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Cyclodextrins, Vesicles and Particles

Keywords: Carrier systems, cyclodextrins, vesicles, particles

Introduction

Carrier systems are becoming increasingly important in the cosmetic field as they support the stabilisation of often expensive active ingredients and/or as carrier sysem by transporting active ingredients inside the skin to the target site. Particles, however, can also be used to avoid the penetration of active substances into the skin by building a depot on the skin's surface.
Table 1 shows the differnt types of carrier systems which are going to be introduced in this article.

Cyclodextrins

Cyclodextrins are produced biotechnologically by enzymatic degradation of starch. In doing so oligosaccharides are cut out from the starch molecule in 6-8 glucose units which are arranged in a conic structure with specific volume. The cyclodextrin molecule has a hydrophilic mantel (primary and secondary hydroxy groups) whereas the inside of the cone has hydrophilic properties (CH-groups and ether oxygens of the glucose units) **(Fig. 1)**.
The most important characteristic of cyclodextrins is their ability to embrace lipophilic actives in a sort of guest/host relationship and therefore to protect them from external factors.
The isolated cyclodextrins (α-, β- and γ-cyclodextrins) differ in their number of glucose molecules and hence in their chemical and physical properties.
The cyclodextrins' topology allows for an encapsulation of hydrophobic actives in the apolar hollow space. The interaction of cyclodextrins and their guest molecules are strictly of physical (*van der Waals* forces and formation of hydrogen bridge bonds) and not of chemical nature (covalent bonds). Therefore, the balance between dissociation and association shows in the solution.
In the watery medium the hydrophobic

Carrier System	Material	Active Substances	Size
1. *Cyclodextrins:*	Oligosaccharides	hydrophobic actives	0.5 – 0.8 nm
2 a *Liposomes - vesicles:*			
Liposomes / Nanoparticles	Lecithin	hydrophobic + hydrophilic	100 – 300 nm
Niosomes / Catezomes	Tensides	hydrophobic + hydrophilic	50 - 100 nm
2 b *other Vesicles*			
Glycospheres	Lecithin + mod. starch	hydrophobic + hydrophilic	200 nm
Thalaspheres	marine collagen + GAG	hydrophobic + hydrophilic	10 - 500 µm
Silica Shells	Silica	highly volatile substances	3 – 12 µm
3. *Particles:*			
Solid Nanoparticles	Lipide	hydrophobic	50 – 1000 nm
Microsponge	Methacrylate	hydrophobic	5 - 50 µm
Unispheres	Lactose/ Cellulose + Derivatives	hydrophobic	500 – 900 µm

Table 1 Different types of carrier systems.

guest molecule has a solvate mantel whereas the unloaded cyclodextrin has intercalated a few water molecules. Both molecules are in an unfavorable energetic state. The hydrophobic active molecule moves to the cyclodextrin's hollow space and strips off the hydration sheath. A gap arises in the medium which is then filled by the water molecules displaced by the dextrin's core. This leads to an energy release. The guest molecule accesses the cyclodextrin's core and is fixed by the hydrophobic interactions. The formation of enclosure complexes in solutions is a reversible procedure. **(Fig. 2)**.
Due to their high molecular weight and their hydrophilic mantel the active complexes do not penetrate into the skin by themselves. The actives are released on the skin and the lipophilic guest molecule accesses the stratum corneum. Attention should be paid to the existence of the ideal interaction between the carrier and the active molecule i.e. it should not be too weak as otherwise too little active molecules are intercalated – neither it should be too strong as subsequently no active molecules will be released from the complex.
There is quite a large potential for the use of cyclodextrin-actives in the cosmetic and pharmaceutical industry as

- the actives are protected from light and other external influences
- the solubility of lipophilic actives in water are improved
- the risk of possible chemical or thermal break down of actives is decreased
- volatile substances are stabilized (flavours and perfumes)
- irritating effects of the actives can be reduced
- it makes the production of powdery active complexes possible (Make up).

