreadability and their excellent film-forming properties, improving the skin hydration.

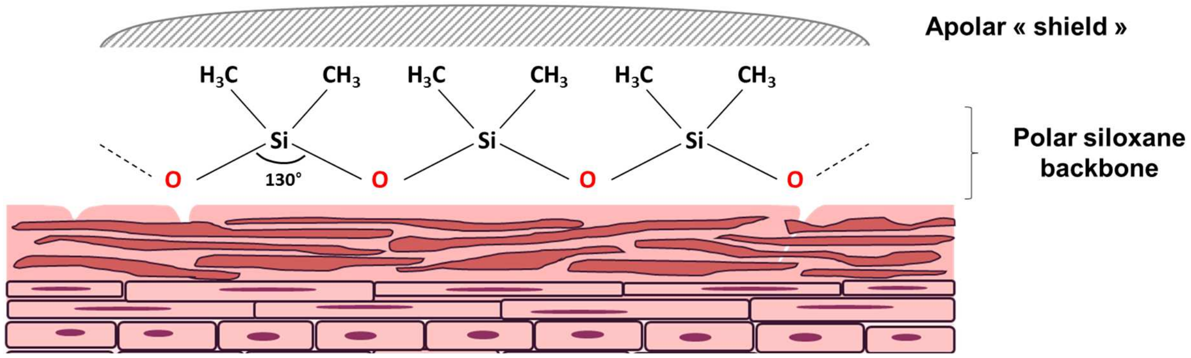


Figure 2 – Schematic spreading of a PDMS chain on a polar surface such as skin (adapted from literature[10,32]).

The dry, light, velvety and non-sticky after-feel mainly results from the volatility of both short-chain PDMS and cyclomethicones. For instance, the combination of a relatively high vapor pressure (> 10 Pa) and a low heat of vaporization of cyclomethicones allow a quick evaporation after application onto to the skin.[12] Table 3 gives an overview of the impact on physicochemical and sensory properties of the specific chemical features of silicone derivatives.

Table 3 – Structural features of silicone oils and consequences on their physicochemical and sensory properties[10,12,27,32,33]

Structural features	**Physicochemical consequences**	**Advantages for cosmetic use**
Strong chemical bonds Si-O: 439 kJ/mol C-C: 353 kJ/mol	High thermal, photochemical and chemical resistance	Chemically and physiologically inert
Strongly polarized Si-O bond	Adhesion to polar surfaces	Substantivity to skin and hair
Wide valence angles O-Si-O: 130° C-C-C: 112°	High chain flexibility Low glass transition temperature	Elastic behaviour, independent of temperature
High interatomic length Si-O: 163 pm C-C: 154 pm		
Low rotational energy 0.8 kJ/mole (C-O) 15 kJ/mole (C-C)		
Apolar methyl groups on Si atom and weak intermolecular interactions	Very low surface tension (17 – 22 mN.m^{-1})	Spreadability, high sliding and lubricant properties

2.1.2 Current debates and concerns with silicone oils

Besides these sensory qualities, the strength of the Si-O bond is responsible for both persistence and bioaccumulation of silicones in the environment, in particular the cyclomethicones. It raises debates regarding their safety for both human health and environment.

a) Silicone oils and health hazards

The Scientific Committee on Consumer Safety (SCCS), in charge of the evaluation of the harmless of the cosmetic ingredients, has studied cyclomethicones for several years.[34] In 2013, Wang et *al.* have reviewed recent toxicological studies on D4, D5 and D6.[35] They highlight the aquatic toxicity of the D4 and listed its different damages on mammals, which has led to its classification as reprotoxic (category 3), i.e. *i)* fertility damage, preventing ovulation and influencing life cycle, *ii)* liver damage and *iii)* oestrogen mimicry. None of such effect or any others has been brought to light regarding the use of D5. Nevertheless, cyclopentasiloxane is responsible for liver enlargement and lung inflammation of male and female rats. Besides, doubts still exist regarding its potential carcinogenic effect after long-term exposure[35], which explains that the D5 remains a highly controlled substance.

b) Bioaccumulation of silicone oils the environment.

A recent increased awareness of both persistence and bioaccumulation of cyclomethicones in the environment has brought these ingredients in several societal debates. Within cosmetic formulations, a part of emollient ingredients remains on clothes before being removed in soils, sewers or atmosphere. In particular, the cyclomethicones exhibit high volatility and accumulate in the ambient air. In addition, their bio-physicochemical stability drastically decreases their biodegradability.[36] Besides, they accumulate in aquatic environment due to their very low water solubility.[12] The bioconcentration factor (BCF) is generally used to quantify the persistence of a substance in the environment. BCF, expressed in L/kg, is the concentration of test substance in/on the fish or specified tissues thereof (as mg/kg) divided by the concentration of the chemical substance in the surrounding medium (as mg/L or mg/Kg). Bioaccumulative and very bioaccumulative substances are thus defined for BCF higher than 2000 and 5000 $L.kg^{-1}$ respectively. The BCF has been evaluated at 12400, 4450 and 1202 $L.kg^{-1}$ for D4, D5 and D6 respectively, accounting for their massive bioaccumulation.[35] In this context, the appendix XIII of the REACH regulation has listed D4 as a PBT and vPvB substance and D5 as a vPvB substance. This has rendered the cosmetic regulation more stringent: the use of D4 and D5 is limited the 0.1 wt% in rinse-off products after January 2020 (76/769/EEC directive from appendix XVII).[17] This societal and environmental context encourages industrials to develop bio-based alternatives to petro-based cyclomethicones and several "silicon-like" and more particularly "D5-like" are currently part of the emollient market. Cetiol Ultimate, hemisqualane, dicaprylyl ether, isoamyl laurate or isodecyl neopentanoate, whose chemical structures and sensory profiles are reported in Table 1 are typical examples of commercial emollients claimed for their "D5-like" profile.

2.2. Hydrocarbons as emollients[37–39]

Hydrocarbons form an important class of emollient ingredients, widely used since the beginning of the twentieth century. Squalene **21** and squalane **9** are two examples of agro-based non-volatile hydrocarbons (Figure 3). For a long time extracted from shark liver, squalene nowadays essentially arises from olive oil.[40] Arguing that it is one of the main components (≈ 13%) of natural skin lipids, vegetable oils rich in squalene are often claimed for their emollient and antioxidant properties[22,41]. This antioxidant claim is somewhat counter-intuitive because the six double bonds present in squalene molecule make it susceptible to free radical oxidation by oxygen[42], but neat vegetable oils naturally contain antioxidants such as tocopherol which considerably slow down the oxidative degradation of squalene[43]. A hydrogenation step gives squalane, which is chemically stable and inert. Due to its high viscosity (η = 28.1 mPa.s) and its non-volatility (BP ≈ 420 °C), squalane is claimed for its occlusive properties, that help to strengthen the skin barrier function and maintain skin hydration. Squalane can also be obtained from sugar cane by biotechnology.[44] The same method is also applied to produce farnesene **22** and farnesane (or hemisqualane) **7** after hydrogenation. Included in the portfolio of the company Amyris, the latter is claimed to be a bio-sourced alternative to cyclomethicones, due to its excellent spreading properties and to its light and smooth "D5-like" sensory profile.[45] Another example of bio-based hydrocarbon alternative to cyclomethicones is the *n*-undecane/*n*-tridecane mixture (Cetiol® Ultimate **5**). Its high volatility leading to a smooth and light "D5-like" after-feel and its excellent spreading properties explain its ubiquity on the cosmetic market.[46] Petro-based hydrocarbons are generally mixtures of several chain lengths that have been refined by distillation of crude oil. Examples of such compounds are paraffin oils or petroleum jelly which have a high occlusive effect due to their high viscosities and high boiling points.[40] The highly branched isoparaffins isododecane **6** and isohexadecane **23**, widely used as volatile emollients, are obtained by hydrogenation of isobutylene oligomers. However, alkanes poorly solubilize polar additives and exhibit less biocompatibility than esters with skin.

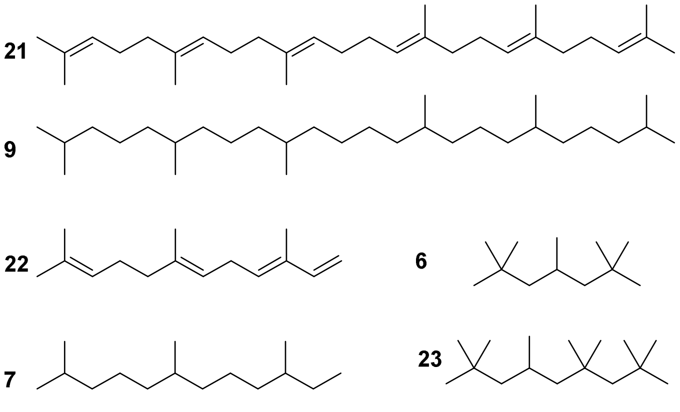
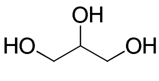
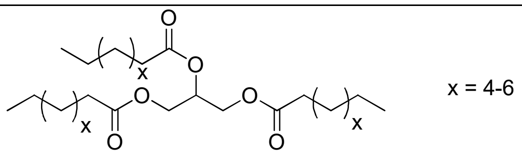
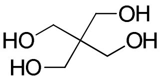
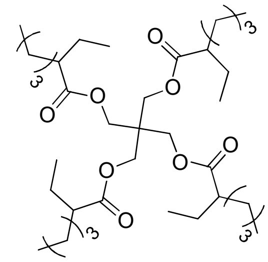
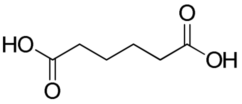
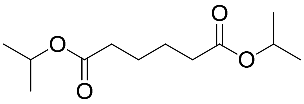
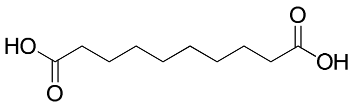
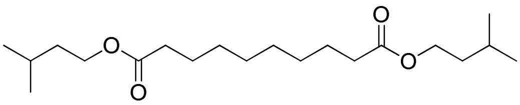


Figure 3 – Examples of hydrocarbons used as emollients: squalene **21** and squalane **9**, farnesene **22** and hemisqualane **7** (natural origin) and isododecane **6** and isohexadecane **23** (petro-based)

2.3. Ester oils as emollients

Ester oils constitute the most important chemical families used as emollients.[1,37,47] The great variety of acids and alcohols raw materials leads to a wide diversity of oils, explaining their pervasiveness in cosmetic end-used products. Moreover, the use of polyols such as glycerol or pentaerythritol and polyacids such as adipic or sebacic acids further broaden the possible candidates (Table 4). Depending on the chains used, i.e. their length and their functionality, the volatile character of the emollients can be adapted to the expected application. For instance, diisopropyl adipate offers a light after-feel, similar to those of the cyclomethicones.

