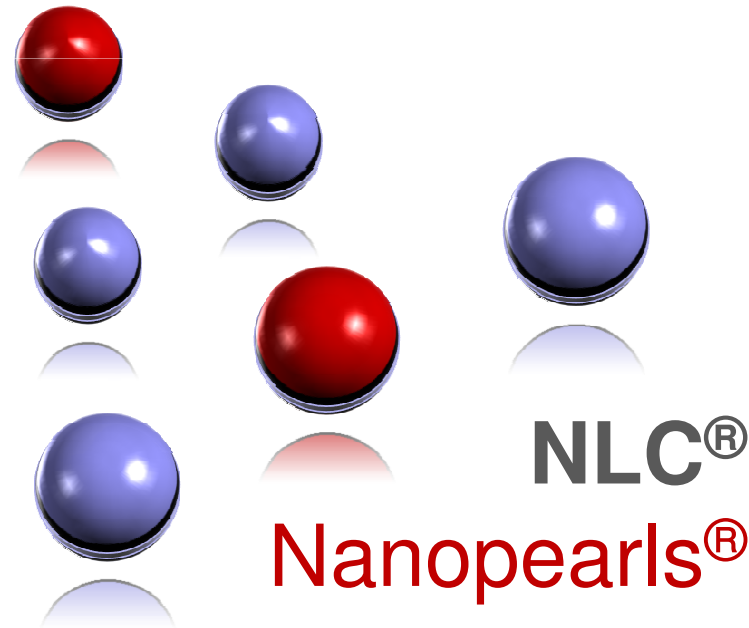


# Lipid Nanoparticles

for the delivery of actives  
in pharma, cosmetics & consumer care

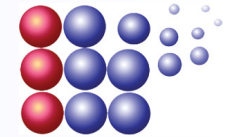
**Cornelia M. Keck**

PharmaSol GmbH  
Berlin / Germany



# Content

- ➔ Short look into history of liposomes
- ➔ Definitions & special features
- ➔ Structure of lipid particle matrix
- ➔ Production process & large scale production lines
- ➔ oral bioavailability – case studies
  - cyclosporine and testosteroneundecanoate (TU)
- ➔ dermal application
- ➔ Make-ability of products – products in the market
- ➔ Lipid Nanoparticles versus liposomes
- ➔ Summary



**Let us go back in cosmetic history.....**

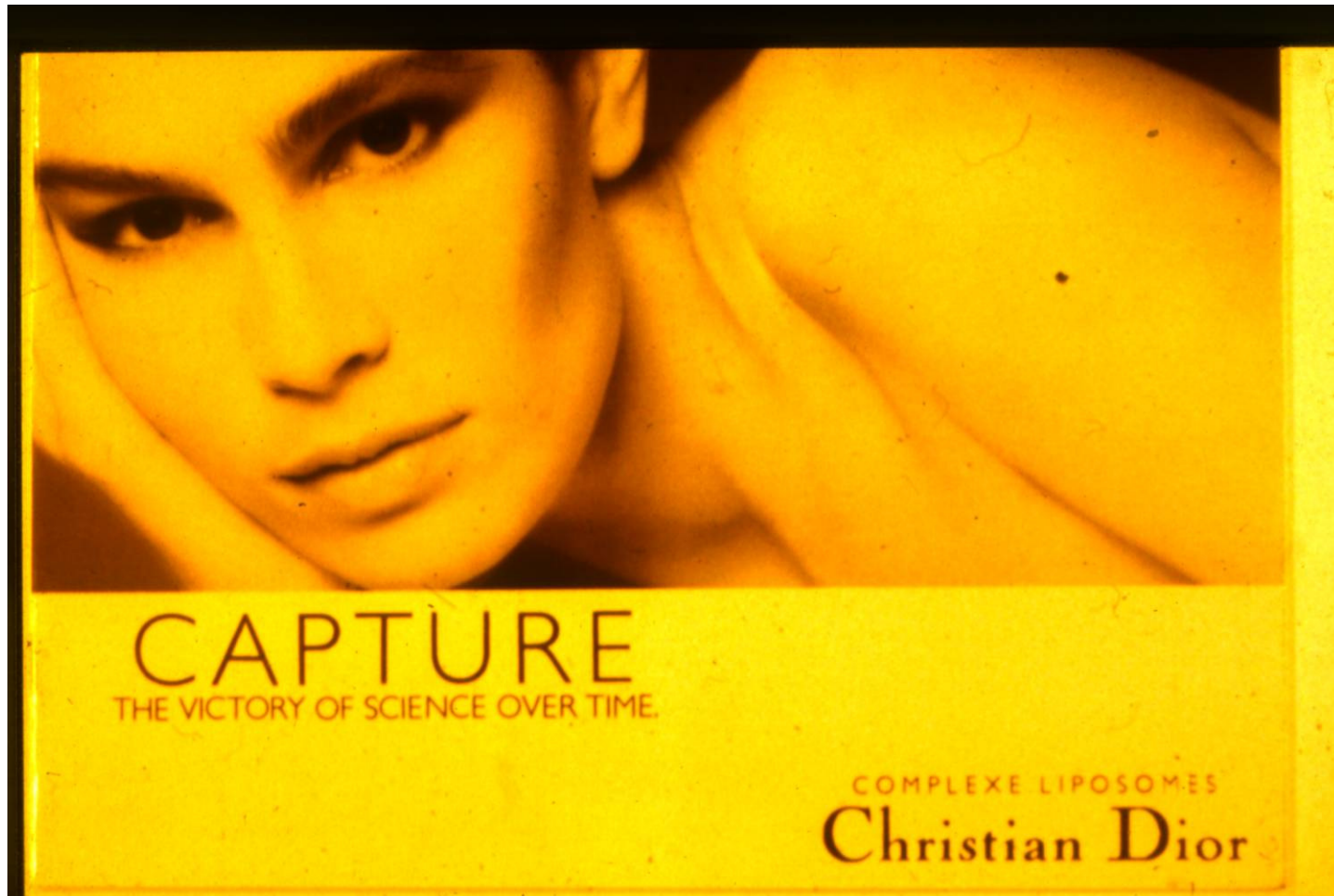
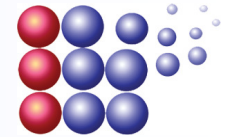
**1968 Invention of liposomes by Bangham**

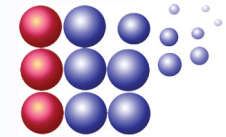
(liposome size in nanometer range, i.e. liposomes were nanotechnology)

**1986 Introduction of first cosmetic product to market:**

**Capture<sup>®</sup>** by Dior

**.....to learn from history for future innovative products**





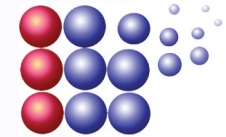
## **Extraordinary market success:**

Most people did not know what a liposome is

**but**

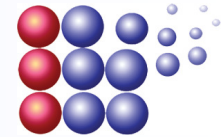
they bought the product when the name liposome was on the packaging!

**Association: liposome = quality**



## **Nanocarrier history since the liposomes**

- **many attempts** to develop a similar successful system
- examples: **nanoemulsions**  
**microemulsions**  
**multiple emulsions**  
**transfersomes** (by Cevc / Munich, Germany)



# 2005

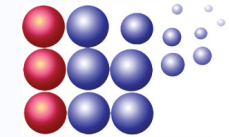
**The novel approach in cosmetics & pharma:**

**NLC = Nanostructured Lipid Carriers**

# Content

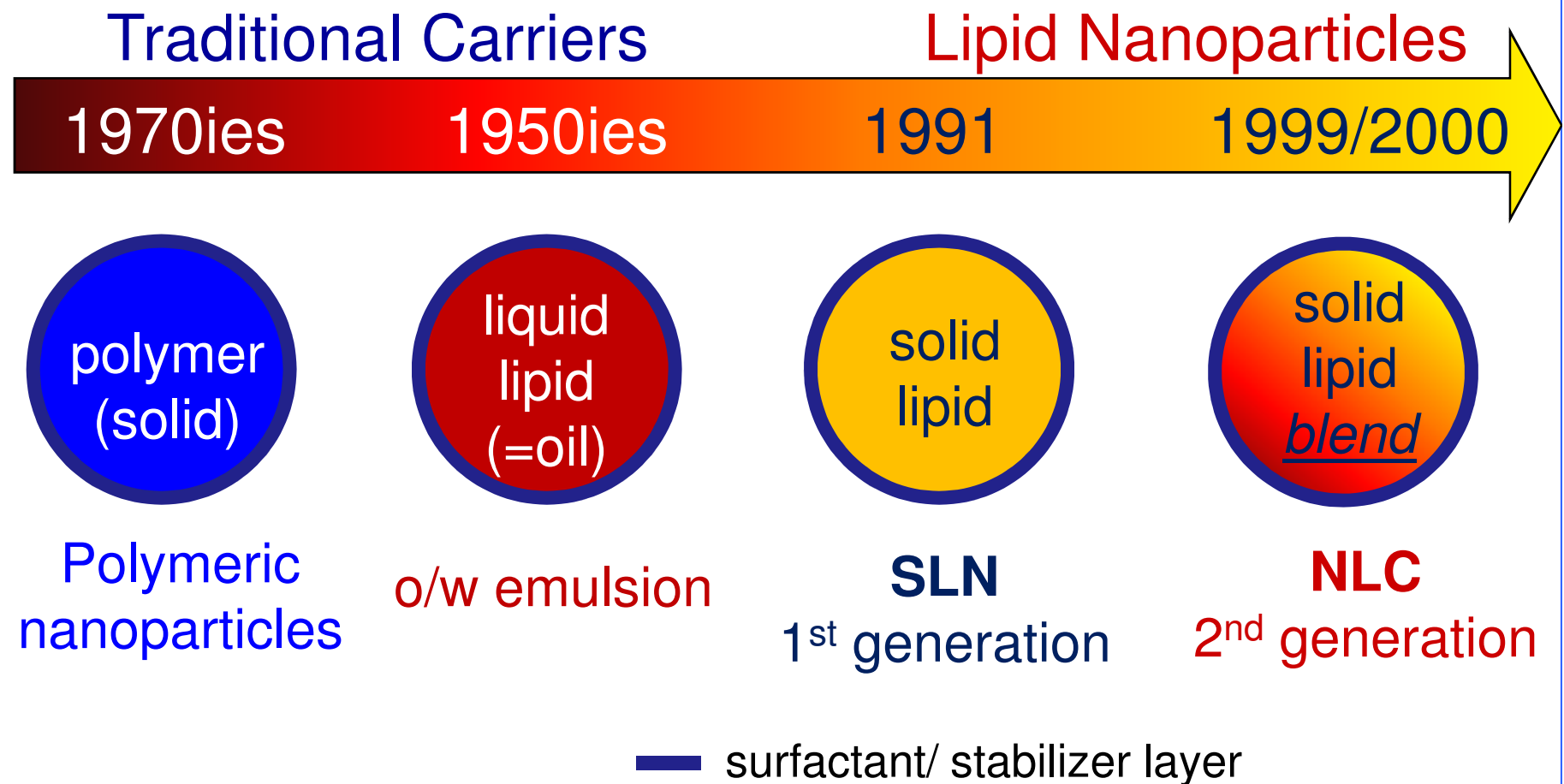
- ➔ Short look into history of liposomes
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## Development of