Furthermore, cyclodextrins have cosmetic effects. In deodorants and anti-acne products they serve as perspiration absorbers. In creams and make-ups they can be used to bind excessive oil and therefore have a matting effect.

Glucose units:	6	7	8
Molecular weight:	973	1135	1297
Foam volume (ml/g)	0.10	0.14	0.20
Water solubility (g/l)	122	18.8	256

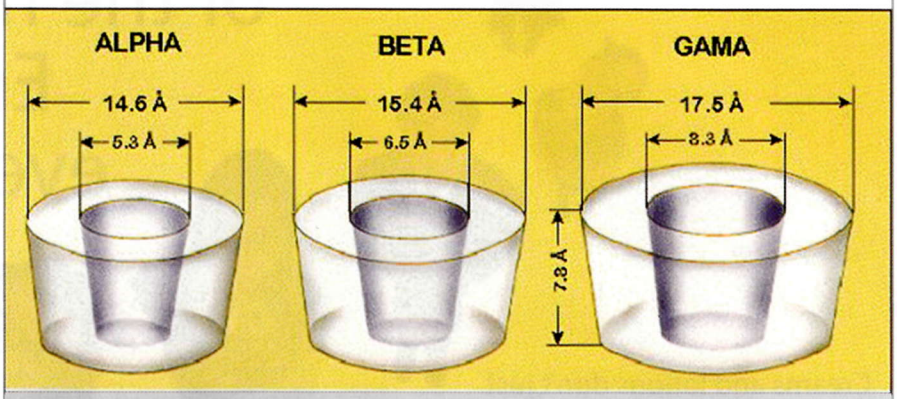


Fig. 1 Properties of Cyclodextrines.

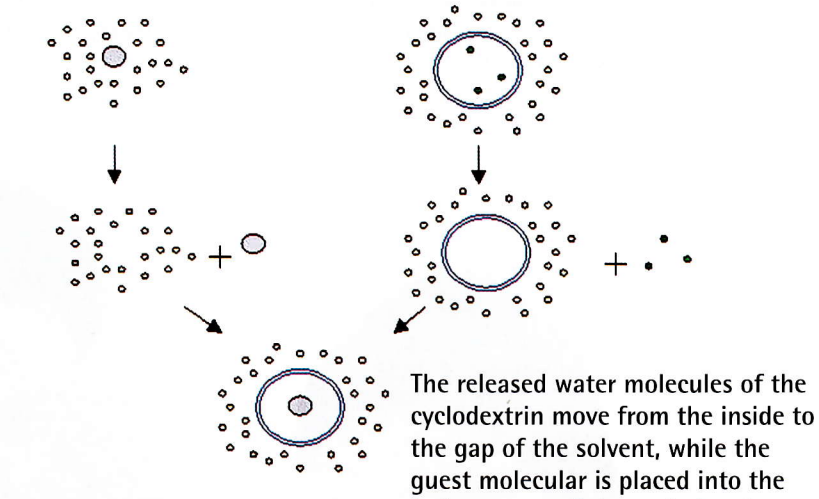


Fig. 2 Formation of enclosure complexes.

Liposomes – Vesicles

The liposomes which have been used in cosmetics since 1986 (»Capture« by Dior) represent the most popular carrier systems. The expression »liposome« originated from the Greek and translated means »fat body« – a very elastic term. According to this definition all vesicles (hollow spheres) that have a natural or synthetic lipid membrane, encircling a hollow core, would be counted among the liposomes.

Liposomes

The firstly described liposomes (*Bangham* 1965) and the biggest part of the lipid vesicles commercially available today were and are made of lecithin.
By »lecithin« the industry refers a complex compound of phospholipids and

triglycerides which can be simply obtained by extraction of soya bean. Through multiple steps of purification the neutral fats are eliminated and therewith the phospholipid fraction is obtained. The latter has a high content of phosphatidyl choline (PC > 80%). If water is added to the phospholipid film multilamellar liposomes (MLV) form spontaneously. Through special production methods (e.g. high pressure filtration, extrusion or ultra sound) the multilamellar vesicles turn into unilamellar, monolayer liposomes (SUV). Both hydrophilic (in the aqueous core) and lipophilic actives (in the membrane) can be encapsulated in liposomes. Aside from their excellent skin smoothing effects liposomes are favored for their ability to act as carrier system.