Table 4 – Chemical structures of ester emollients synthesized from polyols (glycerol and pentaerythritol) and polyacids (adipic and sebacic acids)

Building blocks	Ester emollients	N°
 Glycerol	 Caprylic/capric triglycerides	**16**
 Pentaerythritol	 Pentaerythrityl tetraethylhexanoate	**18**
 Adipic acid	 Diisopropyl adipate	**19**
 Sebacic acid	 Diisoamyl sebacate	**20**

Triglycerides represent a large class of ester emollients. They can be used directly as cosmetic ingredients[48] or as sources of alcohols and fatty acids after hydrolysis, saponification or transesterification.[47] Further reactions with alcohols, polyols or glycerol allow the synthesis of simple esters, polyesters and synthetic triglycerides respectively. The combination of fatty acids and alcohols resulting in esters having less than 18-20 carbon atoms are mostly claimed for their semi-volatile character (see Tables 1 and 5). Coconut and palm kernel oils are the major source of middle chain fatty acids (8 – 14 carbon atoms). Widely used as a cosmetic emollient, middle chain triglycerides (MCT) are synthesized from caprylic and capric acid, with respectively 8 and 10 carbon atoms. Other synthetic triglycerides, with different volatility, such as tricaprylin or triethylhexanoin can also be obtained using the suitable fatty acid chains. Palm oil represents a major source of palmitic and oleic chains. Nevertheless, its extensive cultivation resulted in deforestation, particularly in South America and South East Asia. Nowadays global organizations such as the World Wild Fund for Nature (WWF) or the Roundtable on Sustainable Palm Oil (RSPO) certify the social and environmental non-degradation related to its cultivation. The first sustainable palm oil appears on the cosmetic market in 2008 and accounts nowadays for circa 6% of the palm trees. Other common oils such as soybean, rapeseed and sunflower oils are sources of longer chains, i.e. oleic, linoleic, linolenic and stearic acids. Resulting esters are non-volatile and have properties closer to those of linear PDMS, with viscosities of up to a few tens of mPa.s.

2.4. Other chemical families claimed for their emollient properties

Extracted from triglycerides, fatty alcohols have mostly linear alkyl chains. Primarily used as co-surfactants in emulsion formulations, fatty alcohols are also mainly used as rheological modifiers and texture agents.[48] Indeed, the free hydroxyl group results in a viscosity increase and fatty alcohols used as co-surfactants are generally also claimed for their emollient quality. Guerbet alcohols represent a subdivision of fatty alcohols. They are primary and β-branched alcohols, synthesized by an oxidation of alcohols into aldehydes followed by an aldol reaction.[49] They are also mainly used to modify the consistency of end-use products. Finally, a few synthetic ether compounds play also the role of emollients. This is the case of the dicaprylyl ether (Cetiol® OE (10) from BASF), claimed for the dry "D5-like" touch conferred to cosmetic formulations.[50] Table 5 presents the different chemical families detailed above namely, the structural diversity, the origin, the benefits for a cosmetic use and a few typical examples.

Table 5 – Structural features and advantages for cosmetic use of emollient oils from different chemical families

Emollient family	Structural diversity	Origin	Examples (INCI names)	N°	Advantages for cosmetic use
Silicone oils	Degree of polymerization Cyclisation	Synthetic	Dimethicone D5	**3** **1**	Remarkable sensory properties Excellent spreading properties
Simple esters	Chain length Branching Insaturation	Natural or synthetic	Cetyl palmitate Isopropyl myristate	**-** **13**	Skin hydration Solvents for cosmetic actives Softening of the skin Promote cutaneous penetration Help pigments dispersion Rheological modifiers
Polyfunctional esters			Diisopropyl adipate	**19**	
Triglycerides	Nature of fatty acids	Natural	Olive fruit oil	-	
		Synthetic	Caprylic/Capric Triglyceride	**16**	
Fatty acids	Chain length Branching Insaturation	Vegetal	Palmitic acid, Oleic acid	**-** **-**	Naturally occurring in human tissues Stable to oxidation (saturated oils) Skin moisturizers
		Synthetic	Isostearic acid	**-**	
Hydrocarbons	Chain length Branching Insaturation Monomer unit	Vegetal	Squalane, Hemisqualane	**9** **7**	Dry and non-greasy after-feel Good spreading properties Occlusive properties Chemically inert
		Petro-based	Paraffin oil Isohexadecane	**8** **23**	
Fatty alcohols	Chain length Insaturation	Vegetal	Cetyl alcohol	**17**	High viscosity and polarity Promote interactions with skin lipids
		Synthetic	Cetearyl alcohol	**-**	
Guerbet alcohols	Chain length Branching	Synthetic	Octyldodecanol,	**-**	Similar to fatty alcohols Stability to oxidation
Ethers	Chain length Branching	Synthetic	Dicaprylyl ether	**10**	Light, dry and pleasant after-feel Good spreading properties

3. Functional properties of volatile emollients

3.1. Role of emollients in skin hydration

Skin care formulations are the main applications of volatile emollients. To identify the functional properties of volatile emollients, it is crucial to understand the role of topical emollients once applied onto the skin surface. The following part briefly describes the structural organization of the skin and the skin/emollient interface.

3.1.1. Structural organization of the skin[51–54]

Skin is the largest organ of the whole body and represents the first efficient protective barrier against external stresses. Besides, it performs vital functions such as sensory stimuli transmission or constant moisture content in human body. Skin is divided into three successive layers: hypodermis, dermis and epidermis from the deepest to the one in contact with external environment (Figure 4). The epidermis is itself divided into the viable epidermis, above the dermis, and the upper layer, i.e. the stratum corneum (SC) or the horny layer, which is the layer of interest in cosmetic field. Epidermis is mainly composed of keratinocytes, whose shape changes during keratinization process: cells flatten while getting enriched in keratin, until becoming corneocytes, keratin-rich dead cells of the SC. Such cells remove from the SC surface during the so-called desquamation phenomenon. Elias et al. compared SC to a "brick and mortar" model, where bricks account for flat keratin-rich corneocytes and mortar for the lipid-rich fluid surrounding matrix[55] (Figure 4), the structural organization of the SC forms an efficient barrier, which prevents the skin dehydration by limiting the natural TransEpidermal Water Loss (TEWL).[56]

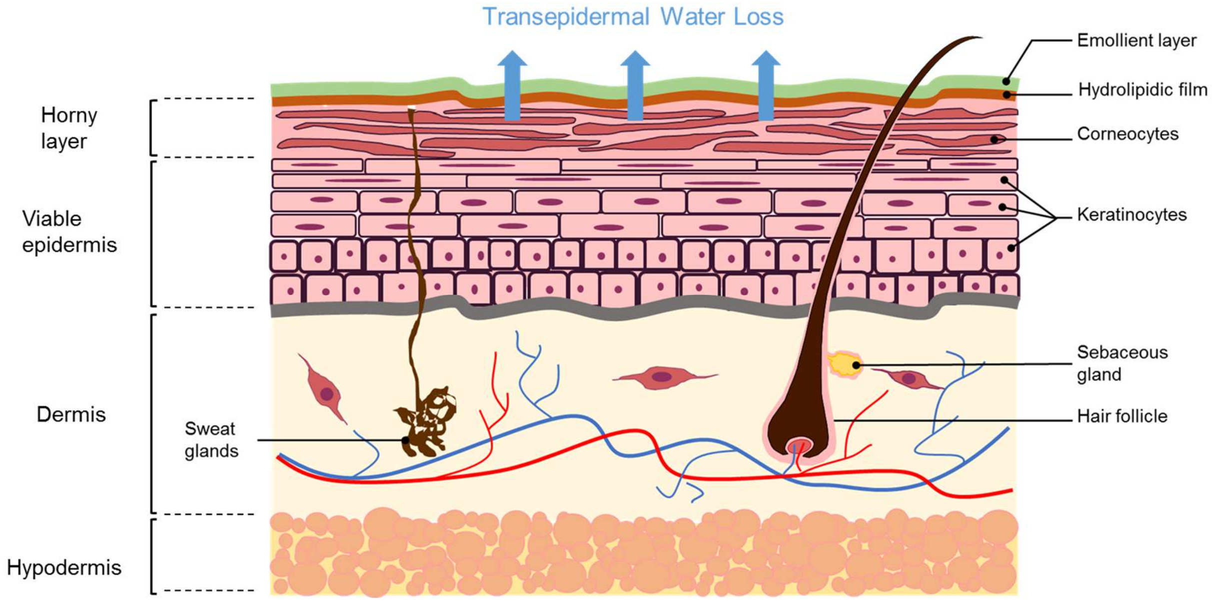


Figure 4 – Sectional view of the different layers of the human skin and illustration of the skin hydration by decreasing the TEWL thanks to the natural hydrolipidic film strengthened by the layer of emollient on the skin surface.

To overcome the skin dehydration, boosted by chemical handling, physiological stress, UV-radiation exposure or even natural aging, the SC is constantly being renewed thanks to the apparition of new cells from keratinization to replace the removed corneocytes. Thus, the appropriate balance between these two phenomena allows keeping constant the moisture content in the skin and consequently contributes to the skin elasticity. Besides, corneocytes contain a set of hygroscopic molecules called Natural Moisturizing Factor (NMF), composed of amino acids, mineral slats, urea and organic acids.[56]. NMF plays an important role in skin layers hydration. Sebaceous and sweat glands are also largely involved in skin hydration. The former result in sebum production, which acts as a natural skin lubricant and plays a major role in cutaneous tissues hydration.[40,51] Mixed with sweat secretions, it forms the hydrolipidic film, which is naturally occurring on the skin surface. It allows to further limit the human body water loss by TEWL and helps to remain the water within the corneocytes.

As a matter of fact, the direct measurement on the skin surface is problematic for ethical and technical reasons and the use of model surfaces able to mimic the surface properties of the skin is recommended. Such surface can be either polymers such as Polymethylmethacrylate (PMMA) or synthetic tissues, like Vitro-Skin® or Bio Skin for instance. Eudier et *al.* recently published an extensive review on the different surfaces used to model the skin. They give a complete overview of the surface energies of both skin and surface models.[57]

3.1.2. Enhancement of the natural barrier function of the skin with emollient oils

The emollients are multifunctional ingredients which are expected to provide a silky after-feel, strengthen the skin barrier function, smoothen and softer both skin and hair, solubilize active ingredients such as UV filters, improve the spreading properties and finally, give consistency to end-use products.[58–60] Skin hydration occurs through two main mechanisms:[61] *i)* With an external water support. This is the role of humectant ingredients, which are able to retain high quantities of water due to their hygroscopic property and *ii)* By limiting the TEWL thanks to the formation of a thin and smooth occlusive film on the skin surface, ensuring the water content constant within skin layers, especially in the horny layer.[62] As illustrated on Figure 4, the emollient layer enhances the skin, hydration by strengthening both the barrier function of the SC and the role of the hydrolipidic film. Occlusive properties are closely related to the molar mass, the viscosity and the spreading properties of the emollient. For instance, a long alkyl chain is likely to increase the substantivity of emollient, i.e. its ability to remain on the skin surface without penetrating the different layers. A typical example are mineral oils such as paraffin oil, which contains long and linear alkyl hydrocarbon chains.[38] Thus, the efficiency of emollients in improving and maintaining skin hydration lies mainly in their ability to spread easily, forming a thin, smooth and substantive film on the skin surface.

3.1.3. Effect of oil penetration on the biomechanical stress of the skin

Consumers of cosmetic products expect a moisturizer to be pleasant to spread on and to maintain or restore the softness of the skin for several hours. Two steps are usually distinguished to fulfil these expectations. The first, quick, is the application phase of the cream on the skin during which D5 and silicone-like emollients are particularly effective. The physicochemical criteria required to maximize this functional property constitute the main subject of this review. The second is the penetration of emollients inside the SC to form partially occlusive films to reduce the total trans-epidermal water loss (TEWL) and the drying of the skin causing a feeling of tightness of the skin. The relationship between the penetration of emollients and the biomechanical properties of the SC was, until recently, unclear due to the complexity of the phenomena of diffusion of water, emollients and other ingredients of cosmetic creams through the different skin layers.