## lipid nanoparticle concept



➔ **Lipid Nanoparticles in solid state:**

- derived from o/w emulsions
- simply replacing the liquid lipid (= oil) by a solid lipid
- (i.e. solid at body temp.)

➔ **SLN** – Solid Lipid Nanoparticles

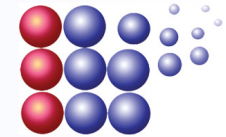
- produced from 1 solid lipid

➔ **NLC** – Nanostructured Lipid Carriers:

- produced from **blend of solid and liquid lipids**
- but particles are in solid state at body temperature

# Features

- ➔ Lipid nanoparticles with solid matrix
  - ➔ Mean particle diameter: 80 - 1000nm
  - ➔ Production by dispersion techniques, e.g. high pressure homogenization
  - ➔ **Loading\* with active compounds**, e.g.
    - ➔ 1-2% prednicarbate, prednisolone, cyclosporine etc...
    - ➔ 10% Benzophenone-3, Allure
    - ➔ 6% Retinol (Vitamin A)
    - ➔ 24% Tocopherol (Vitamin E)
- (\* calculated as %age of solid lipid matrix)



→ novel **particulate carrier**

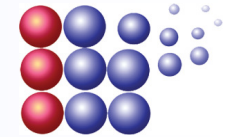
- for pharmaceutical / cosmetic / nutraceutical products

→ Nanoparticles **based on**

- regulatory **accepted excipients**
- physiological / natural solid lipids (renewable resources)

→ **Application** examples:

- **protection** of chemically labile active compounds &
- controlled release (**CR**) - because of solid matrix
- **penetration enhancement** of actives
- **dermal CR** (e.g. drugs, perfumes, repellents)
- **oral absorption enhancement**

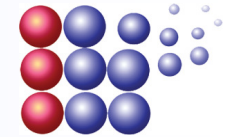


What exactly is the **improvement**?

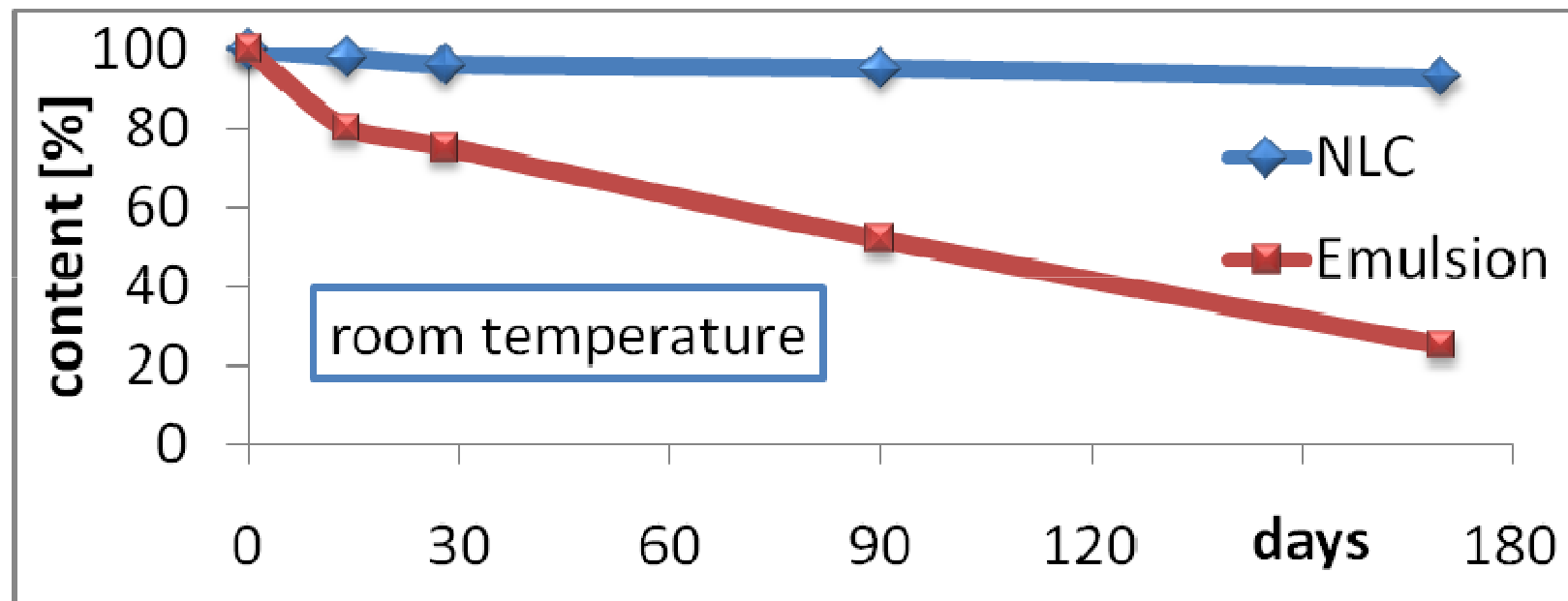
&

What are the **benefits of NLC**?

# Chemical stabilisation



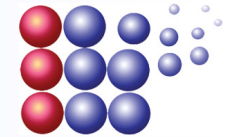
## ➔ Stability of Retinol: NLC vrs. Emulsion<sup>1</sup>