Small unilamellar liposomes which are made of purified phospholipids (PL 80; phosphatidylcholin content > 80%) with unsaturated fatty acids (linoleic acid) form flexible vesicles with the ability to penetrate **(Fig. 3)** Accordingly, they can transport the actives into the deeper skin layers and provide them in higher concentrations. In contrast, liposomes made of hydrated soya lecithin (PL 90 H) form rigid vesicles. Such liposomes remain in the upper layers of the stratum corneum (- meaning they do not show any ability to penetrate -) where they form depots for the active. It is therefore incidental that from the modification of the lipid compound a carrier system's ability to penetrate can be determined. **(Fig. 4)**.

The encapsulation of actives in liposomes can offer a.o. further advantages,

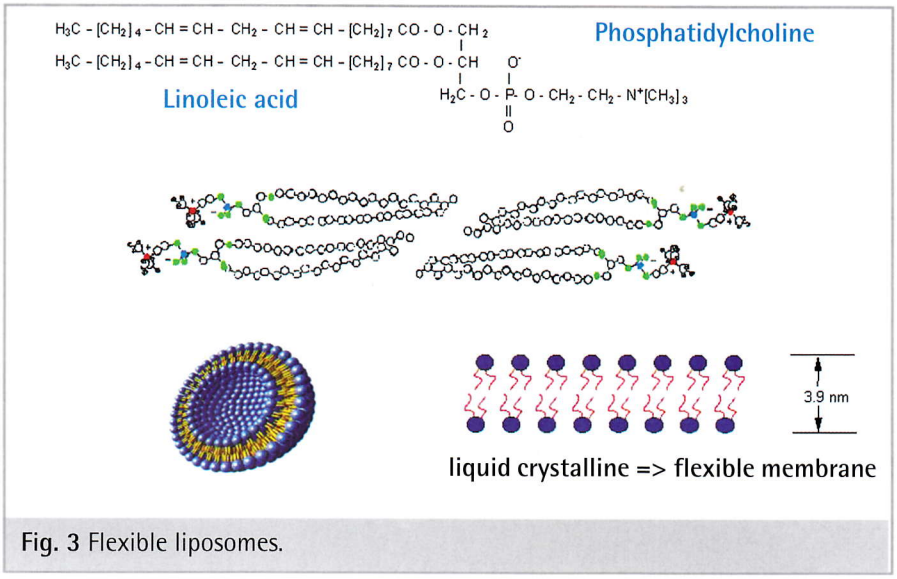


Fig. 3 Flexible liposomes.

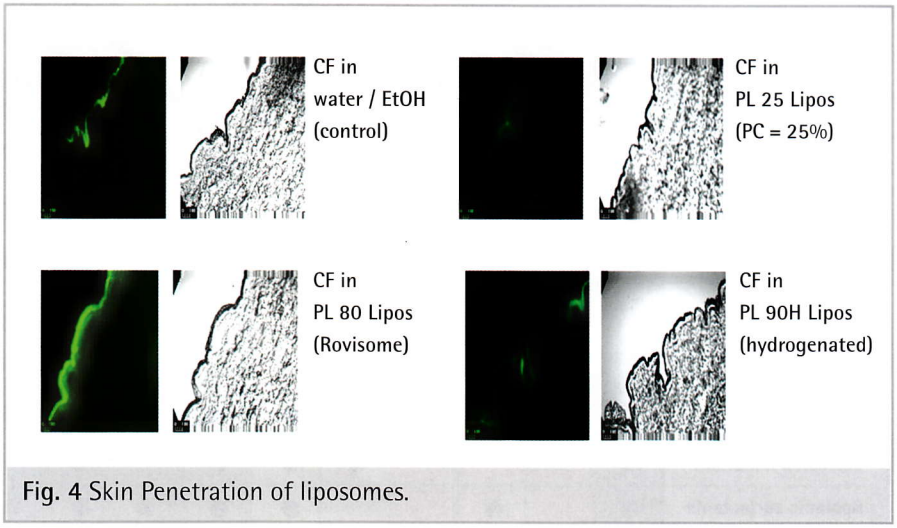


Fig. 4 Skin Penetration of liposomes.