To overcome the complexity due to the epidermal layer underlying the SC, Dauskardt's group has designed the so-called "substrate curvature method" that allows quantitative and selective measurement of the biomechanical stress of the SC.[63] According to this method, the SC layer of human skin (15 µm thick) is first detached from the epidermal layers by soaking in a trypsin solution. Then, SC is adhered on an elastic glass cover slips (177 µm thick) and subjected to different levels of relative humidity (RH) before and after topical treatment with cosmetic emollients. In-plane stresses that develop in the SC result in concave or convex elastic curvature of the glass substrate which is measured optically and quantitatively related to the mechanical stress of the SC film. In parallel, the diffusion of emollients and the alterations of the lipid content in SC are analysed by ATR-FTIR (Attenuated total reflectance Fourier transform infrared) spectroscopy. Maximum emollient penetration volume in the SC is also assessed to elucidate the mechanisms underlying the emollient effects on stress. A special feature of this method is that moisture cannot be replenished by the underlying layers of skin unlike conventional methods such as Franz cell which studies the permeation of molecules through the entire skin. Hence, the effect of emollients alone on the biomechanical stress of CS can be investigated unambiguously.

Thus, the influence of the chemical structure of emollients on their penetrating power and on the reduction of the biomechanical stress of a partially dried SC has been studied for a series of emollients including alkanes, esters, ethers, carbonates and alcohols.[64,65] The application of all cosmetic emollients caused a reduction in SC mechanical stress under dehydrating conditions and a linear correlation was highlighted between the emollient penetration volume and the degree of stress reduction. The least penetrating oils were linear alkanes (C15-C16) and dipropylheptyl carbonate (C21), while the most penetrating were esters and one ether (C14-C18). With regard to D5, it is well established that this emollient penetrates the SC[66] but unfortunately it cannot be compared to other emollients because the penetrating power of D5 has not yet been studied by this technique. A clear finding from these works is that the more emollients penetrate into the SC, the more its biomechanical stress is reduced. Two interdependent mechanisms appear to be involved. The first is the well-known property of emollients to form a diffusion barrier which slows down water loss. The second, usually overlooked, concerns the most penetrating emollients which replace lost volume of water and reduce the stress of SC and the perception of skin tightness and stiffness.

The same group recently developed a model capable of accurately predicting the drying stress profile of SC subjected to different RH and various skin-care treatments.[65] This model is based on the well-accepted assumption that the SC can be assimilated to a first approximation as a finite homogeneous Fickean membrane from which part of the internal water desorbs and diffuses into the gas phase while the emollient diffuses into the membrane. This model adequately describes the drying stress profiles after application of non-volatile emollients.

However, to rationalize the behaviour of the most volatile emollients (D5, isododecane, cetiol ultimate) which are the focus of this review, a more complex Fickean model would be necessary considering both the penetration of volatile oils into the SC and its evaporation into the gas phase. It is also interesting to note that this technique can also be applied to other ingredients in moisturizing emulsion such as humectants (glycerol) and surfactants.[67]

3.2. Odourless exigency for volatile emollients

Besides the excellent film-forming properties, the volatility of emollients is of major importance to reach the light and non-greasy after-feel. Using light emollients in end-use products mainly contribute to reduce their greasiness and tackiness and fully contribute to the consumer welfare.[54,68] Such evanescent behaviour can be evaluated by thermo gravimetric analysis, by monitoring the percent loss with time.[68] Apart from cyclomethicones, short alkanes such as isododecane or *n*-undecane/*n*-tridecane (Cetiol ultimate®) mixture exhibit a high volatility. In addition, odourless emollients are a prerequisite of cosmetic formulators. Thus, it is important to link the odour of a molecule to its chemical structure, in order to anticipate the olfactory intensity of the emollient candidates. Indeed, low odour intensity and high volatility are contradictory requirements as the odour intensity increases with the concentration of molecules in the ambient air.

4. Required physicochemical properties for an effective emollient

4.1. Physicochemical characterization of emollient oils

The main physicochemical properties and methods used to characterize emollients are listed in Table 6.

Table 6 – Relevant physicochemical properties, experimental methods and range of values for typical emollients.[58,69,70]

Physicochemical properties	Measurement methods	Values for cosmetic use
Density	U-tube densimeter	0.70 – 0.97
Dynamic viscosity (mPa.s)	Cone-plate rheometer, falling ball viscometer	1 – 1000
Surface tension ($mN.m^{-1}$)	Pending drop, Wilhelmy plate, Du Noüy ring	17 – 35

Interfacial tension (mN.m^{-1})	Pending drop, Du Noüy ring	10 - 50
Contact angle (°)	Sessile drop	≈ 0
Polar and dispersive components (mN.m^{-1})	Calculated from contact angle on specific surfaces	Polar: 0 – 15 Dispersive: 15 – 30
Vapor pressure (Pa)	Calculated from temperature and heat of vaporization	10^{-6} - 10^{2}
Boiling point (°C)	Differential Scanning Calorimetry	175 – 400
Refractive index	Abbe refractometer	1.38 – 1.50

Refractive index values are correlated to the brightness of the emollient, as an increase of the refractive index of the thin emollient layer on the skin or hair surface results in a glossy appearance. Brightness is generally a drawback for skin care products but a sought-after property for conditioners in hair care. Therefore, in the following part, brightness will not be discussed in priority, in contrast to physicochemical properties related to spreadability. Some of the properties listed in Table 6 are interdependent: this is the case for the contact angle, the surface and interfacial tensions. When a droplet of liquid is deposited on a flat surface, it does not always entirely spread out but takes the shape of a spherical cap. At equilibrium, such a system is described using the contact angle θ defined between the solid/gas interface and the tangent of the liquid drop.[71]. Measuring the contact angle of emollients on skin or hair is a popular method to quantify the wettability of these complex surfaces by a given liquid. The lower the contact angle, the better the spreading properties. A perfect spreading corresponds to an angle equal to zero when the surface is entirely covered by a molecular thick layer.[72] Experimentally, a very low but non-zero experimental value of contact angle is measured just after the drop deposit on the skin surface or on a skin model surface and this contact angle quickly decreases in the few seconds after the drop deposit. The equilibrium at the triple-point gas/emollient/skin is governed by the Young's relation, which relates the contact angle θ to the skin surface energy γ_S, the emollient surface tension γ_L and the skin/emollient interfacial tension γ_{SL} (Eq. 1). Strictly speaking, relation (1) only applies for systems in equilibrium, i.e. when the surface (here the skin) and the droplet of liquid are in equilibrium with their saturated vapor at the skin temperature. Note that this condition is rarely met experimentally when contact angles are measured on biological surfaces. As displayed on Figure 5, the lower both surface and interfacial tensions, the higher the wettability of the skin.

$$\gamma_S = \gamma_{SL} + \gamma_L . \cos\theta \tag{1}$$

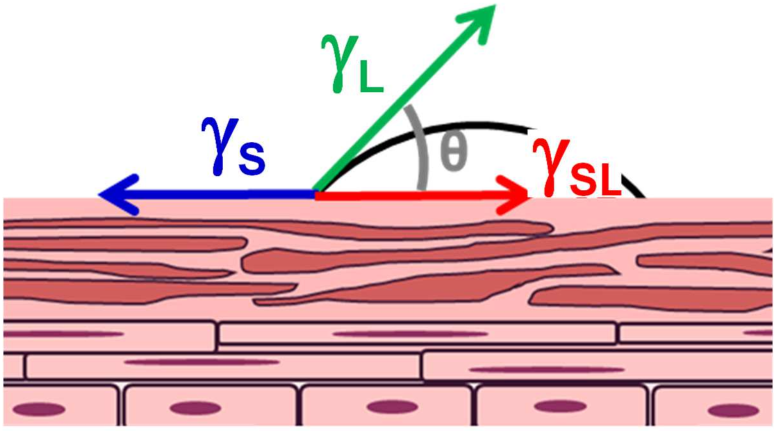


Figure 5 – The contact angle θ of an emollient droplet on a skin or a skin model depends on the surface energy of the skin, γ_S, the surface tension of the emollient γ_L and the skin/emollient interfacial tension γ_{SL}.

Physicochemical characterization of several commercial emollients allows drawing the Figure 6 where emollients are placed according to their boiling point and surface tension, which roughly express their volatility and their spreading properties respectively.[73] Another impacting spreading property, namely the dynamic viscosity, is displayed as the diameter of the different dots. Such chart is helpful to compare emollients and to quickly identify which chemical family offers the best chances to mimic silicone properties. Figure 6 outlines the difficulty to match the silicone oils physicochemical properties, especially their very low surface tension values (17 – 22 mN.m^{-1}). Nevertheless, the highly branched volatile hydrocarbon, isododecane **6** (21.6 mN.m^{-1}), exhibits the closest physicochemical properties compared to all other commercially available emollients.

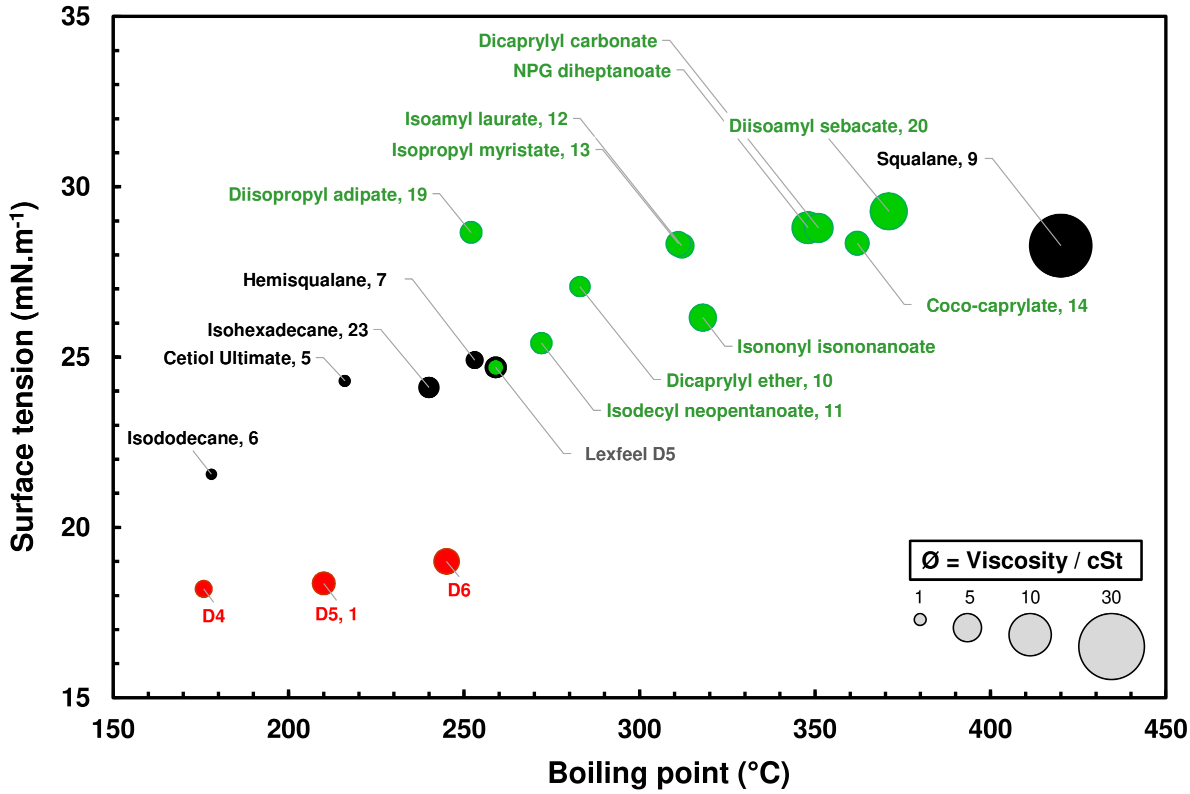


Figure 6 – Mapping of some typical commercial emollients according to their chemical family (● cyclomethicones, ● alkanes, ● emollients with oxygen atoms), their boiling point, their surface tension and their dynamic viscosity expressed by the size of the dots. The number indicated after the name of the emollient corresponds to its chemical structure (see Tables 1, 4, 7 and Figure 3).