NLC: Compritol ATO 888 10% stabilized with Miranol C32

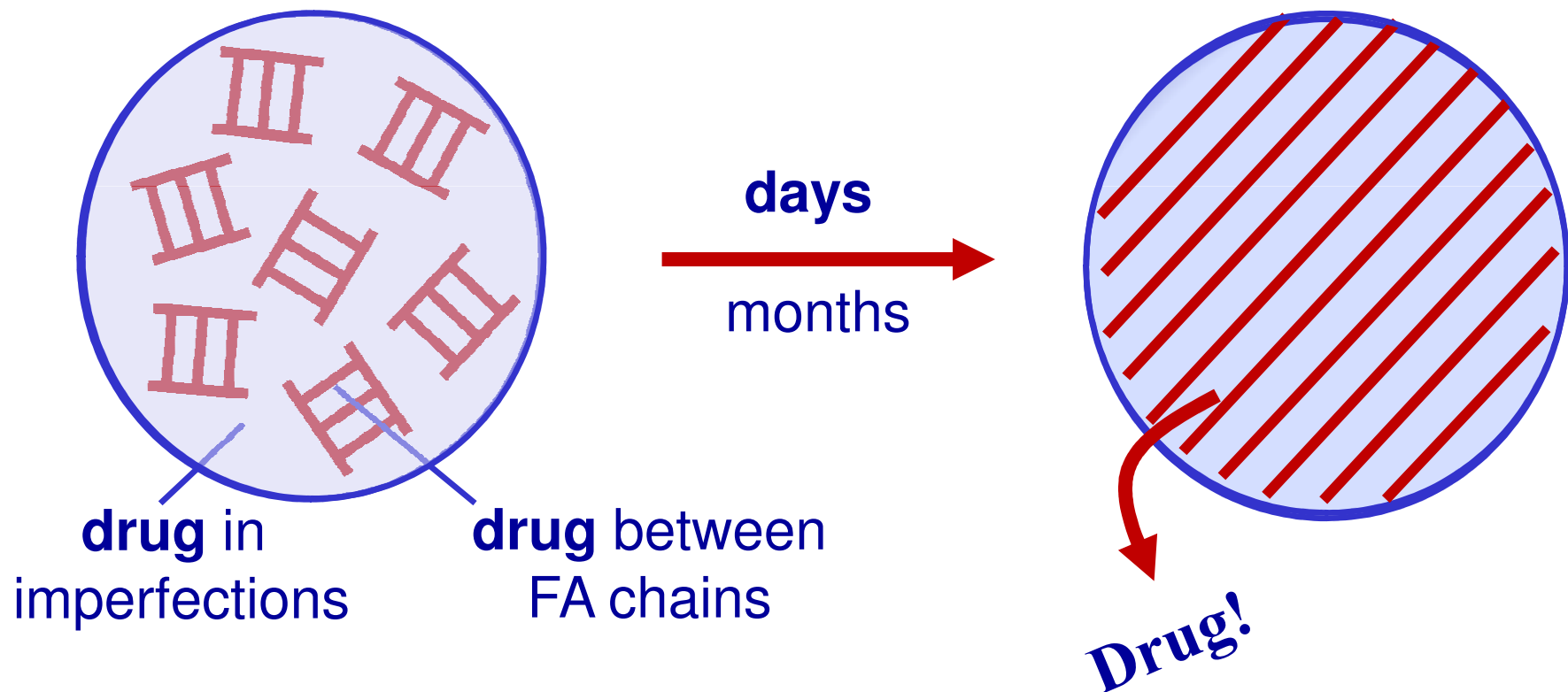
Emulsion: 10% Miglyol, 1.5% Tween 80

<sup>1</sup> V. Jennings (1999), Ph.D. thesis, Free University of Berlin

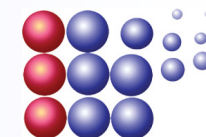


## Problems of “old” SLN

- ➔ formation of “perfect” crystalline structure during storage ( $\beta$  modification)  $\Rightarrow$  drug expulsion

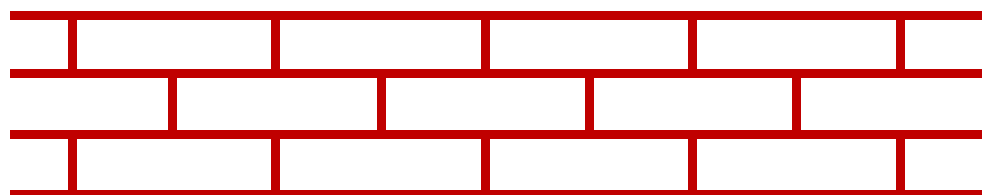


# NLC the more intelligent system



## SLN:

tendency to form perfect crystals → active expulsion

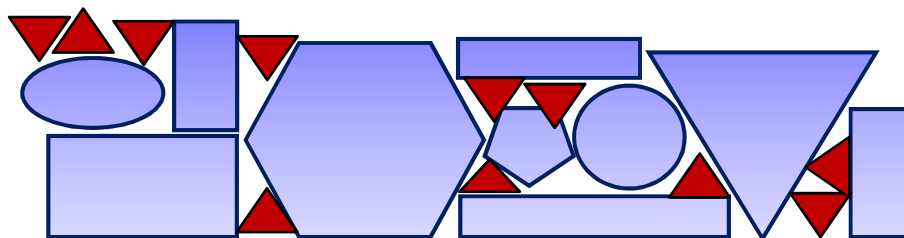


e.g. tristearin

## NLC:

inhibit crystallization process by mixing “spatially” very different molecules

→ imperfections in lattice → more space for drug



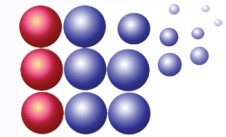
mixture  
solid & liquid lipids

▼ drug



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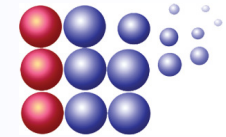


# PharmaSol Production Technology

## Basic principle:

### high pressure homogenization

- ➔ equipment can be **qualified & validated**
- ➔ **accepted by regulatory authorities** in production lines used for pharmaceutical parenterals
- ➔ **existing industrial production lines** for cosmetics / i.v. pharmaceutical parenteral emulsions can be used



## basic mixture:

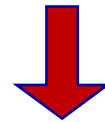
1. solid lipid
2. liquid lipid
3. emulsifier
4. (co-emulsifier)
5. water

NLC  
solid content > 30%

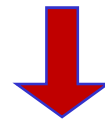
(according to SLN patent: solid lipids, 0.1% - 30% solid)

## Principle: High pressure homogenization

1. Melt lipid ( $>40^{\circ}\text{C}$ ) & dissolve active compound



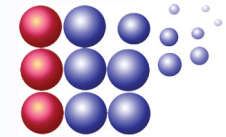
2. Disperse active-containing lipid melt  
in hot surfactant solution = **pre-emulsion**



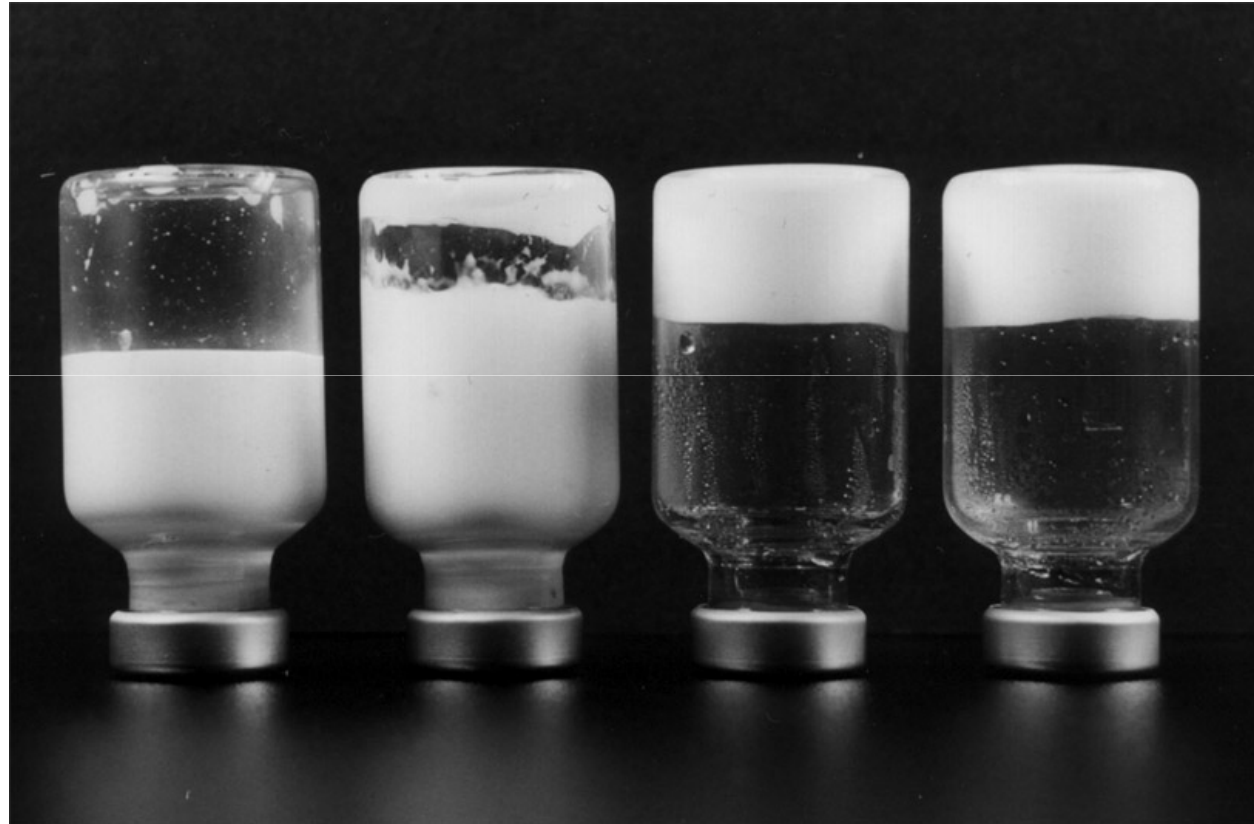
3. Homogenize pre-emulsion  
at  $>40^{\circ}\text{C}$ , 250 bar, 2 cycles = **nanoemulsion**

cooling ↓ solidification

**NLC**

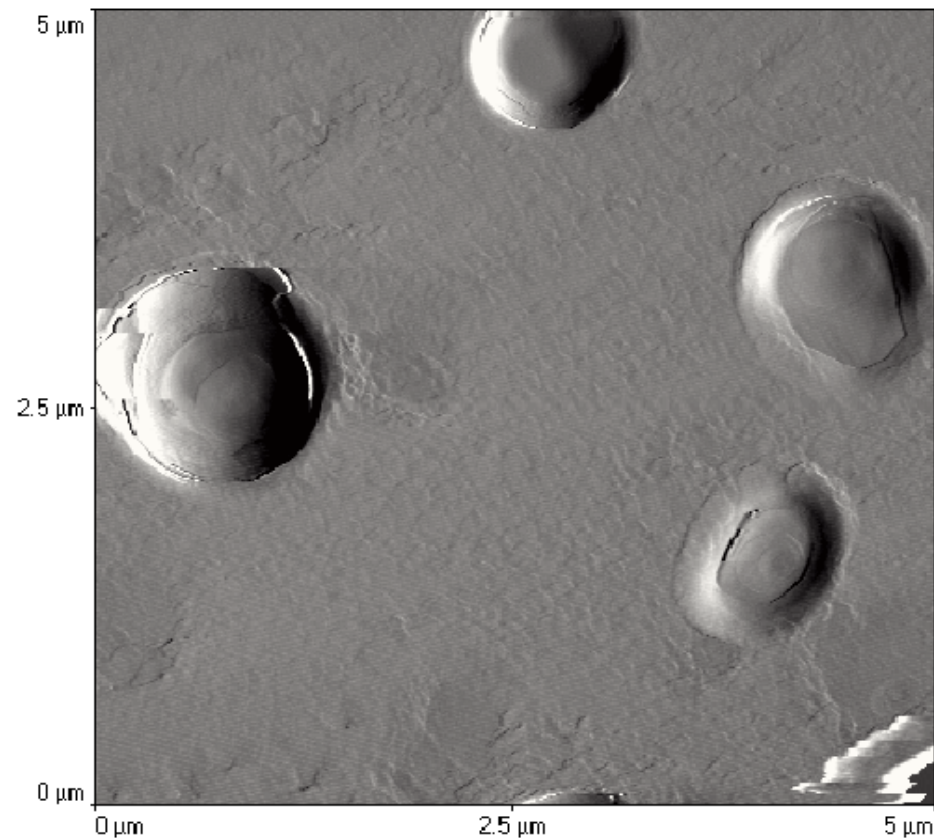


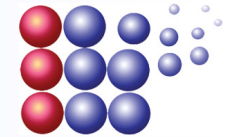
## Lipid nanoparticles of increasing concentration



