Nanoemulsions for topical applications

Summary:
This presentation will introduce new nanoemulsions being able to act as drug carriers for improving the delivery of actives into the deeper skin layers.

This technology is based on a skin-friendly emulsifier derived from sunflower which forms stable nanoemulsions in very low concentrations of emulsifier. Depending on the usage of an additional oil/stabilizer different emulsions can be obtained: a multiple nanoemulsion (mNE) for the encapsulation of hydrophilic / amphiphilic / lipophilic actives and an oil/water nanoemulsion (NE) for the incorporation of high concentrations of lipophilic or oily components.

Under extensive investigation, it was proven that the multiple nanoemulsion (w/o/w) exhibits a better performance than the well known flexible liposomes. The encapsulation of epigallocatechin gallate (EGCG) in these vesicles leads to an improved stability and an excellent penetration even from different formulations compared to liposomes. The use of higher lipid concentrations facilitate a much higher loading of actives into the carrier system and determine also the penetration behavior.

The nanoemulsion containing pure tocopherol showed a prolonged anti-oxidative capacity in the viable skin area which prevents the formation of free radicals and skin ageing.

Introduction:
Multiple water-in-oil-in water (w/o/w) emulsions gain new interests for their potential to incorporate hydrophilic and amphilic drugs. These actives can be incorporated in the aqueous droplets protected by the lipophilic medium both surrounded by a hydrophobic monolayer. Normally a hydrophilic and a lipophilic surfactant is used for this type of emulsion and also high diligence has to be taken in the two-step emulsification process. Sometimes natural polymers are added to remarkably increase the long-term stability (1.Hoppel et al.).

Nanoemulsion (o/w) become more and more important as potential vehicles for controlled delivery of lipophilic components into the skin. In contrast to the thermodynamically stable microemulsions (sizes < 100nm) which are transparent low viscous dispersions, the nanoemulsions are milky formulations with lower concentrations of emulsifiers. The NE can be formulated more skin-friendly by the use of non-pegylated unsaturated C18 emulsifiers like lecithin (Lipoid Ultraspheres) or sucrose stearate-based preparations (2. Klang et al.).

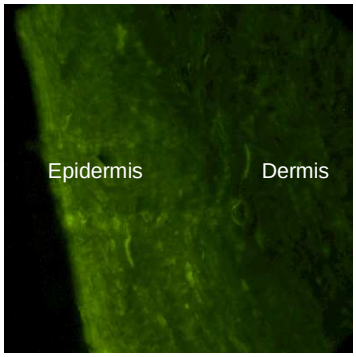
This study reveal the possibility to create new stable multiple and o/w nanoemulsions with the use of a skin-friendly, non pegylated emulsifier and an emollient /oil and by an easy production process.

Methods:
The emulsifier for all formulations was Imwitor 375 (Glyceryl/citrate/lactate/linoleate/oleate. Emollient was ethyl oleate for the mNE and the stabilizer for the o/w nanoemulsion was diglycerol monooleate.
Emulsifier, oil and lipophilic actives were solubilized in ethanol and the hydrophilic components were solved in water. The water phase was slowly given to the lipid phase under strong homogenization. The nanoemulsions were produced by high pressure homogenization (1 cycle by 800-1200 bar). Sizes and polydispersity were determined by photon correlation spectroscopy (PCS). The penetration kinetic was performed with human skin obtained from surgery using Franz diffusion cells. The formulations with different actives were applied onto the surface of the skin (10 mg formulation / square centimeter) und the amount of actives in different skin layers were determined by suitable techniques (fluorescence spectroscopy, confocal laser scan microscopy and ESR measurements).

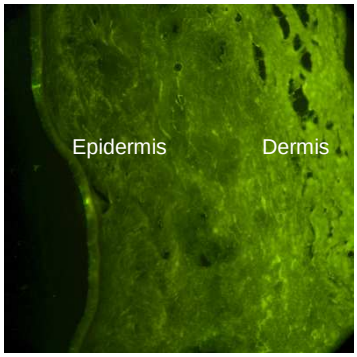
Results:

The multiple nanoemulsion (mNE) was developed to get nanovesicles with better characteristics than conventional flexible liposomes (bilayer system). The encapsulation of FITC-BSA (protein with MW of 70.000 Da) into the new nanoemulsion conducted smaller vesicles and homogenous distribution compared to liposomes (size < 150 nm and PDI <0.15 for the mNE / size 100 – 240 nm and PDI > 0.3 for liposomes). After 24 hours the penetration of FITC BSA was determined with confocal laser scan microscopy. BSA was spread over the total skin area by the use of the multiple nanoemulsion.