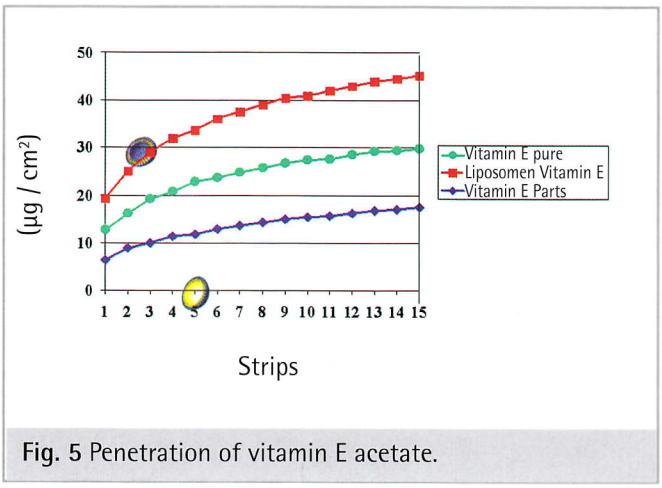


Fig. 5 Penetration of vitamin E acetate.

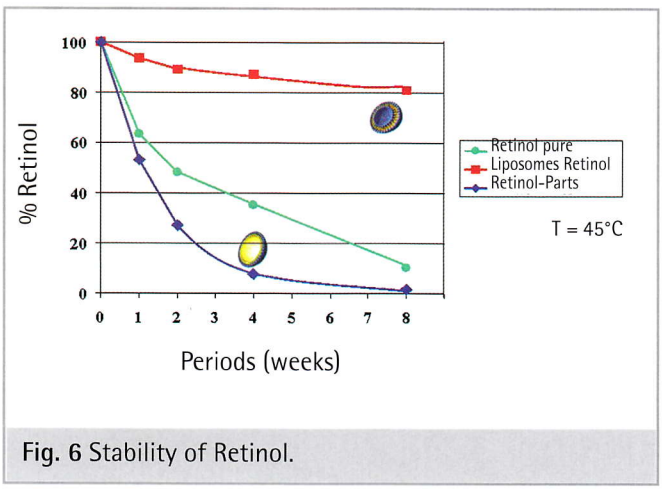


Fig. 6 Stability of Retinol.

e.g. stability increase of sensitive actives (vitamines) and/or the reduction of the irritation potential of some compounds. **(Fig. 5)**.

Nanoparticles

Nanoparticles differ from the conventional liposomes. The vesicle's core accommodates an oily phase and is surrounded by half a lipid membrane. Due to their lipophilic volume these vesicles are able to encapsulate a much higher content of hydrophobic actives (appr. 10 - 30%) compared to the conventional liposomes (2-5%).

The stability of pure retinol, that of retinol encapsulated in liposomes (PL 80 liposomes) and encapsulated in nanoparticles was determined by HPLC method. This test exemplifies that aside from the lipid composition of the liposomes, *the method* of encapsulation is of vital importance **(Fig. 5)**. Even though a higher concentration of lipophilic actives can be encapsulated in the nano particles, the »half« bi-layer accounts for an instabilisation of the membrane which results in a fast degradation of the retinol. Furthermore, compared to vitamin E encapsulated in liposomes, the ability to penetrate of those actives encapsulated in nanoparticles wanes notedly **(Fig. 6)**.