conc: from 10% to about 50%

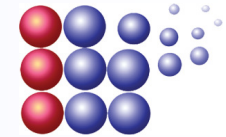
## AF-MICROGRAPH of Q10-loaded Nanoparticles





## LAB 40 discont. - 40 g batch

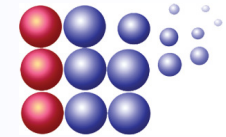




## LAB 60 - 2-10 kg batch







## Gaulin 5.5 - 150 kg/h

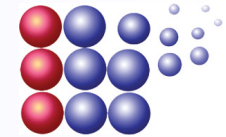


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# Oral administration

- ➔ **Example:** cyclosporine
- annual sales:** appr. 1.2 billion US \$
- “old” Sandimmun:** **problem:** variation in BA
- “new” Sandimmun:** **problem:** high plasma peak  
(microemulsion) (> 1000 ng/ml)
- target of previously developed SLN:**  
combine advantage of “old” & “new” Sandimmun  
i.e. no plasma peak & low variation in bioavailability



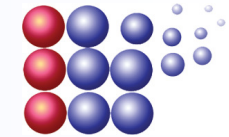
## Oral administration - cyclosporine study

animal: pigs (n=3)

application: via gastric catheter

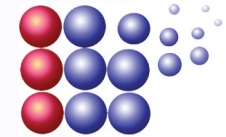
comparison:

- SLN dispersion vs.
- Sandimmun<sup>®</sup> Neoral vs

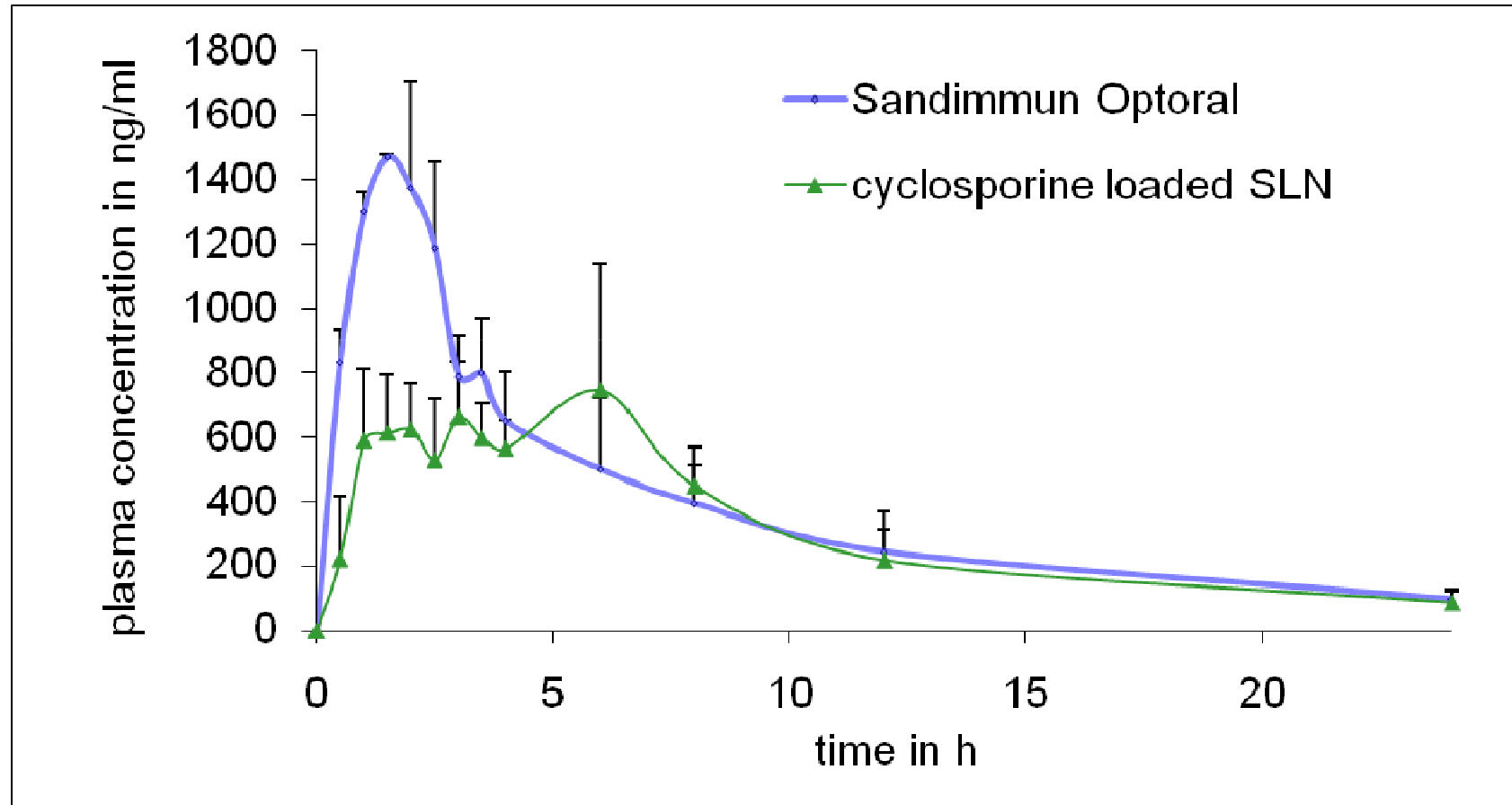


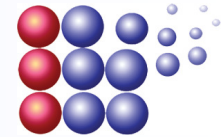
## one of the volunteers





## Oral cyclosporine - blood profiles

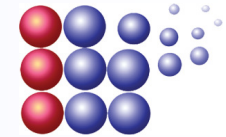




## Oral drug delivery with lipid nanoparticles

➔ What are the mechanisms?

➔ What are the advantages?



## **Mechanisms of oral lipid nanoparticles**

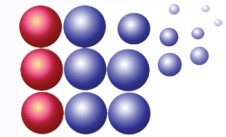
- ➔ general adhesiveness of very fine particles (nanoparticles)
- ➔ adhesion processes very reproducible (= little variation in bioavailability)
- ➔ lipids known to support absorption of a number of drugs\* (Trojan horse)

\* W. N. Charman, Proc. of 26 th Int. Symp. of CRS, Boston 1999



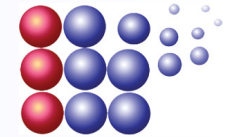
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## Product Andriol

- ➔ oral testosterone formulation on the market
- ➔ use as testosterone supplement therapy  
in case of lack of endogene production
- ➔ regular dose: 4 capsules a day
- ➔ very fragile & sensitive product:
  - has to be kept away from light and
  - stored at temperatures between 15°C-25°C