Figure 6 emphasizes the increase of viscosity, surface tension and boiling point values with polarity and molecular weight. Commercial emollients with the closest physicochemical properties to those of volatile silicon oils are the alkanes, the ethers and the short chain esters (with 18 or less carbon atoms). Mixing and alkane and an ester (Lexfeel D5) appears to be an effective strategy to approach the properties of cyclomethicones.

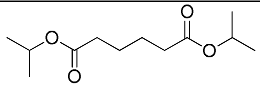
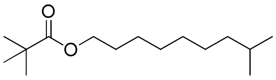
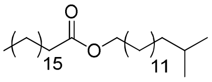
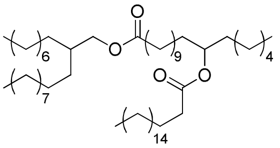
4.2. Required physicochemical properties for spreading improvement

Spreading is a key property for emollients, that has been studied by several authors.[58,60,69,74–77] Spreading properties can be evaluated by direct measurement on the skin surface but it is not always possible for new compounds whose toxicological tests have not been carried out. Moreover, such studies are expensive and time-consuming and that is why measurement on skin model surfaces is often preferred. The model surfaces are either synthetic rebuilt skin tissues such as Vitro-Skin® or Epi-Skin, or polymeric surfaces such as polymethylmethacrylate, which has a similar surface energy than the skin surface (γ_{PMMA} = 39-48 mN.m^{-1} [74,78–81] ; γ_{SKIN} = 37-46 mN.m^{-1} [79,81–87]). Eudier et al. have recently published a review about skin surfaces models.[57]

Different methods have been used to quantify spreading properties of emollients on their own or in cosmetic emulsions, using skin surface models *i)* measurements of physicochemical properties correlated with spreading properties, especially viscosity, surface tension and contact angle.[58,74,77] *ii)* measurement of a spreading value, expressed in terms the area of skin or skin model covered by a fixed volume of emollient after a given time.[69,74,75,77] *iii)* using sensory analysis, with an expert panel.[74,76] Spreading an oil onto the skin surface is also related to the friction, i.e. the motion resistance of the liquid between two solid surfaces.[88] This is generally quantified by the friction coefficient, which represents the ratio between the force required to move one of the two solid surfaces and the force normal to the plan. Therefore, it depends on many interactions existing at the solid/liquid interface and thus on the polarity of oils. Hughes et al. have shown that the friction coefficient of ester emollients (from 0.059 to 0.174) on the skin surface or on skin models is higher than the friction coefficient of hydrocarbon or silicone emollients (0.060 in average). This is due to a higher affinity of ester compounds for polar surfaces.[58]

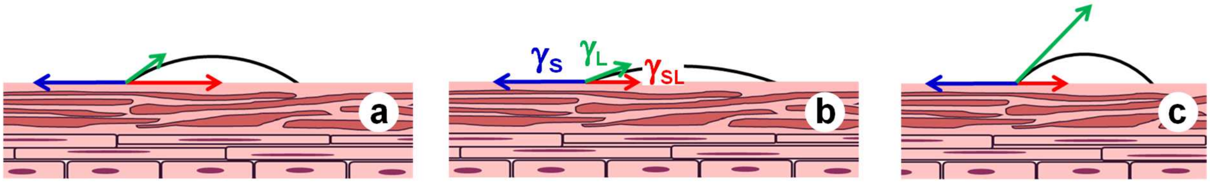
As explained previously, the sensory qualities of formulations or ingredients remain difficult to anticipate. On the contrary, physicochemical properties can be readily measured or even predicted.[89] Therefore, linking the sensory profiles of ingredients such as emollients to their physicochemical properties is of major importance for the formulator. Several authors have already established such relationships, with end-use products[90,91] and with ingredients.[37,40,58,69,74–77] Stern et al. highlighted the strong dependence of spreading, brightness and hardness of 15 creams and 15 body lotions (O/W and O/W emulsions) on viscosity.[90] In 1985, Zeilder pointed out that the lower their viscosity and their surface tension, the better their spreading properties.[75] This had been confirmed by Savary et al., who conclude that the easiness to spread results from a low contact angle value.[74] In 2005, Parente et al. showed that the brightness, the presence of a residual film and the greasy touch increase with the surface tension and that the difficulty to spread and the stickiness result from high viscosity values. On the contrary, low viscosity values provide smoothness and slipperiness on the skin.[76,92] In 2010, Gorcea and Laura, by studying four ester emollients, concluded that reduction of the stickiness and presence of a residual film arise from low viscosity values and therefore low molar masses. Regarding structural features, short chain esters show better spreading properties and impart light and non-greasy after-feel on the skin.[77] The four emollients gathered in Table 7 illustrate such relationships. Indeed, volatile emollients such as diisopropyl adipate **19** and isodecyl neopentanoate **11** have high spreading values (1140 and 878 mm² respectively) correlated with low values of both surface tension and viscosity. Such emollients are preferably embedded in light day creams or body lotions, for which a light after-feel is required. Isocetyl stearate **24** spreads less easily (738 mm²) according to higher surface tension and viscosity values. Finally, octyldodecyl stearoyl stearate **25** has significantly higher surface tension and viscosity values than the previous oils, which results in very low spreading value (205 mm²). This kind of emollient is typical for lipidic-rich night creams, whose high occlusivity is obtained by the remaining thick lipidic film on the skin.

Table 7 – Chemical structures and sensory and physicochemical properties of four ester emollients.[77]

N°	Chemical structure	Spreading value (mm²)	Viscosity (cSt)	Surface tension (mN.m^{-1})	Sensory aspects
19		1140	3.7	27	Light and dry
11		878	3.7	25	Light and velvety
24		738	23.7	29	Medium
25		205	83	33	Heavy and greasy

More recently, Grisel et al. have investigated the relative influence of viscosity, surface tension and density on the spreading properties of 53 commercial emollients from different chemical families, i.e. esters, hydrocarbons and silicone oils. They concluded that the viscosity mostly governs the spreading behaviour, followed by the surface tension and the density in this order. Besides, they highlight that within the ester family, the viscosity remains the most influent property for the most viscous compounds whereas for the less viscous ones (< 20 mPa.s), the influence of structural features should carefully be taken into account. The authors explained that the spreading properties highly depend on the degree of unsaturation, number of ester functions and number of branching groups.[69]

In brief, low values of viscosity and surface tension of the emollients are required to enhance their spreading properties. Nevertheless, alkanes such as isododecane, which has very low viscosity (1 mPa.s) and surface tension (21.6 mN.m^{-1}), exhibits poor spreading properties. This is directly related to its low affinity for polar surfaces such skin or skin models. Actually, high affinity between the oil and the solid on which it has to be spread is crucial to promote the spreading. Such high affinity results from a low interfacial tension between the emollient and the skin. For instance, ester emollients easily spread on the skin surface because of the degree of similarity between their chemical structure and those of epidermis lipids. These different behaviours depending on the chemical structures explain why mixing a polar and an apolar oils is an effective way to approach the properties of D5. Actually, within a droplet containing a polar oil and an apolar oil, a partial segregation occurs. The apolar oil, i.e. the one having the lower surface tension, diffuses preferentially at the liquid/air interface in order to decrease the surface tension and therefore the surface energy of the mixture. The polar oil preferably lies at the skin surface because of its greater affinity for this slightly polar surface than hydrocarbons. This results in a decrease of the interfacial tension value. Combination of these two phenomena explains how the spreading properties could be considerably improved, as illustrated schematically on Figure 7. Such combination is clearly illustrated with the Lexfeel® D5. Composed of a mixture of isododecane and neopentyl glycol diheptanoate, this emollient is claimed for its excellent spreading properties and its "D5-like" light and pleasant sensory profile.[93]



Alkane
Low γ_L, High γ_{SL}

Alkane + Ester
Both γ_L and γ_{SL} low

Ester
High γ_L, Low γ_{SL}

Figure 7 – Illustration of the influence of the emollient surface tension and the skin/emollient interfacial tension on the contact angle and the spreading properties. A typical example is the Lexfeel® D5 (b), for which both the surface tension, γ_L, and the interfacial tension, γ_{SL}, are low.

It should be noted that this interpretation assuming a perfectly flat and isotropic surface is not sufficient to describe the complex phenomena occurring during the spreading of an oil on a complex and living surface such as the skin. Indeed, the human skin presents a physicochemical heterogeneity and a micro-roughness which influence the measured contact angle. In addition, the spreading of the oil on the skin is accompanied by its penetration inside the stratum corneum which reduces its micro-roughness and increases the sensation of softness.

4.3. Wetting envelopes as an efficient tool to foresee spreading properties

4.3.1. Assessment of polar and dispersion forces components of liquids and solids

Since the ability of a liquid L to spread on a polar organic surface S depends on the surface energy (γ_S) of S and on the surface (γ_L) and interfacial (γ_S) tensions of L, it is clear that the single parameter γ_L is insufficient to rationalize the spreading of emollients on skin or skin models. To account for the different types of interactions between L and S, one may resort to Fowkes approach[94,95] which is based on 2 fundamental assumptions:

(i) the different types of surface energy (London, Debye, Keesom, H-bonding) are additive (Eq. 2) and can be separated into two parts, on one hand a “dispersion” forces contribution γ^d consisting mainly of London interactions and, on the other hand, a “polar” forces contribution γ^p including all other types of interactions (Eq. 3).