Liposomes and nanoparticles simply have to be stirred into the finished formulation. However, not every formulation is suited (e.g. W/O-formulation resp. shampoos) for liposomal preparations. Emulsifiers can interact with the lipids, solubilise the vesicles and form co-micelles. Beforehand compatibility tests have to be carried out by determining the vesicle size before and after adding the respective emulsifier. The hydrolysis of the natural lipids still depends on the pH-value (optimum at pH 6.5). However, as vesicles the unsaturated phospholipids show a good stability against oxidation (OSI-value: > 150 -hours, rancimeter at 110°C).

Niosomes

Niosomes consist of non-ionic tensides which have properties similar to phosphatidylcholine that – added into water – spontaneously form vesicles. According thereto niosomes and liposomes do not differ in their structure. While phospholipids are generated from natural resources (soya or eggs), tensides are generated synthetically. The pros and cons: chemically speaking, niosomes are much more stable (pH-value, heat and oxidation) as they consist of polyoxyethylenalcylethers ($C_{12-18}EO_{3-7}$) and cholesterol. But by means of these vesicles a significant amount of tensides is brought into the skin which leads to an adverse effect on its barrier function. Depending on the chain length of the fatty acid, the tensides – similar to the phospholipid vesicles – can form flexible and/or rigid membranes which also determine the penetration properties of the carriers **(Fig. 7)**.

The niosomes by L'Oréal show good transport properties of hydrophilic actives into the stratum corneum.

Catezomes

The substances used in Catezomes are Catemol 220 (Behenamidopropyl Dimethylamin) and fatty acids (behenic acid) which form an amphiphilic salt at neutral pH-value which then forms liposome-like vesicles in water. Depending

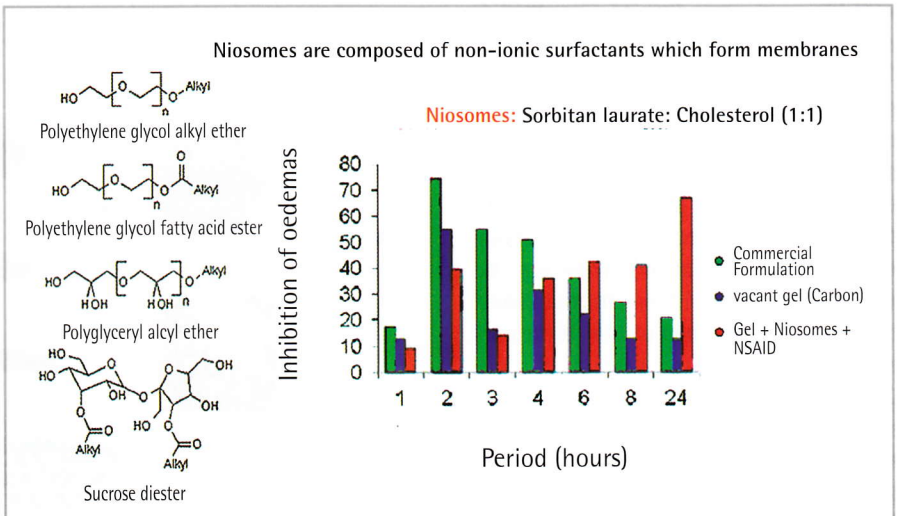


Fig. 7 Niosomes (non ionic surfactant vesicles).