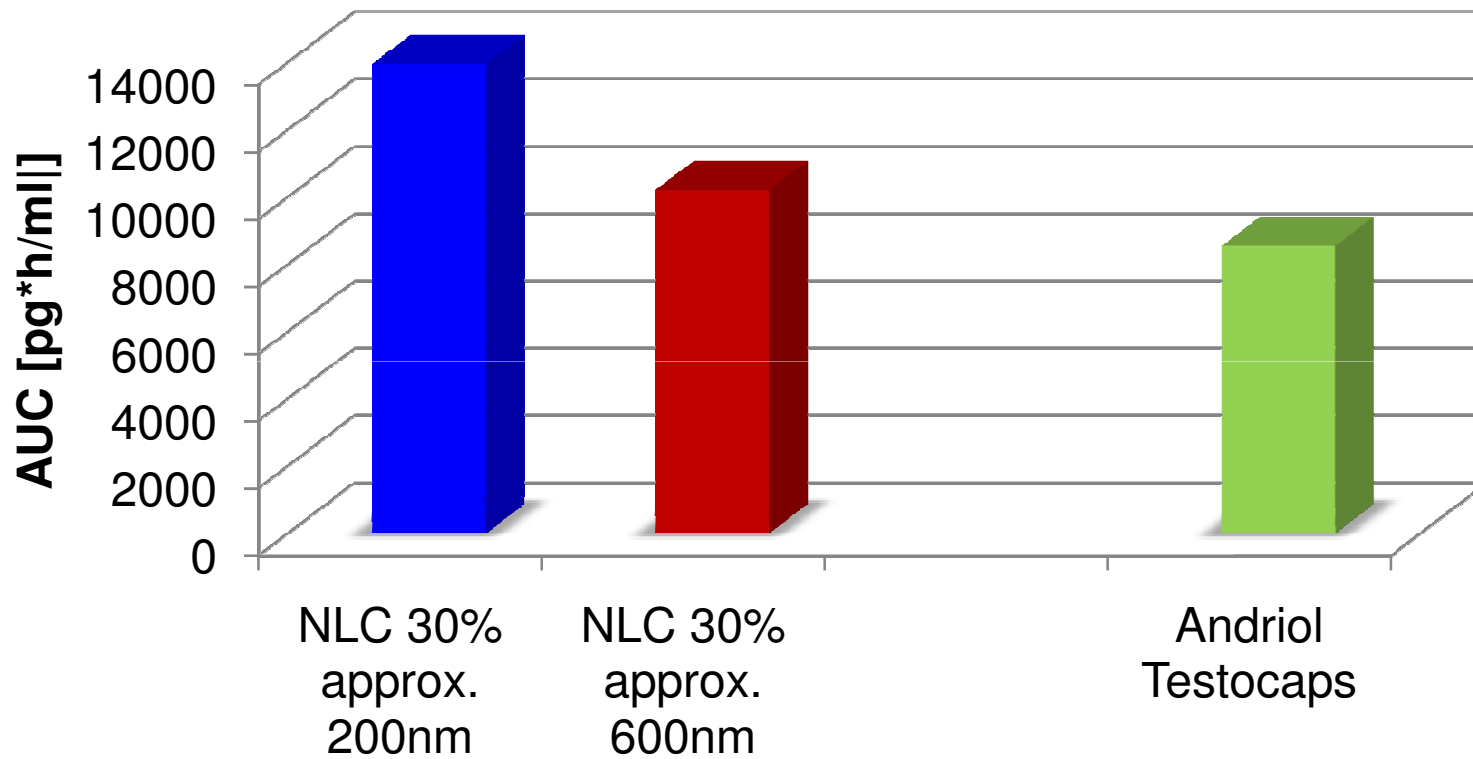


## Parameters of in vivo study

- ➔ comparison of **Andriol vrs NLC**
- ➔ 3 groups of 4 male Wistar **rats** were used
- ➔ animals were deprived from food 12 hours prior to sample administration
- ➔ **oral administration** by using a feeding needle
- ➔ blood sampling was performed at t=0h, 1h, 2h, 3h, 4h, 6h, and **8h** after administration. Approx. 400µl of blood were collected
- ➔ serum was stored at -80°C directly after  
centrifugation

# Results:

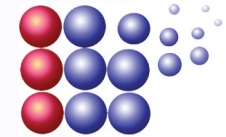
## AUC values after 8 hours



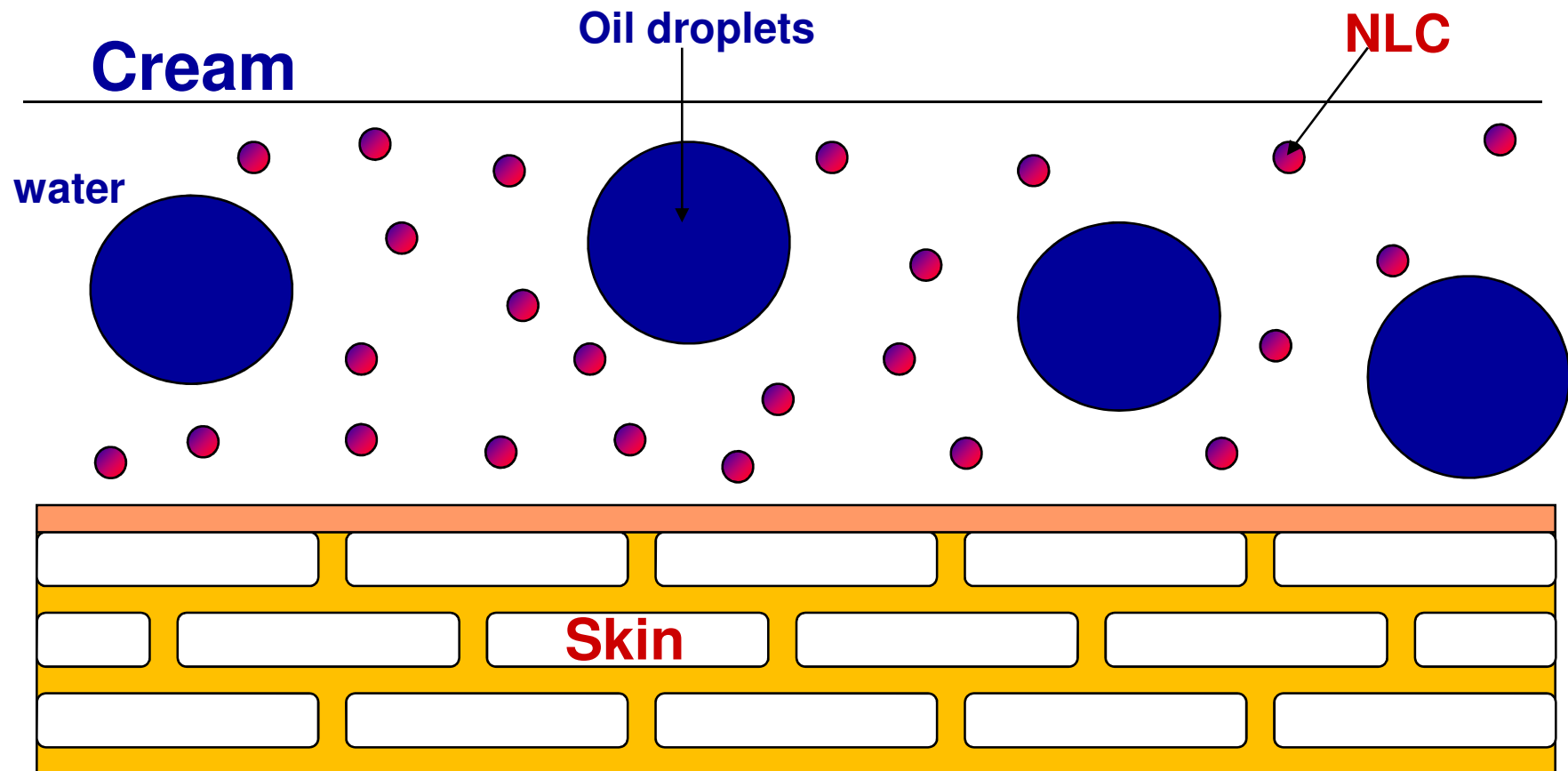
**smaller size (200 nm) is more effective**

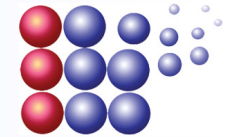
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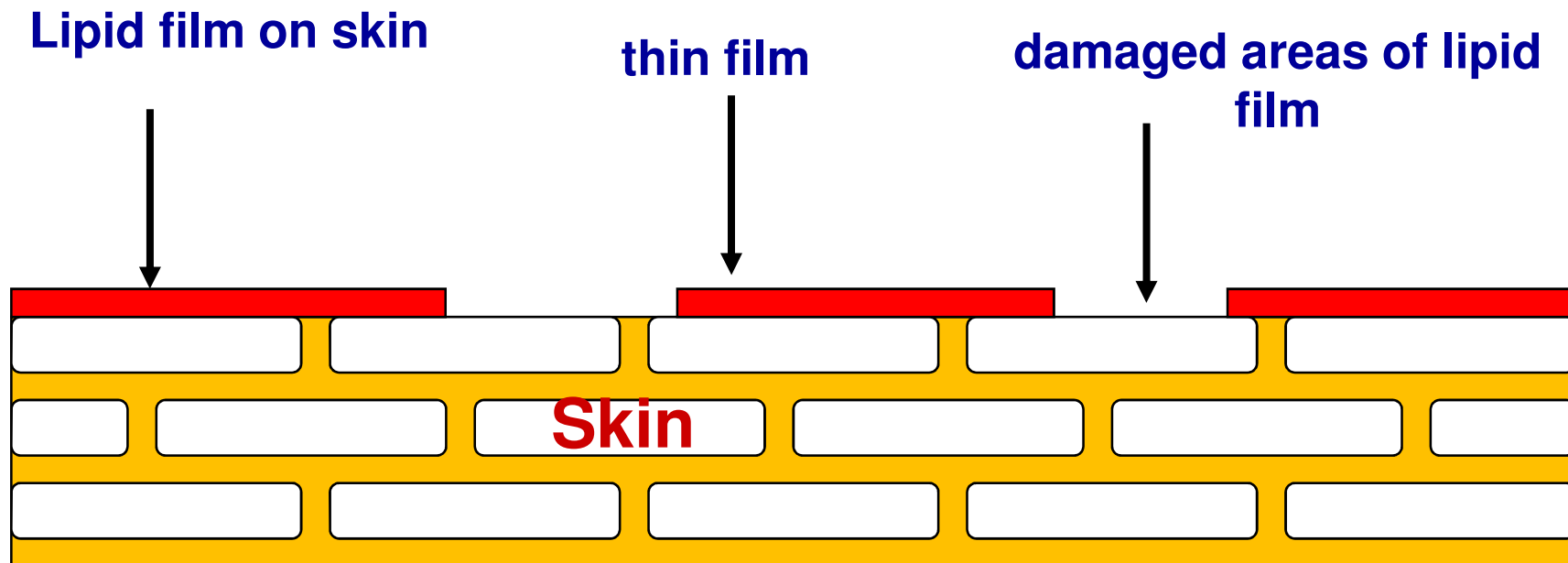