(ii) furthermore, *when S and L only interact through dispersion forces*, the surface tension term resulting from the intermolecular attraction of dissimilar molecules at the interface S/L is the geometric mean of the interacting tensions γ_S^d and γ_L^d. This assumption leads to express the interfacial tension γ_{SL} according to Eq. 4.

$$\gamma = \gamma^{London} + [\gamma^{Debye} + \gamma^{Keesom} + \gamma^{H-bond}] \tag{2}$$

$$\gamma = \gamma^d + \gamma^p \tag{3}$$

$$\gamma_{SL} = \gamma_S + \gamma_L - 2\sqrt{\gamma_S^d \gamma_L^d} \tag{4}$$

As the surface energy γ_S of the solid S and the interfacial tension γ_{SL} between S and L are not directly measurable, they must be expressed as a function of the experimentally accessible contact angle θ using Young's relation (1). These transformations lead to Eq. 5 *which is only valid when L and S interact exclusively through dispersion forces, rather than polar forces.*

$$\gamma_L(1 + \cos\theta) = 2\sqrt{\gamma_S^d \gamma_L^d} \tag{5}$$

This equation can be used to determine the dispersive component γ_L^d of liquid emollients by measuring the contact angle θ of a droplet of this liquid on an apolar solid surface such as PTFE that is not capable of polar interactions (γ_S^p = 0 and γ_S^d = 19 ± 1 mN.m^{-1}).[78,95] Since the overall surface tensions of emollients γ_L can be easily measured, their components γ_L^d and γ_L^p are calculated from Eqs. 3 and 5 and are reported in Table 8. In a similar way, the dispersive and polar components of the four probe liquids used to measure the surface energy of the skin are also reported in this table.

Table 8 – Dispersive and polar components of the surface tension γ of emollients and of the four standard test liquids used to measure contact angles on human skin.[73,83,96]

Liquid	γ_L/mN.m^{-1}	γ_L^d/mN.m^{-1}	γ_L^p/mN.m^{-1}	Solid surface	θ/°
Water	72.8	21.8	51.0	Forearm skin	88
Water	72.8	21.8	51.0	Forehead skin	55
Water	72.8	21.8	51.0	Episkin	56.9
Glycerol	64	34	30	Forearm skin	74
Glycerol	64	34	30	Forehead skin	56
Formamide	58	39	19	Forearm skin	64
Formamide	58	39	19	Forehead skin	45
Formamide	58	39	19	Episkin	42.5
Diiodomethane	50.8	50.8	0	Forearm skin	41
Diiodomethane	50.8	50.8	0	Forehead skin	34
Diiodomethane	50.8	50.8	0	Episkin	53.6
D4	18.2	16.7	1.5	PTFE	17.3
D5	18.4	16.1	2.3	PTFE	25.5
Cetiol Ultimate	24.3	24.2	0.1	PTFE	40.1
iso-Dodecane	21.6	20.9	0.6	PTFE	31.7
Hemisqualane	24.9	24.3	0.6	PTFE	43.5
iso-Hexadecane	24.1	23.5	0.6	PTFE	41.1
Squalane	28.3	26.9	1.4	PTFE	53.3
Dicaprylyl ether	27.1	25.8	1.3	PTFE	50.7
Isodecyl neopentanoate	25.4	23.9	1.5	PTFE	47.3
Isoamyl laurate	28.3	27.0	1.3	PTFE	53.1
Isopropyl myristate	28.3	27.2	1.2	PTFE	52.9
Isononyl isononanoate	26.2	24.2	1.9	PTFE	50.2

Coco caprylate	28.3	27.5	0.9	PTFE	52.3
Diisopropyl adipate	28.7	25.8	2.9	PTFE	57.1
NPG diheptanoate	28.8	26.6	2.2	PTFE	56.0
Diisoamyl sebacate	29.3	26.3	3.0	PTFE	58.4
Dicaprylyl carbonate	28.8	26.6	2.2	PTFE	55.9
Lexfeel D5	24.7	24.6	0.1	PTFE	41.2

Similarly, the dispersive component γ_S^d of the skin (forearm or forehead) can be determined by measuring the contact angle formed on the skin by a droplet of an apolar liquid such as diiodomethane for which γ_L^p = 0 and $\gamma_L^d = \gamma_L$ = 50.8 mN.m^{-1}.[95]. However, unlike liquids, the overall surface energy of solid surfaces γ_S are not measurable and it is necessary to incorporate new assumptions and additional experiments to determine their polar components γ_S^p. For such polar solid surfaces, Owens and Wendt proposed to extend the Fowkes geometric mean assumption to the polar interactions. As a result, equations 4 and 5 are replaced by equations 6 and 7.

$$\gamma_{SL} = \gamma_S + \gamma_L - 2\sqrt{\gamma_S^d \gamma_L^d} - 2\sqrt{\gamma_S^p \gamma_L^p} \tag{6}$$

$$\gamma_L(1 + \cos\theta) = 2\sqrt{\gamma_S^d \gamma_L^d} + 2\sqrt{\gamma_S^p \gamma_L^p} \tag{7}$$

As noted by the authors themselves, this assumption is questionable since hydrogen bonding exhibits more specific characters than those implied by the additional term $[\gamma_S^p \gamma_L^p]^{0.5}$. To address this issue, Van Oss split up the polar contribution γ^p into an electron-donor component γ^+ and an electron-acceptor component γ^- that better reflects the complementary acid-base nature of hydrogen bonds.[97] Nevertheless, the approximate expression (7) is sufficient here because emollient oils and skin surface are only moderately polar and are not supposed to form strong hydrogen bonds.

To determine the components γ_S^d and γ_S^p of a polar solid from equation 7, it is necessary to measure the contact angles with at least two probe liquids whose γ_L^d and γ_L^p components are available. It should be noted that these liquids must have a sufficiently high surface tension so as not to spread completely over the solid. In addition, it is preferable that one of the liquids is very polar, such as water and the other one non-polar as diiodomethane. The contact angle measurements carried out with these two solvents on the forearm and the forehead skins make it possible to estimate the components γ_S^d and γ_S^p of these two areas of the epidermis as well as the values for two skin models namely the poly(methyl methacrylate) PMMA, the vitro skin and the Episkin (Table 9). The low values of the polar component, show that the skin is naturally hydrophobic, in particular on the forearm. In addition, it is also observed that the two skin models are well suited for mimicking the spreading of an emollient on the skin because they have surface energies close to that of the skin.

When more than two probe liquids are employed to measure contact angles, a graphical method is more convenient to determine the mean values of γ_S^d and γ_S^p. Indeed, Eq. 7 can be rewritten according to a linear relation Y = a.X + b (Eq. 8) to highlight the two variables Y = $\gamma_L[1+\cos\theta]/2\left[\gamma_L^d\right]^{0.5}$ and X = $[\gamma_L^p/\gamma_L^d]^{0.5}$

$$= \sqrt{\gamma_S^p}\cdot\left[\frac{\sqrt{\gamma_L^p}}{\sqrt{\gamma_L^d}}\right] + \sqrt{\gamma_S^d} \qquad (8)$$

Figure 8 illustrates the application of Eq. 8 to PMMA as a model surface on which contact angles were measured for a series of polar oils.[80] The dispersive γ_S^d and polar γ_S^p components of PMMA are equal to the square of the intercept and of the slope of the straight line respectively.

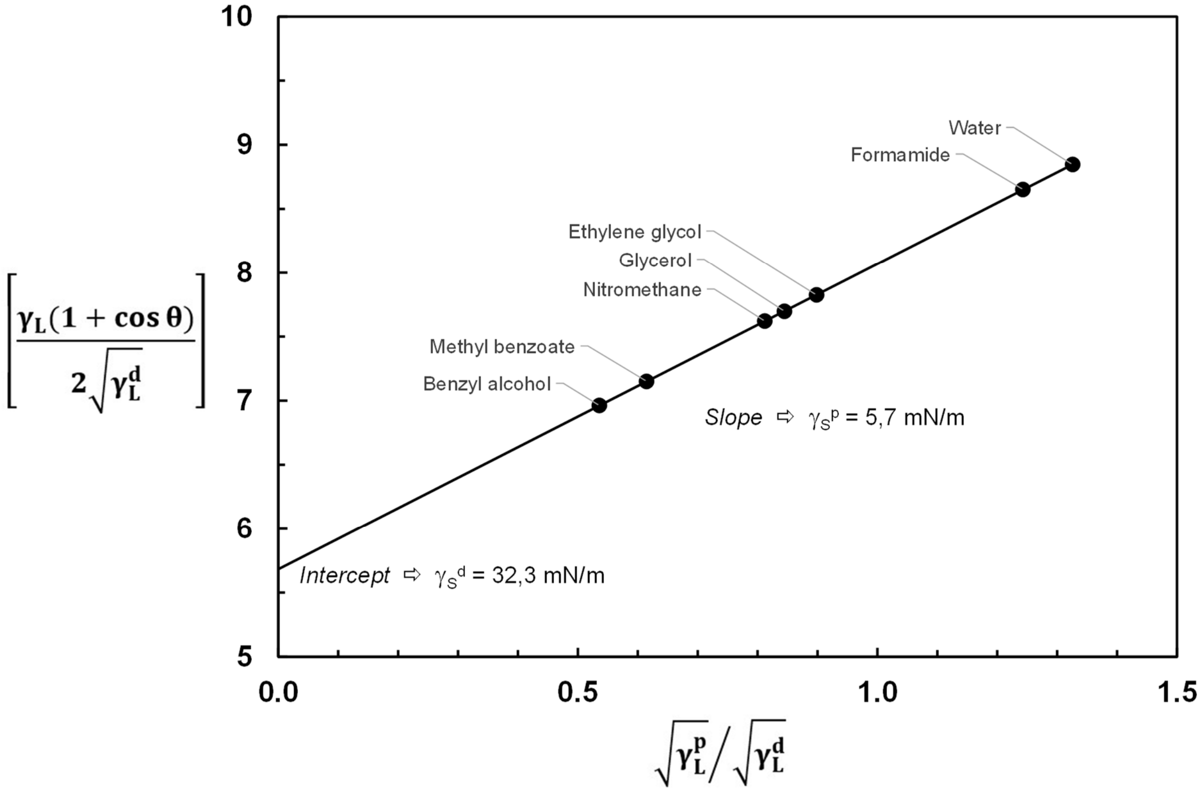


Figure 8 – Owens/Wendt plot to graphically determine the dispersive γ_S^d and polar γ_S^p components of the PMMA model surface by exploiting the contact angles according to the linear relationship 8 (redrawn from [80])

Table 9. Overall surface energy γ_S, dispersive γ_S^d and polar γ_S^p components of human skin and skin models.

Solid surface	γ_S/mN.m^{-1}	γ_S^d/mN.m^{-1}	γ_S^p/mN.m^{-1}	Ref
PTFE	18.0	18.0	0	[80]
PMMA	38.0	32.3	5.7	[80]
Vitro-skin	31.8	25.1	6.8	[73]
Forearm skin	38.4	35.6	2.8	[80]
Forehead skin	43.1	35.3	7.8	[80]

4.3.2. Wetting envelopes of skin and skin models

For an emollient to exhibit satisfying sensory properties, it is essential that it spreads completely over the skin with a zero contact angle. Now, if the dispersive and polar components of the skin and of the emollient are known, Eq. 7 makes it possible to calculate the contact angle that will form an emollient unto the skin without requiring any wetting experiments. This is a great advantage, as these experiments are technically tricky and ethically problematical when carried out on human skin. To graphically express the wettability of a surface and intuitively predict the ability of a liquid to wet it, Janssen et al. introduced the notion of wetting envelopes. They consist of a series of curves constructed from equation 7 which can be rewritten as equation 9 by replacing γ_L with its two components γ_L^d and γ_L^p.

$$(\gamma_L^d + \gamma_L^p)(1 + \cos\theta) = 2\sqrt{\gamma_S^d \gamma_L^d} + 2\sqrt{\gamma_S^p \gamma_L^p} \qquad (9)$$

For example, if we consider the PMMA model surface whose components γ_S^d and γ_S^p are known (Table 9) and that the contact angle θ is set at a given value, the values of γ_L^d and γ_L^p verifying the Eq. 9 can be calculated. When the polar component is plotted against the dispersive component, a close loop is obtained which is called the wetting envelope. By performing the same calculation for different angle values, the abacus shown in Figure 9 is obtained.