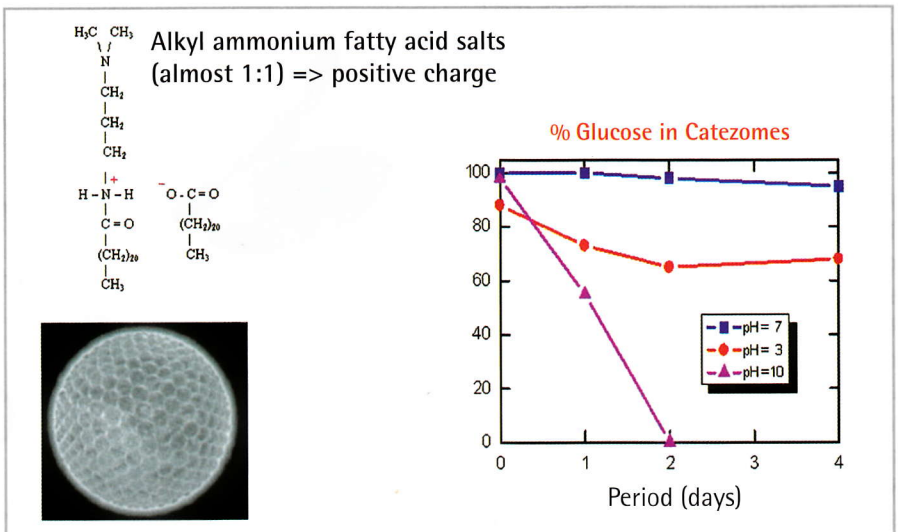


Fig. 8 Catezomes (positiv charged vesicles).

on the ratio of the Catemol and the fatty acid positively charged vesicles are formed which show a high affinity to the hair surface. The particularity of these non-penetratable vesicles is that the salification is stopped when changing the pH-value or the ionic strength. This results in a controlled release of the encapsulated actives but also in a sensitivity to some formulations **(Fig. 8)**.

■ Other vesicles

Glycospheres

Compared to the liposomes, glycospheres have a solid nucleus which consists of modified starch. The outer lipid membrane surrounding the nucleus is composed of fatty acids and polar lipids. Thus, like liposomes these vesicles consist of natural raw materials. The hydrophilic actives (especially anionic) are solid and are surrounded by positively charged cellulose polymeres and are therefore well protected against outside effects (heat, oxidation). They can be used both in o/w and w/o formulations. It needs to be pointed out that these carrier systems can include proteins of up to 200 000 Da into this network. Due to their rigid nucleus these vesicles (200nm) are not able to penetrate. They release their actives by increasing the ionic strength **(Abb. 9)**.

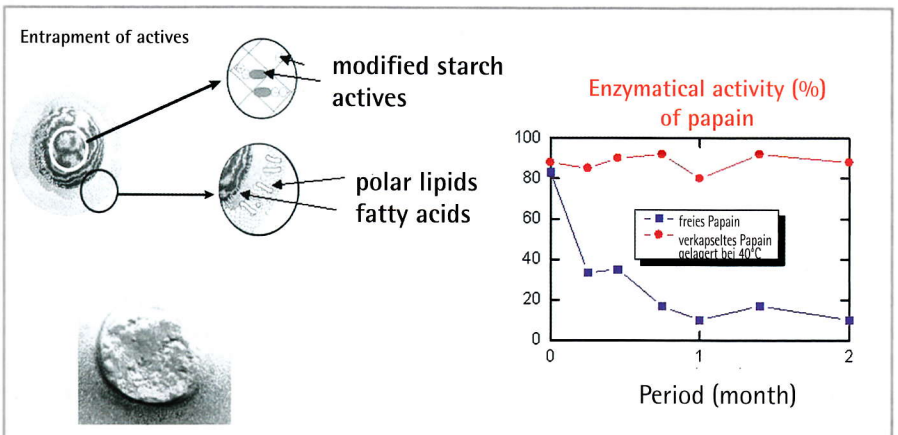


Fig. 9 Glycospheres.