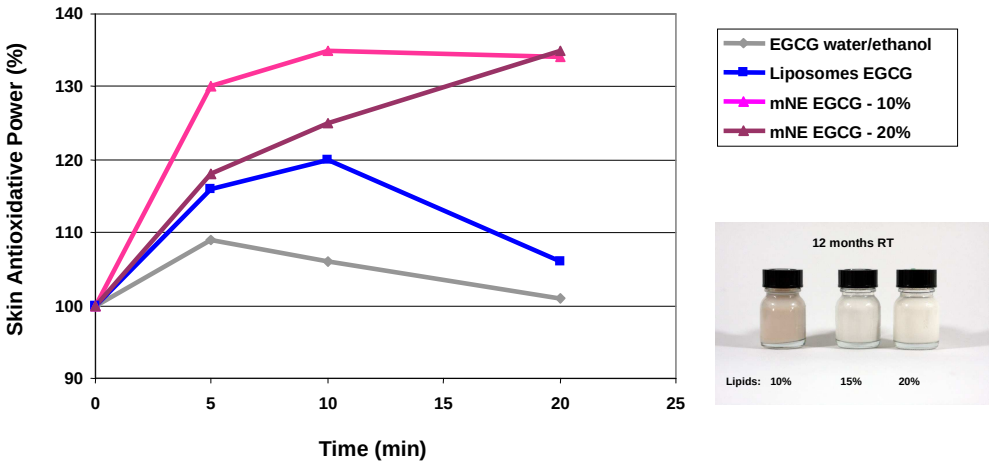
Flexible liposomes



multiple nanoemulsion



Depending on concentration of the emulsifier in the mNE different kinetics in the penetration of the active into skin could be achieved. The anti-oxidative power of EGCG in the epidermis (viable skin) was proven by ESR measurements – this means the potential in free radical scavenging (3. Jung et al.)

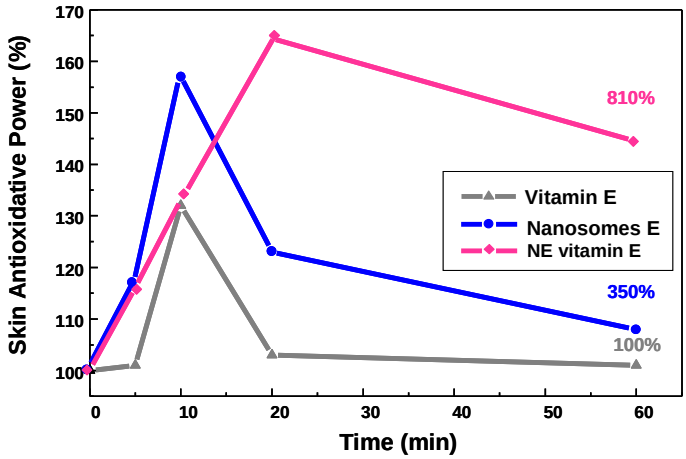


Due to the increased lipid concentration a higher encapsulation efficiency could be achieved which leads to an improved stability of EGCG and no changes in color (see CARRI ACTIVE GTE by NCD Ingredients; Germany).

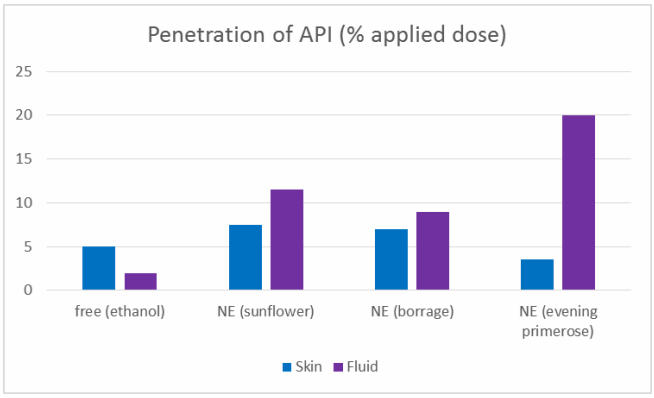
The penetration of the novel mNE vesicles into human skin as well as into human hair follicles was determined and gave superior results. The integrity of the vesicles in cosmetic and pharmaceutical formulations was checked and showed good stability data.

The NE with an oily core was developed to get vesicles with a high encapsulation efficacy of lipophilic components (up to 20%). The stability of sensitive substances could be enhanced by the encapsulation into these vesicles.

Also significantly higher dermal penetration of tocopherol with a prolonged efficacy was determined compared to conventional formulations being prepared by phospholipids (see CARRI ACTIVE tocopherol by NCD Ingredients; Germany).



Depending on the oil used for producing the nanoemulsion the depth in the penetration of active ingredients could be influenced (24 hrs).



Discussion:

The new nanoemulsions open the chance to encapsulate a huge variety of different components and to enhance their solubilty (e.g. polyphenols), their stability (e.g. vitamins) and their penetration depth into the skin (e.g. proteins or antioxidants).

These nanoemulsions consist of small nano-sized flexible vesicles with an unique homogenous size distribution (100-200 nm) and very low polydispersity index (<0.15)

In comparison to well known carrier systems like "Liposomes" or "Nanosomes" based on phospholipids – these new types of nanoemulsions allow higher encapsulation efficiency and improved penetration efficacy and offers new formulation strategies

1. M. Hoppel et al.; Journal of Pharmacy and Pharmacology , 66 (2013) 658-667
2. V. Klang et al.; European Jpurnal of Pharmaceutics and Biopharmaceutics, 80 (2012) 604-614
3. K. Jung et al.: SÖFW Journal 132 (2006) 38-44