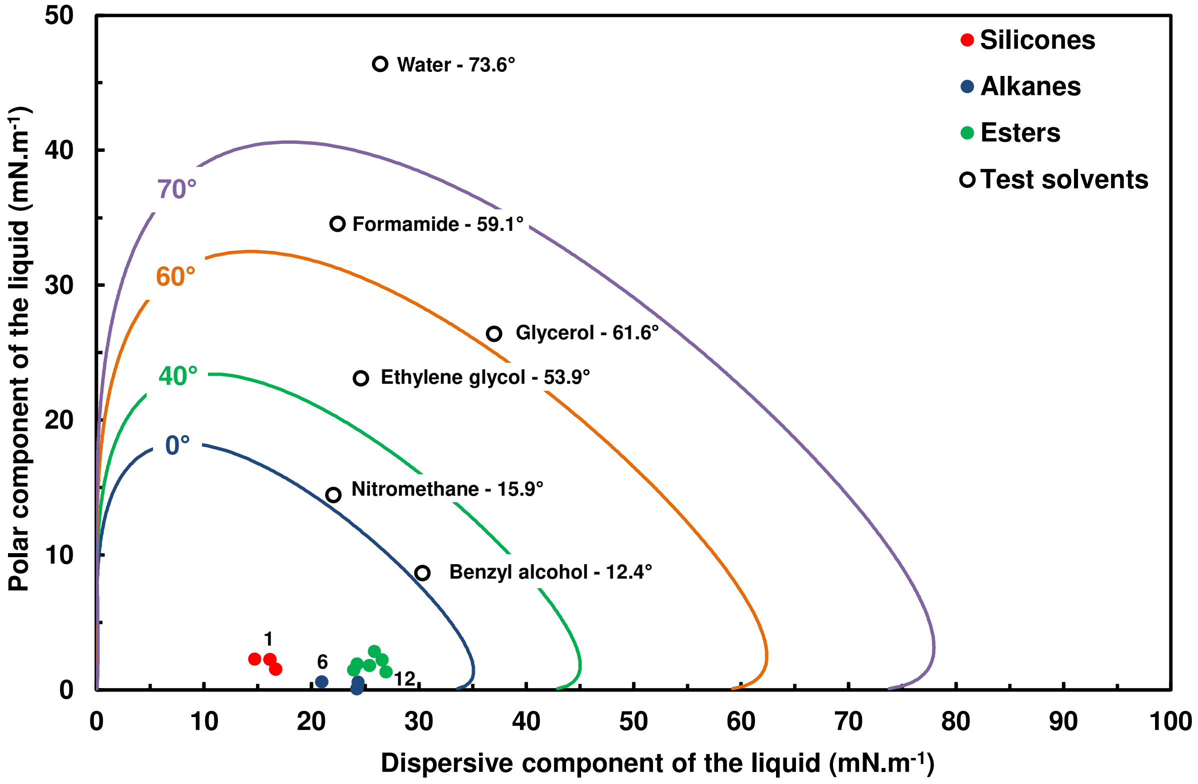


Figure 9 – Wetting envelopes of the PMMA surface as a skin model. The numbers **1**, **6** and **12** refer to the typical volatile emollients cyclopentasiloxane, isododecane and isoamyl laurate respectively.

Wetting envelopes are an effective tool to estimate how a liquid will spread on a specific solid surface. Each envelope accounts for one accurate contact angle. The standard test liquids used to determine the polar and dispersive components of PMMA are well outside the envelope θ = 0° since they form significant contact angles. For instance, ethylene glycol, which spreads on PMMA with a contact angle equal to 54°, is well placed because it lies within the wetting envelope θ = 60° but oustide from the wetting envelope θ = 40°. It is noteworthy that all commercial emollients lie within the wetting envelope θ = 0° as they totally spread onto the skin model surface PMMA. Similar results are obtained with Vitro-Skin® and with Episkin® as other commercial model skin which exhibit comparable surface energies.[57,96]

5. Structural features governing physicochemical and sensory properties of emollients

The wide variety of emollients available is a direct consequence of the diversity of the structural features, i.e. nature of the polar group, chain length and degree of branching. Such structural modifications mostly influence physicochemical properties of emollients. The analysis of the literature allows drawing some structure/properties relationships. The evolution of the surface tension and the viscosity of oils with the number of carbon and silicon atoms are plotted on Figures 10 and11 for relevant chemical families, i.e. alkanes, ethers, esters, acids, alcohols and silicone derivatives. As expected, they both increase with chain length and polarity of the molecules. The peculiar behaviour of silicone derivatives results from the apolar shield offered by the methyl groups. As the presence of cycles significantly reduces the degree of freedom, cyclic siloxanes exhibit higher viscosity values than linear siloxanes.[98] In the same way Figures 10 and 11 (right) show that the branching of the chemical backbone significantly decreases the surface tension while the viscosity is only moderately reduced as the intermolecular interactions are weaker.

For alkane and ether compounds, solely London weak interactions are involved, which explains the low values of surface tension and viscosity. With the presence of a polar ester groups, additional interactions, i.e. Keesom and Debye, take place which lead to increase both physicochemical properties. Finally, the free terminal hydroxyl groups of alcohols and carboxylic acids allow forming strong hydrogen bonds which increase surface tension and viscosity.

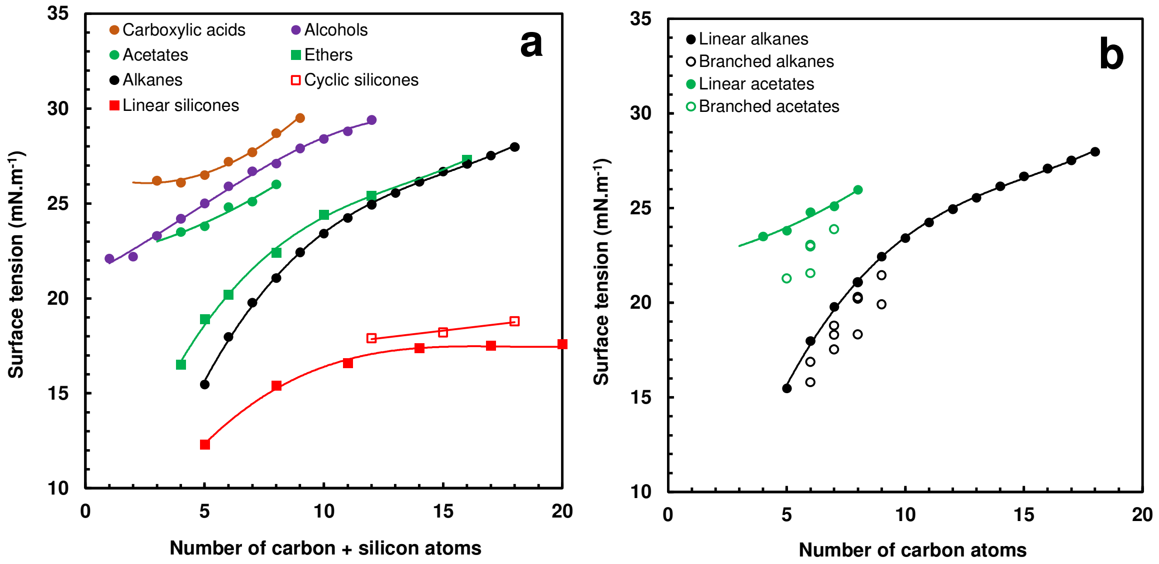


Figure 10 – Evolution of the surface tension of homologous (a) and isomeric (b) liquids with the nature of the polar group, the chain length and the degree of branching.

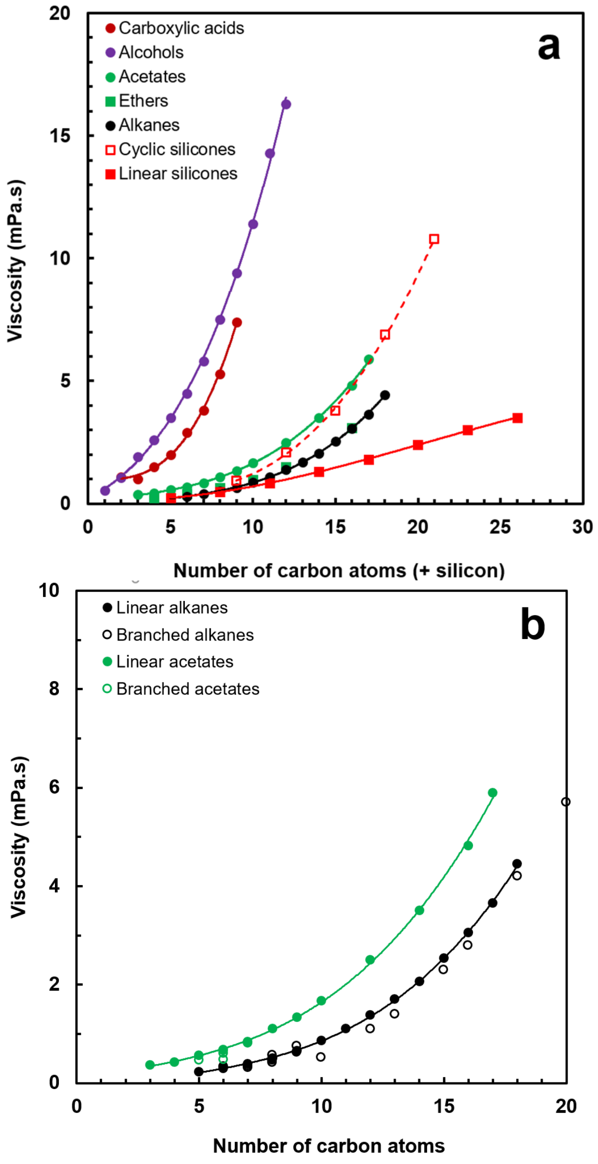


Figure 11 – Evolution of the viscosity of homologous (a) and isomeric (b) liquids with the nature of the polar group, the chain length and the degree of branching.

6. The ideal profile of a bio-based volatile emollient

The structure/properties relationships highlighted above allow to define the ideal chemical structure of a volatile emollient able to mimic effectively the physicochemical and sensory properties of the cyclomethicones. Figure 12 gives an overview of the effect of chemical structure on the physicochemical properties of emollients and on the resulting sensory profile. It may be used by oil designers as a general guideline to develop new alternatives to cyclomethicones

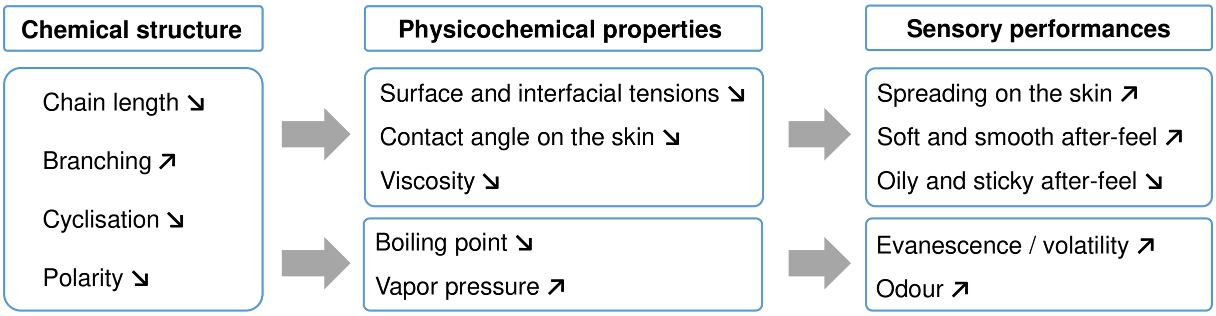


Figure 12 – Overview of the relationships between the chemical structures of the emollients, their physicochemical properties and their sensory performances.