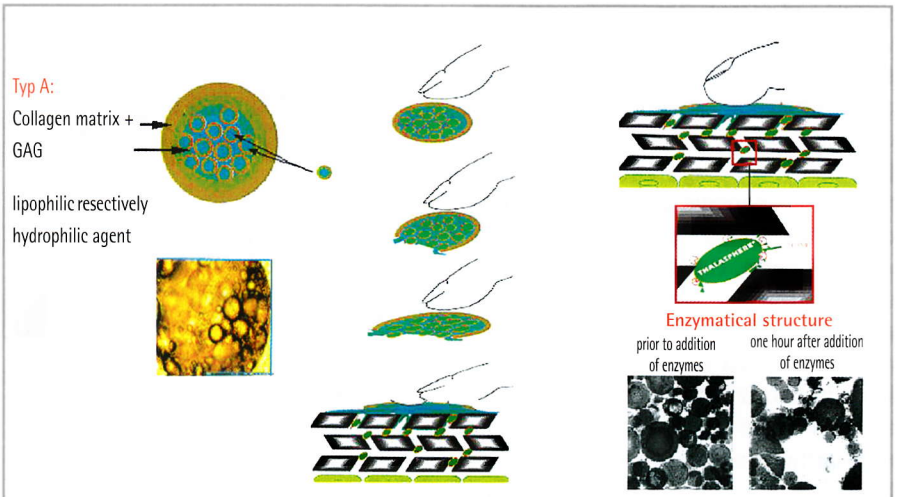


Fig. 10 Thalaspheres.

Thalaspheres

Thalaspheres are an extremely diverse carrier system. Their vesicle sizes reach from 200 nm (microscopically not visible, milky supension) to 900 µm (visible, partly coloured »beads«). They have a stable vesicle membrane respectively a spherical matrix which is made of natural polymers of marine origin. They contain atello collagenes (from sole fish) and glycosaminoglycanes (GAG) (chondrium sulfate from shark cartilage) which are bound by divalent ions. The membrane/matrix can encapsulate both a hydrophlic and a lipophlic core depending on the solubility of the respective active. There is a special kind of Thalaspheres (> 100 µm) which is suited for the encapsulation of small spheres which again contain actives. A visual effect/marketing effect can be obtained by colouring these particles.

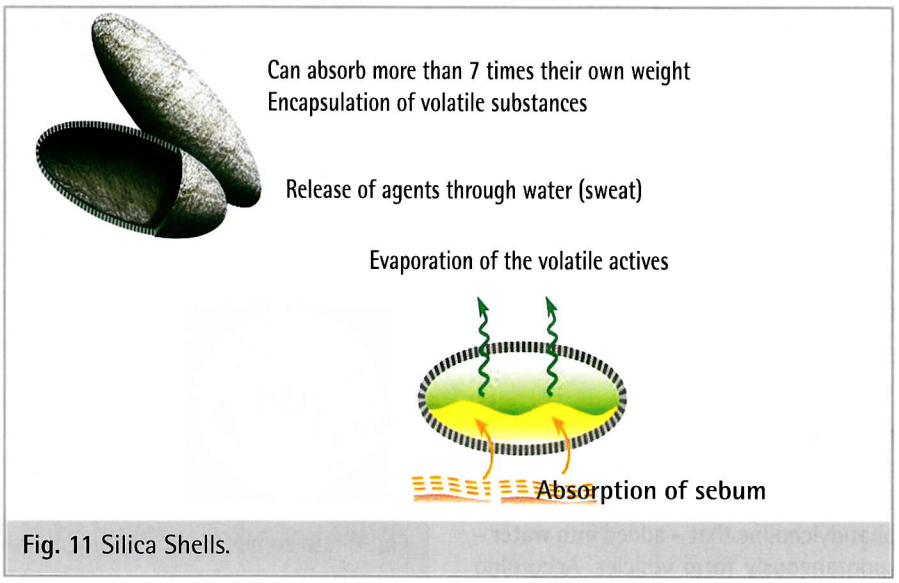


Fig. 11 Silica Shells.

The actives stabilised in Thalaspheres are released differently, depending on their vesicle size. Large carriers can be destroyed mechanically (friction, massaging in etc.), which makes a fast release of the actives possible. Small carriers (<100 µm) degrade enzymatically by means of proteases in the upper layers of the stratum corneum. This leads to a better biological availability of the cosmetically relevant ingredients. **(Fig. 10)**.

Silica shells

Silica Shells are ellipsoid mantles – consisting of silicates. Silicats can encapsulate volatile substances with 7 x their own molecular weight. They form a micro reservoir on the skin which slowly releases its volatile actives by evaporation but at the same time it is able to absorb lipophilic substances (sebum) **(Fig. 11)**. As Silica Shells dissolve in aqueous solutions they are only suitable for solid formulations (e.g. Deodorant-Sticks).