## How work NLC in cosmetic creams and lotions?

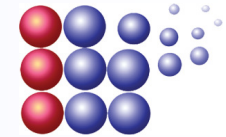




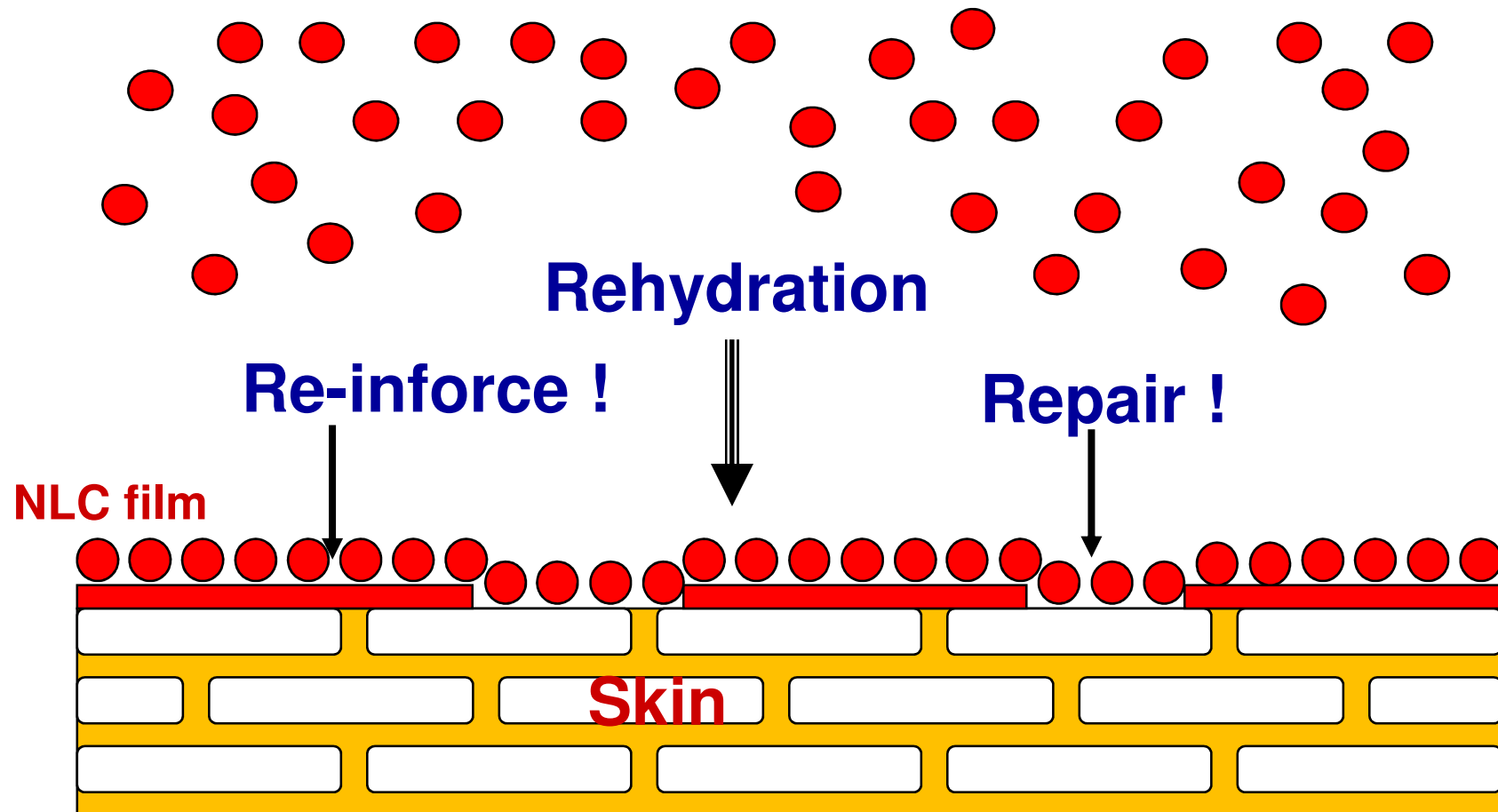
## Situation on damaged skin



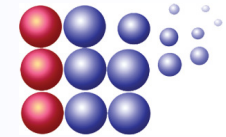
**Reduced protection, moisture loss, distorted cell function**



## Action of NLC in creams

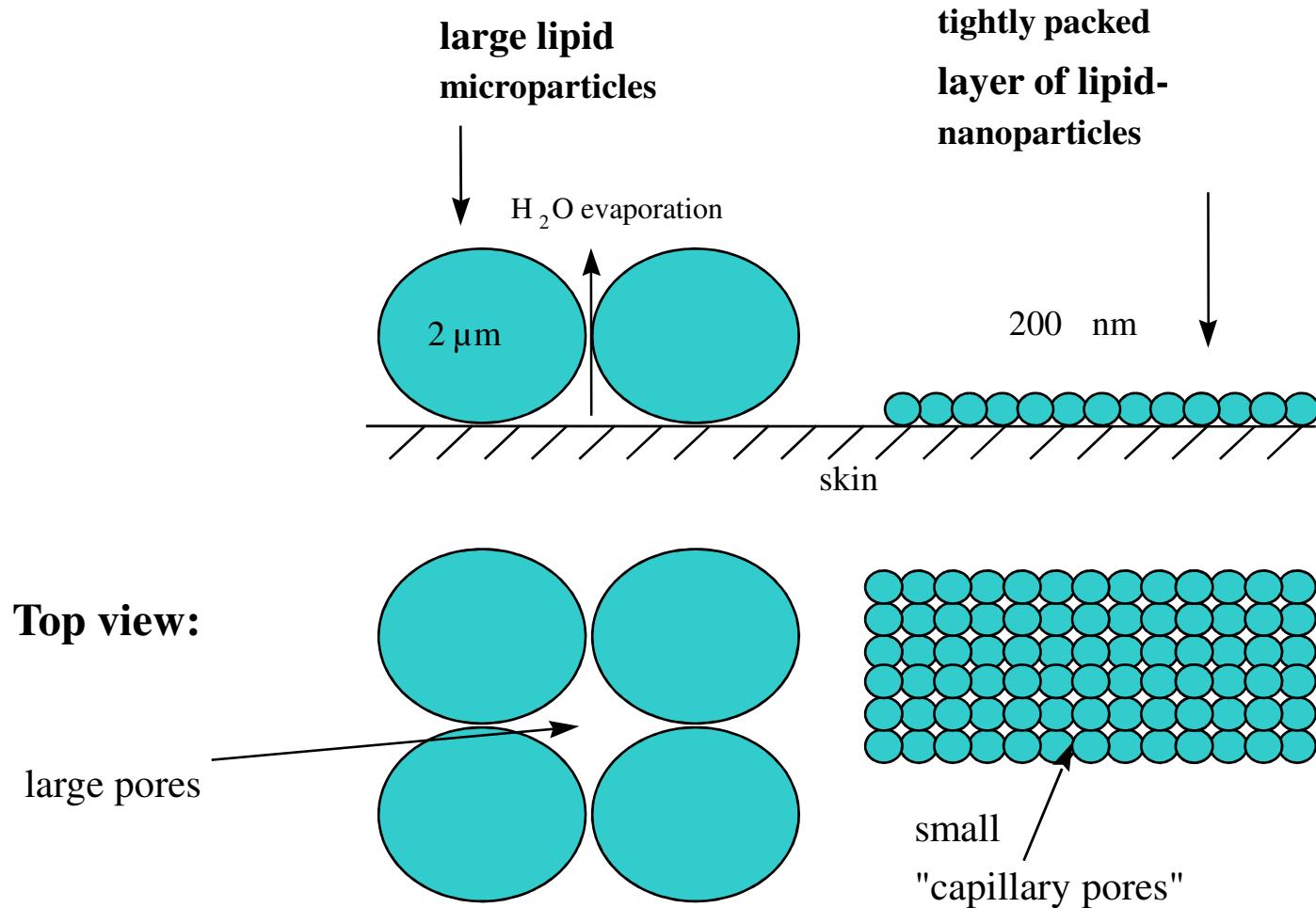


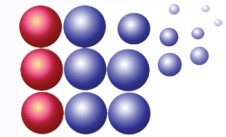




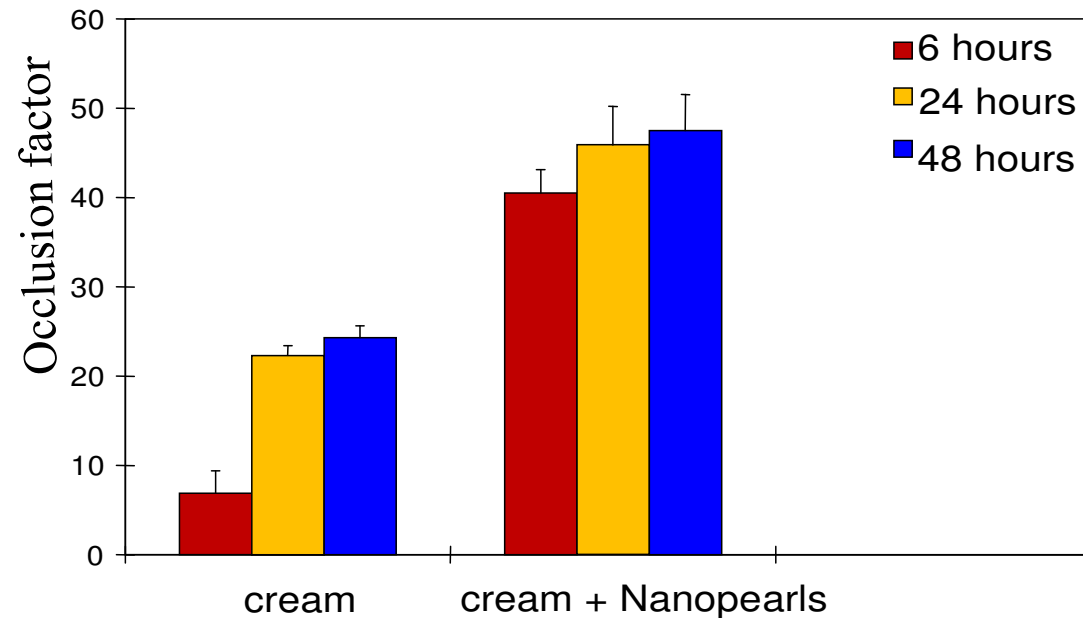
# Film formation on skin - principle mechanism