According to Figure 12, an effective silicone-free emollient should have a branched hydrocarbon backbone, moderate polarity, and medium chain length. (C_{11}-C_{20}) which offers a compromise between the desired volatility and the odorless of the emollient. These conclusion are consistent with the map of commercial emollient presented on Figure 6 which confirms that the oils having the closest properties to those of silicone oils are the alkanes, the ether and the short-chain esters, especially the branched-one. Thanks to these relationships, it is possible to anticipate the sensory profile of an emollient by measuring the relevant physicochemical properties. However, such measurements are not always possible and especially when hundreds of virtual candidates are generated in silico by computer-aided-product-design.[99] Actually, it is time-consuming and costly to synthesize and evaluate the performances of new emollients. It is more effective to design virtually hundreds of potential structures and to predict their physicochemical properties for selecting and synthesizing only the most promising.

7. Modelling tools to predict physicochemical properties of virtual emollients

Nowadays, the increase in the computing power and speed of desktop computers on the one hand and the development of theoretical models and artificial intelligence tools on the other hand allow any scientist to predict number of reliable physicochemical properties relevant to a particular application. In the field of cosmetic emollients, it has been shown previously that volatility, viscosity, surface and interfacial tensions and the ability to penetrate into the stratum corneum govern the functional performances of emollients. However, most of these data are not available in the literature and are difficult or even sometimes impossible to measure experimentally. This is for example the case of the largest emollients for which the boiling temperature and the vapor pressure at the temperature of the skin are hardly measurable. This is even more the case for the hundreds of virtual emollients that can be automatically generated *in silico* thanks to computer-assisted organic synthesis programs.[73,100,101] Estimating the key properties of virtual candidate emollients by a simple calculation makes it possible to anticipate their application interest and to carry out the synthesis *in vitro* of only the most promising candidates. Another good reason to limit the number of candidate emollients is the obligation to check their harmlessness before having them tested *in vivo* by a panel trained in sensory analysis.

A large number of theoretical and empirical methods have been developed to predict the physicochemical properties of a liquid compounds. Nieto-Draghi et al. recently published an extensive review on the theoretical approaches available for the estimation of physicochemical properties.[102] Among them, we must distinguish the "first principle methods" which calculate physical properties directly from the chemical structure and quantum mechanics and the QSPR (Quantitative Structure Properties Relationship) methods which use linear and non-linear models to correlate experimental data available in the literature to various molecular descriptors. This empirical approach therefore requires the prior knowledge of a large number of reliable experimental values to establish the correlation. Once a robust mathematical model is obtained, the properties of new emollients can be predicted satisfactorily provided that their chemical structures are close to those of the training set. In particular, several works have sought to predict by a QSPR approach the ability of a molecular compounds to penetrate into the dermis through the skin because this phenomenon is crucial for pharmaceutical applications.[103–106] These studies have shown that the main molecular characteristics determining the permeability are the molecular weight (MW), the logP and the ability to form hydrogen bonds. Regarding the cosmetic ingredients, Berkey et al. found that the MW, the polarity and the viscosity of the oils played an important role for the penetration of emollients into the stratum corneum but the number of emollients studied was too limited (fourteen) to conclude without ambiguity which one is the leading parameter.[64]

Here, we will focus on two methods that have been shown to be effective in accurately predicting some relevant physicochemical properties of emollients. The first, called COSMO-RS (COnductor like Screening MOdel for Real Solvents), is a first principle method which allows to calculate any physicochemical properties (boiling point, vapor pressure, equilibrium constant, solubility, octanol-water partition coefficient) derived from the chemical potential of a molecule in a given environment. The second, called graph machine, is one of many QSPR methods. Although empirical and requiring a training set of known molecules, it has the advantage over other QSPR methods of using as an input molecular descriptor the simple structure of the molecule under study through its SMILES code. Furthermore, it allows the prediction of key properties such as viscosity which do not derived from the chemical potential of the molecule and which are therefore beyond the scope of COSMO-RS.

7.1. The COSMO-RS approach

Developed by Klamt in 1995, the COSMO-RS theory uses a combination of quantum chemistry and statistical thermodynamics, to predict a wide range of physicochemical properties of organic liquids.[107] Figure 13 illustrates the COSMO-RS methodology on the example of the D5 molecule. In a first step, only based on quantum chemistry (COSMO model), the molecule under study is placed in a polarizable dielectric continuum. The internal charge distribution of the molecule induces the polarization of the surrounded continuum which imparts, in return, an opposite surface charge to the molecule. The 3D molecular surface thus obtained is called *"σ-surface"* because it visually represents at each point of the surface the polarization charge density σ (expressed in $e \cdot Å^{-2}$) according to a colour code. The green, red and blue areas of the σ-surface represent the non-polar, electro-negative and electro-positive molecular zones, respectively. The σ-surface of D5 is shown at the top of Figure 13 as an example. The distribution of σ on this σ-surface is the fundamental descriptor of a molecule for COSMO-RS theory. Based on this distribution, a smoothed histogram of charge densities, called *"σ-profile"*, can be established for each molecule (curve on the right of figure 13).

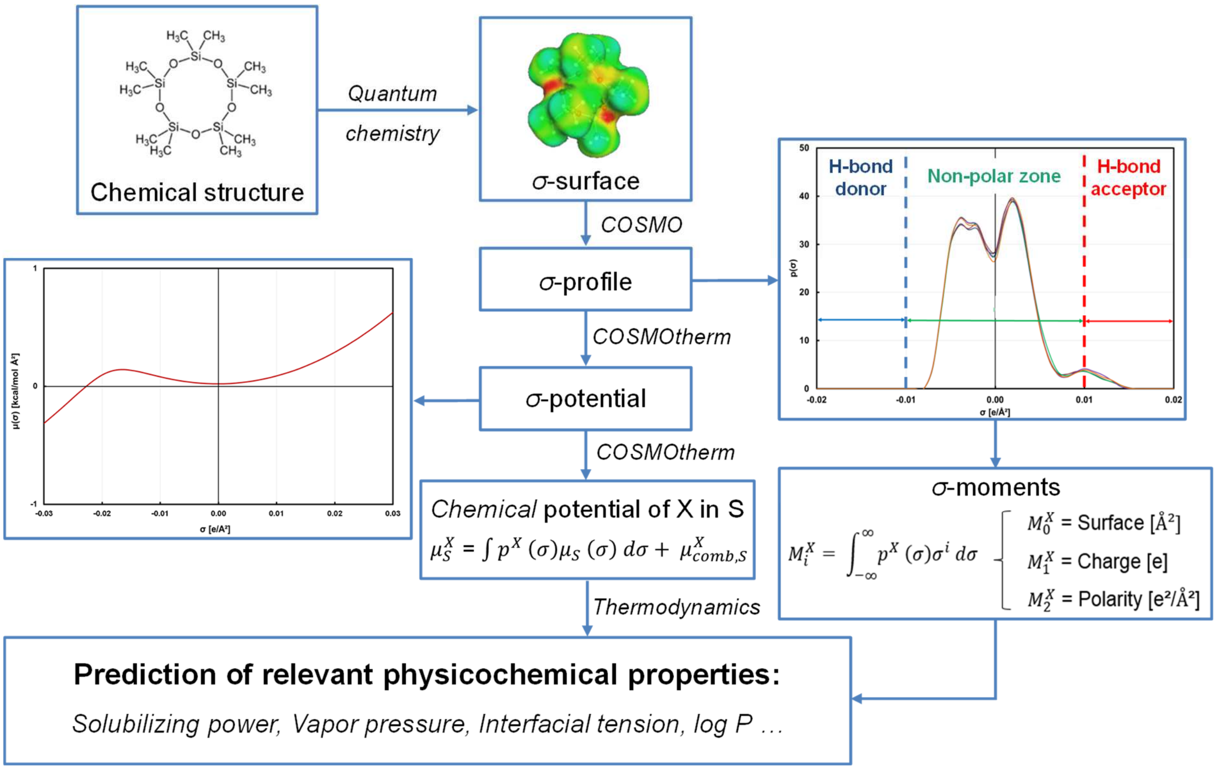


Figure 13 Overview of the different steps involved in the COSMO-RS approach to predict some relevant physicochemical properties of potential or existing emollients.

In a second step, the solute-solvent interactions are considered by replacing the dielectric continuum by a solvent phase. At this stage, the dispersive interactions are introduced as a function of the underlying element below each solvent. The dispersive interaction between two segments is either parameterized as a function of the underlying element pair in contact, or as a simple sum of element-specific contributions. Then, thanks to a thermodynamic approach, the affinity of the solute i for a given solvent S can be assessed. Such information is available from the so-called *"σ-potential"* (curve on the left of figure 13). of the solvent for which a negative value of the chemical potential reflects a strong affinity for the areas of the solutes having an identical electron density. Both the σ-profile of the solute i and the σ-potential of the solvent S are used to calculate the chemical potential μ_i^S of i in S (Eq. 10). The combinatorial term μ_i^C is a corrective factor, which accounts for the difference of size and volume between the solute and the solvent.

$$\mu_i^S = \mu_i^C + \int p_i(\sigma)\,\mu_S(\sigma)d\sigma \qquad (10)$$

With $\boldsymbol{\mu_i^S}$: chemical potential of the solute i in the solvent S (kcal.mol^{-1})

$\boldsymbol{\mu_i^C}$: combinatorial term (kcal.mol^{-1})

$\mathbf{p_i(\boldsymbol{\sigma})}$: σ-profile of the solute i (10^3. Å^4/e)

$\mu_S(\sigma)$: σ-potential of the solvent S (kcal.mol^{-1}·Å^{-2})

σ: polarization charge density (e.Å^{-2})

Once the chemical potential of the solute in the phase(s) of interest has been obtained, the equations of classical thermodynamics make it possible to calculate all the physicochemical properties resulting from a phase equilibrium Gas/Liquid, (with simple approximations for the chemical potential in the gas phase), Liquid1/Liquid2 or Solid/Liquid (including an experimental, or estimated, Gibbs free energy of fusion for the solid components). Thus, in a recent publication, Dupeux et al. showed that the experimental values of boiling points, log Ps, vapor pressures, water solubilities and Henry's constants of more than a hundred perfume molecules correlate very well with the values predicted by COSMO-RS.[108] Similarly, Goussard verified that COSMO-RS satisfactorily predicts the boiling points of 300 known liquids with an accuracy of ±15 °C. The method was then successfully applied to virtual emollients to select candidate molecules to be synthesized based on volatility similar to that of D5.[73]

7.2. QSPR and graph machine models

QSPR regressions are very popular to quantitatively correlate molecular descriptors to physicochemical properties. Such descriptors fall into five classes: topological, geometrical, thermodynamic, electronic or constitutional .[102] QSPR models are regression and classification, that are based on the simple idea that similar structural features are likely to modify physicochemical properties in a similar way.[102] QSPR methods can take the form of multilinear regression (MLR), Partial Least Squares (PLS) or artificial neural networks (ANN).[89,109–114] Such models require to build an extensive dataset of molecules, which gathers for each structure a set of well-chosen molecular descriptors and the values of the property of interest. Such database is also known as learning database, because it allows carrying out the required first learning phase. This step consists in learning the structure-property relationships from the examples of the dataset in order to then be able to generalize, i.e. to predict the physicochemical properties of unknown molecules. The accuracy of the estimation strongly depends on the quality of the learning step. Examples should be carefully gathered and the selected values cautiously extracted from the literature: two independent and consistent bibliographic references are required to ensure the reliability and the learning dataset.[89]

Based on neural networks, an alternative method to conventional QSPR models has been proposed by Goulon et al. i.e. the “graph machines” approach.[115] It differs from the QSPR regressions by the input parameters that are required. Indeed, graph machines compute the physicochemical properties directly from the molecular structures of the compounds, available from the SMILES (Simplified Molecular Input Line Entry Specification) codes. Each molecule is described as a graph reflecting its molecular structure and the property of interest is computed thanks to a parameterized function defined from the graphs.