■ Particles

At first glance, these carrier systems compared with the afore mentioned vesicles literally differ in their size – they are visible. They consist of polymers. The actives are embedded into their network (pores). Due to their size these particles remain on the skin where they form a depot from which the actives are slowly released in a controlled manner.

Solid Nanoparticles

Solid Nanoparticles (SLN) are generated from lipids by high pressure homogenisation, which are solid at room temperature. Their size is similar to liposomes. Therefore, they are among the smallest particles. The lipophilic actives are tightly integrated in the ceraceous membrane. Unlike the other very large particles they have small encapsulation rates and therefore a quicker release of the substances on the skin **(Fig. 12)**.

Microsponge

Microsponges consist of vinyl-derivatives which, depending on the chemical modification, form particles with pores in different sizes. The large inner surface which is generated thereby (30 – 500 m^2/g particle, similar to charcoal) allows for a

Solid Nanoparticles
Lipids solid at room temperature
(Cetyl palmitate, Dicetyl phosphate, Glycerin trilaurate, Polysorbate 80)

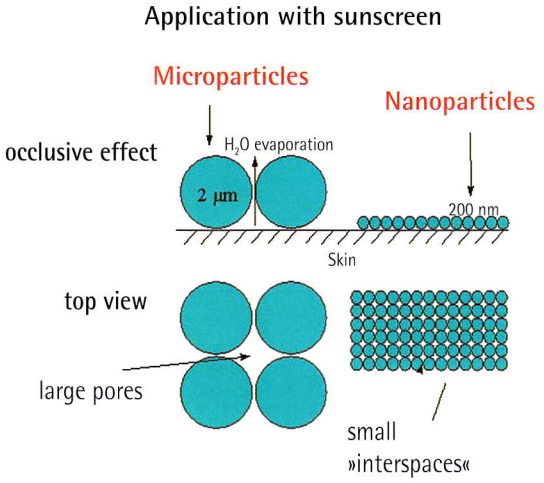
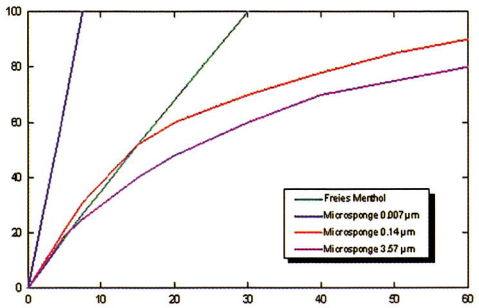


Fig. 12 Nanoparticles.

Microsponge
Methyl acrylate + vinyl derivative

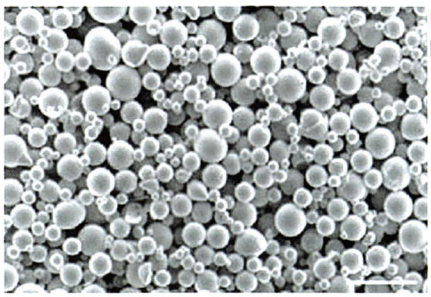
Menthol release from microsponge depending on pore size

Encapsulation of lipophilic agents from physical absorption



Period (hours)

Fig. 13 Porous microparticles (microsponge).



Unispheres
lactose + cellulose + hydroxy methyl cellulose

Encapsulation of the lipophilic agents as micro droplets by dispersion

Fig. 14 Unispheres.

high encapsulation rate – also for volatile substances like perfumes. Liquid actives therefore become powdery. The pore size as well as the interaction of pore and active determines the encapsulation and the release of the molecules **(Fig. 13)**. These particles are very stable and can easily be incorporated into all sorts of formulations.

Unispheres

Unispheres are water-insoluble but water-swellable particles, consisting of lactose, cellulose and cellulose derivatives. In dry condition Unispheres are solid and very indelible, but incorporated into an aqueous basis they become soft and can be levigated on the skin without a trace. For formulations a pH-value of 3.5 – 7.5 is important. The basis should also show a certain consistency to avoid sedimentation of the particles **(Fig. 14)**.

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