## Occlusion effect



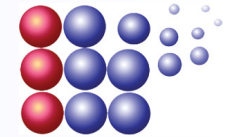


## Occlusion effect Cream vs. Cream with Nanopearls<sup>®</sup>



Occlusion factor of a commercial o/w cream (left) and a cream with incorporated Nanopearls<sup>®</sup> (right) as a function of time.

(Dingler et al., J. Microencapsulation, 1999)



## Increased penetration of actives

Penetration of:

**coenzyme Q10** and  
**Tocopherol**

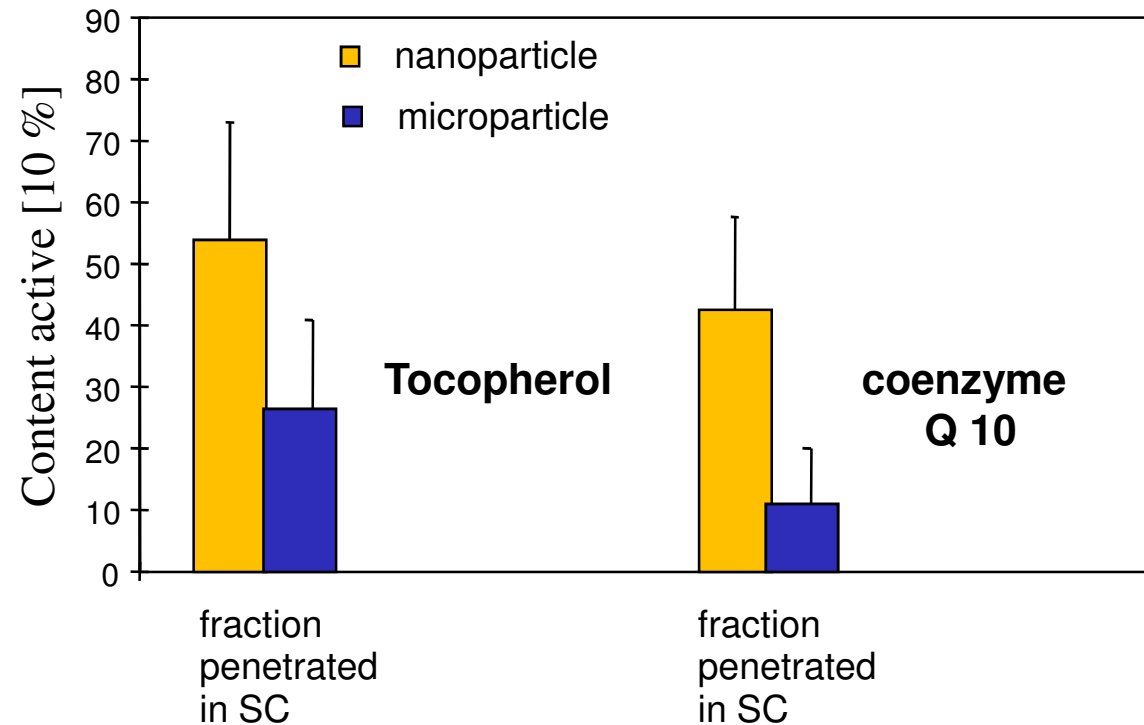
into the stratum corneum  
(SC) from aqueous

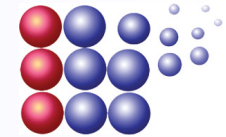
**NLC<sup>®</sup>** dispersion

vs.

solid lipid **microparticles**  
dispersion

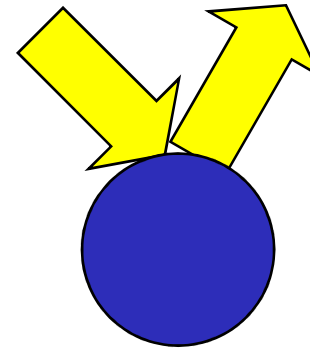
(cumulative amount of skin strips 2-9; skin strip 1 = non-penetrated fraction).



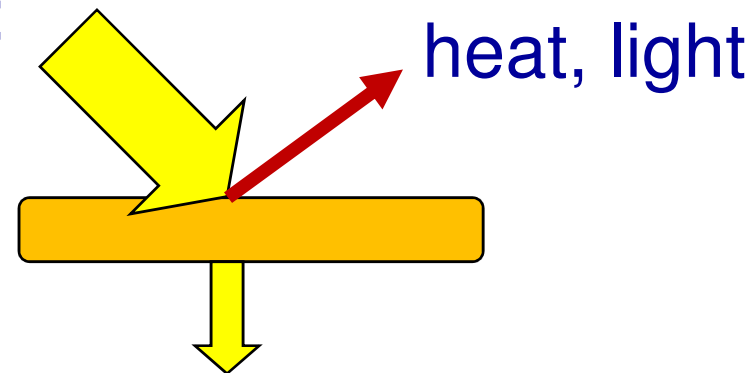


## Principle mechanisms of UV protection

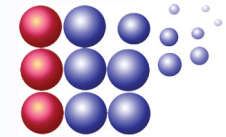
➔ Particular sunscreen: **UV**



• Molecular sunscreen:



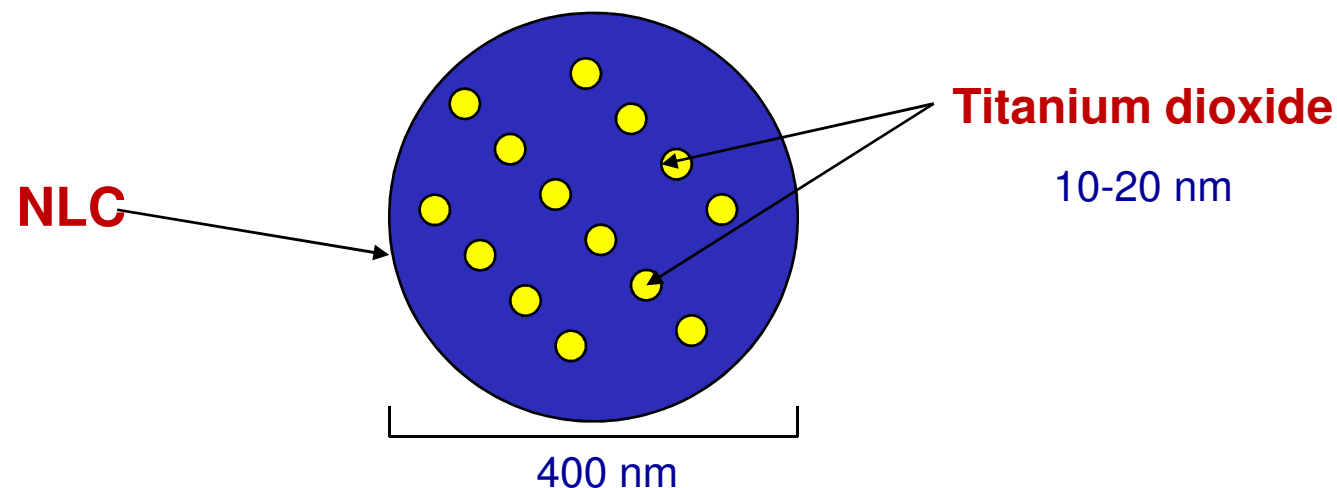
**synergistic effect: sunscreen in NLC**

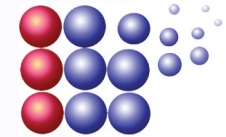


## Protection by incorporation of $\text{TiO}_2$ in NLC

**Potential Problem:**  $\text{TiO}_2$  might penetrate into skin, side effects

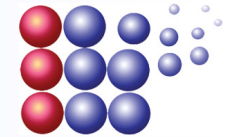
**Solution:** firm encapsulation of  $\text{TiO}_2$  into NLC  
should avoid/ minimize potential penetration into the skin





## Summary: Performance & Effects on Skin

- ➔ adhesiveness to skin
  - ➔ film formation, repair of stratum corneum
  - ➔ occlusion effect
  - ➔ skin hydration ↑
  - ➔ wrinkle depth ↓
  - ➔ increased / modulated penetration of actives
  - ➔ UV protection system
- ⇒ **i.e. skin healing, caring & protective effects!**



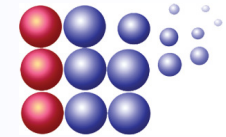
## **Examples for use in consumer care**

- ➔ sunscreen products (more efficient, “safe-nano”)
- ➔ mouth sprays/washes
- ➔ tooth pastes
- ➔ hair conditioning products
- ➔ disinfectant sprays
- ➔ insect repellents
- ➔ fabric softeners.....etc...etc.....