These graphs are constructed following the rules below:

- Each atom, except hydrogen atoms, forms a node.
- Each link forms an edge.
- Each node is associated with a label, indicating the nature of the atom and its connectivity, i.e. the number of bonds connecting it to neighbouring atoms, excluding the hydrogen atom.
- The graph is oriented, i.e. a central node is chosen, also called the exit node.
- In the case of a cyclic molecule, an edge is removed in order to form an acyclic graph, in which each trajectory of the graph ends on the exit node. The initial connectivity of the atoms concerned by the deletion of the edge is however preserved

Figure 14 illustrates the construction of the graphs of 3-buten-1-ol (left) and 2,3-dimethylphenol (right) starting from their chemical structures. As graphs should be acyclic, one edge of 2,3-dimethylphenol is removed. In this case, the degrees of atoms involved in the removed edge remains unchanged (dotted red line in Figure 14). In the specific case of graph machines, the database gathers the graph of each compound and the physicochemical value associated.

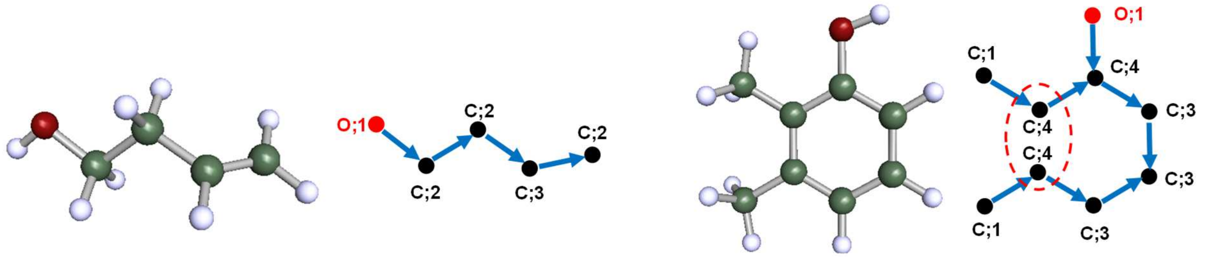


Figure 14 – Construction of the acyclic oriented graphs used for predictions thanks the graph machines approach, starting from chemical structures: examples of 3-buten-1-ol (left) and 2,3-dimethylphenol (right).

Goussard et al. compared the efficiency of four modelling approaches, namely, group contributions, corresponding-states principle, neural networks, and graph machines, for the estimation of the surface tension of 269 pure liquid compounds from their molecular structure. This study focuses on liquids containing only carbon, oxygen, hydrogen, or silicon atoms since our purpose is to predict the surface tension of cosmetic oils. The graph machine approach provides the best results, estimating the surface tensions of 23 cosmetic oils, such as hemisqualane, isopropyl myristate, or decamethylcyclopentasiloxane (D5), with accuracy better than 1 $mN \cdot m^{-1}$.[89] These authors adopted the same strategy to investigate the viscosity of liquids at 25 °C by comparing several modelling tools. Models were trained from a database of viscosities of 300 molecules covering a wide diversity of chemical structures, namely, alkanes, ethers, esters, ketones, carbonates, acids, alcohols, silanes, and siloxanes, as well as different chemical backbone, i.e., straight, branched, or cyclic chains. Comparing the predicted and measured viscosities of 22 cosmetic oils showed that the graph machine provided the most accurate estimates.[116]

8. Conclusion

Nowadays, cosmetic products must both present high technical performance and meet the requirements of public health agencies in terms of health risks and environmental protection. Furthermore, consumers are more and more suspicious of synthetic ingredients derived from petroleum and give preference to bio-based compounds that are harmless to humans and the environment. Such a strong emerging trend for naturalness has encouraged industrials to develop new bio-based emollients, with a sensory profile as close as possible to that of the poorly biodegradable silicones. However, finding silicon-free substitutes is a huge challenge due to their outstanding sensory properties i.e. excellent spreading and light, dry and smooth after-feel which results directly from the great flexibility and the polar/non-polar Janus character of the $Si(Me)_2$-O- $Si(Me)_2$ moiety.

Structure/properties relationships turn out to be an effective approach to identify innovative chemical structures that can offer physicochemical and sensory properties as close as possible to those of cyclomethicones D4 and D5. Indeed, the sensory qualities of the emollients are highly correlated to their physicochemical properties. In particular, low values of viscosity, surface tension and interfacial tension with the skin (or hair) are required to improve the spreading properties of emollients on skin (or hair). Besides, both relatively low boiling point and high vapour pressure *inter alia,* are essential to imitate the expected light and volatile character of cyclomethicones. Figure 16 shows the positioning of some typical emollients according to their volatilities. The area including volatile compounds complies with the European regulations defining the volatile organic compounds (BP ≤ 250 °C). The border between semi-volatile and non-volatile compounds has been chosen arbitrarily, taking the 17-carbon macrocyclic ketone civetone as a limit because it is an extremely low volatility musk but nevertheless fragrant. This figure shows that only the two alkanes isododecane (C_{12}) and cetiol ultimate (C_{11}-C_{13}) exhibit volatilities comparable to those of the cyclomethicones D4 and D5. Despite their high volatility, these highly hydrophobic oils are odourless because they are very poorly soluble in nasal mucus. In contrast, since the ethers and esters having the same number of carbons are slightly soluble in the nasal mucus and may interact with the olfactory receptors, they exhibit a strong odour, unacceptable for an emollient. This is the reason why emollients comprising an oxygen functional group must have a number of carbon atoms between 17 and 20, preferably branched, to be practically odourless while being sufficiently volatile to give an evanescent feel.

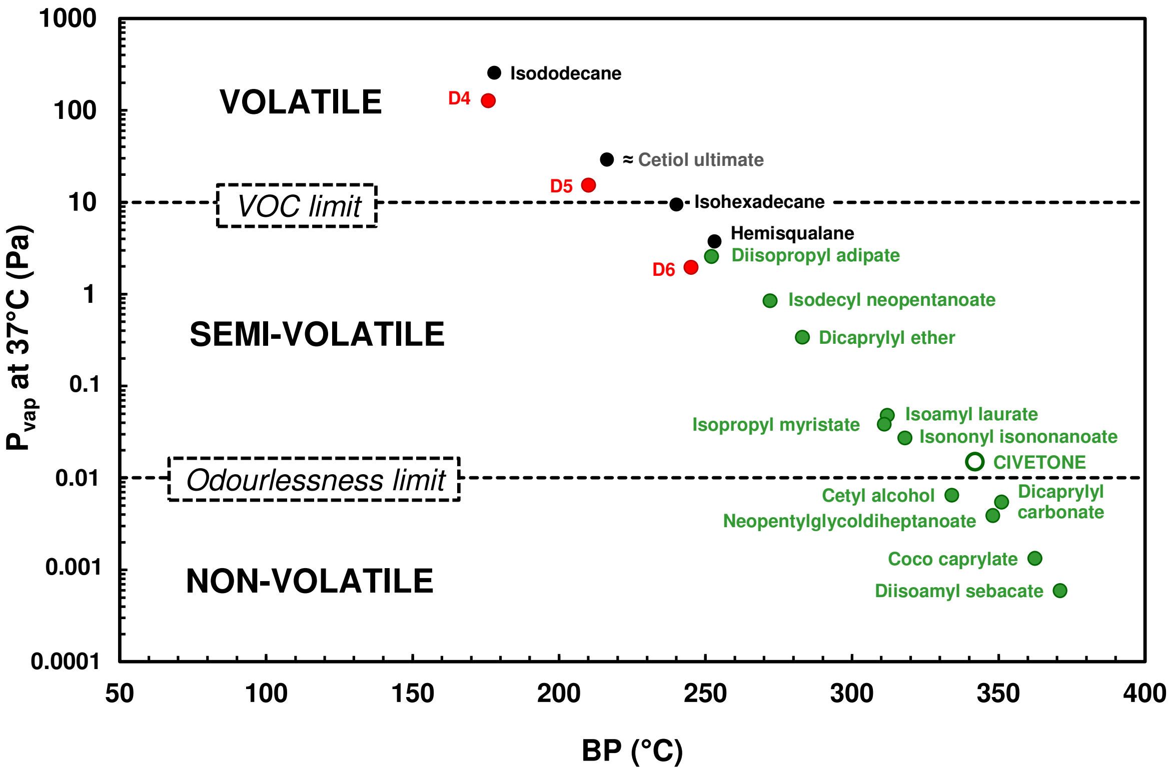


Figure 16 – Positioning of some typical emollients according to their volatility.

However, none of the current emollients of the alkane, ethers or esters type succeeds, on their own, in perfectly mimicking the sensory profile of cyclomethicone D5. Indeed, alkanes and oxygenated emollients exhibit poorer spreading properties on the skin than those of silicones for different reasons. The alkanes have low surface tensions, favourable to spreading, but high interfacial tensions with the skin, unfavourable to spreading, while it is the reverse for oxygenated emollients. By mixing a non-polar oil with a polar oil, it is possible to benefit from the respective physicochemical properties of these two types of oils. Actually, such a mixture exhibits a non-ideal behaviour at the G/L and L/S interfaces in order to minimize its energy, i.e. the concentration of the alkane is higher at the emollient/air interface while the concentration of the ester is higher at the emollient/skin interface. This synergistic effect significantly improves the spreading properties of the oil and thus offers an effective way to match the properties of cyclomethicones. More prospectively, computer-assisted synthesis coupled with predictive tools based on quantum chemistry or on neural networks makes it possible to generate, in silico, hundreds of emollient candidates and to predict their relevant properties to point out the most promising that deserve to be synthesized first.

Acknowledgements

The authors would like to thank Dr Pieter Van der Weeën and Mrs Aurélie Fievez for fruitful discussions and the company Oleon for its financial support through a PhD grant. Chevreul Institute (FR 2638), Ministère de l'Enseignement Supérieur et de la Recherche, Région Hauts de France and FEDER are also acknowledged for supporting and funding partially this work.

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