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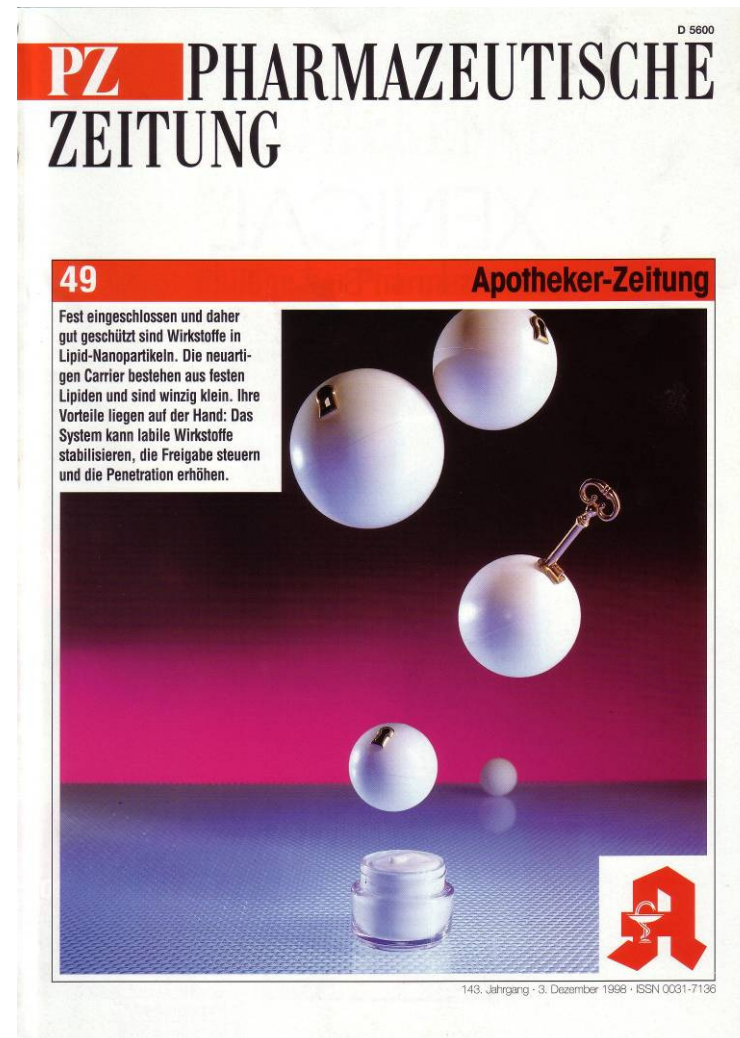




# Lipid Nanoparticles in the German Pharmaceutical Press

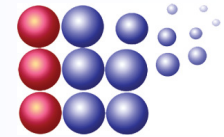
## Lipid Nanoparticles

## Smart delivery system for dermal actives



2005

PharmaSol  
The Solubility People



# NANOREPAIR Q10

DAS GEHEIMNIS VON ANTI-AGING



**Dr. RIMPLER**

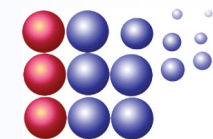


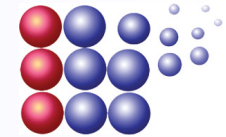
Welcome to the future!

No. 50

2005

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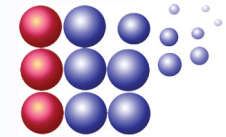


## Measurement of skin hydration: Corneometer

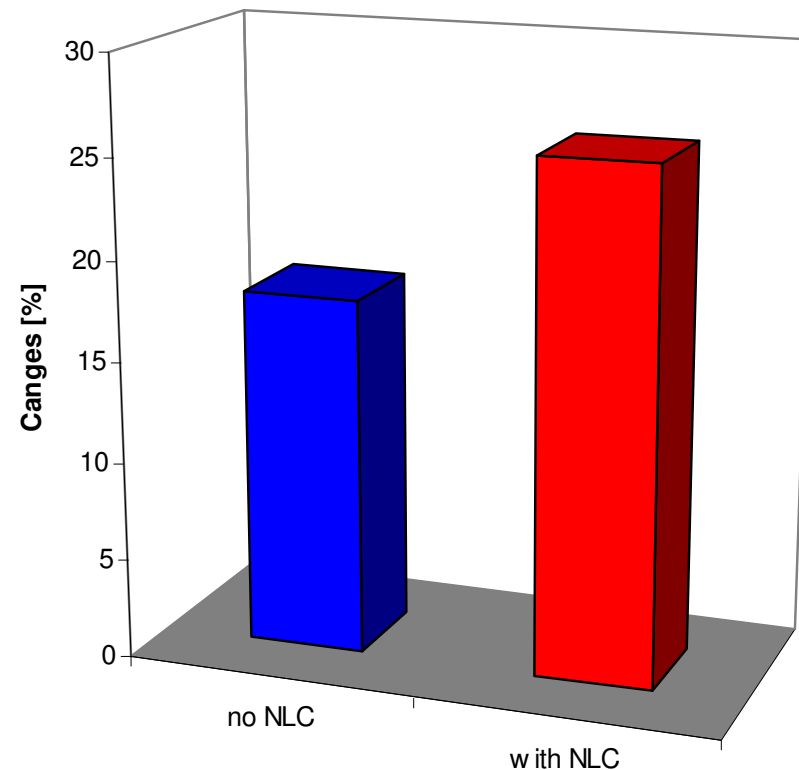


MPA5 with Corneometer 825  
(Courage and Khazaka, Köln)

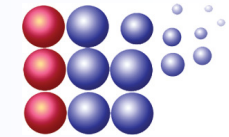
- Not invasive method
- Measuring time: 1 sec
- Principle: capacity changes
- Capacity changes are dependent upon the water content in stratum corneum ( $\epsilon = 78$  at  $32\text{ }^{\circ}\text{C}$ )



## Q10 skin hydration in vivo: NLC vs. NLC-free



**Long-term study, 42 days,  
measurement 12 h after last application**



South Korean

**Top Model no. 1**

for the introduction of the

**NLC Supervital** products

in the pretigious line

**IOPE**

**by Amore Pacific**

**1. Sept. 2006**

No. 54

건성피부의  
다양한 피부노화를  
걱정한다 **78%**

피부가 생명을 되찾으면,  
모든걸 되찾는다

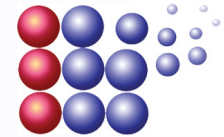
아이오페 슈퍼바이탈

**IOPE**

IOPE  
SUPER VITAL  
ultra moist cream



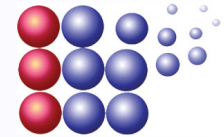
**PharmaSol**  
The Solubility People





# Products under PharmaSol license

**PharmaSol**  
The Solubility People



Fußgesundheit auf dem  
neuesten Stand  
der Wissenschaft

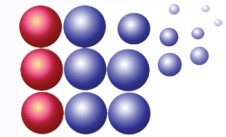


Fußgesundheit aus professionellen Händen



- ✓ Regeneriert raue, trockene und spröde Fußhaut
- ✓ Spürbar geschmeidige Füße durch patentiertes Nano-Lipid-Pflegesystem
- ✓ Für Diabetiker geeignet

**Regenerationscreme Intensiv**  
Intensivpflege für trockene und spröde Fußhaut



## **Dr. Rimpler GmbH – partner of PharmaSol**

for introducing NLC technology



### **Dr. Rimpler GmbH**

Neue Wiesen 10

D-30900 Wedemark

Founded 1986 by Prof. Dr. Manfred Rimpler

**Health & Care** development, production

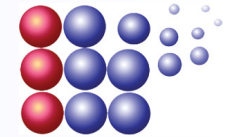
Cosmetic-GMP & approved by §13 AMG

### **Company Profile**

54 employees

Production capacity 2500 kg per shift

**[www.Rimpler.de](http://www.Rimpler.de)**

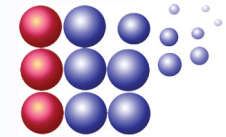


## Examples of commercially available loaded NLC

- ➔ Coenzyme Q10
- ➔ Vitamin E
- ➔ Tocotrienol
- ➔ Retinol
- ➔ Black current oil (BCO)
- ➔ KuKui oil
- ➔ Makui oil
- ➔ use of special lipids: e.g. Carnauba wax

# Content

- ➔ Short look into history of liposomes
- ➔ Definitions & special features
- ➔ Structure of lipid particle matrix
- ➔ Production process & large scale production lines
- ➔ oral bioavailability – case studies
  - cyclosporine and testosteroneundecanoate (TU)
- ➔ dermal application
- ➔ Make-ability of products – products in the market
- ➔ Lipid Nanoparticles versus liposomes
- ➔ Summary



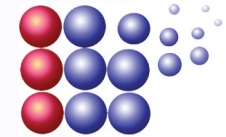
## **Technical advantages of NLC vs. liposomes**

### **Problems of liposomes:**

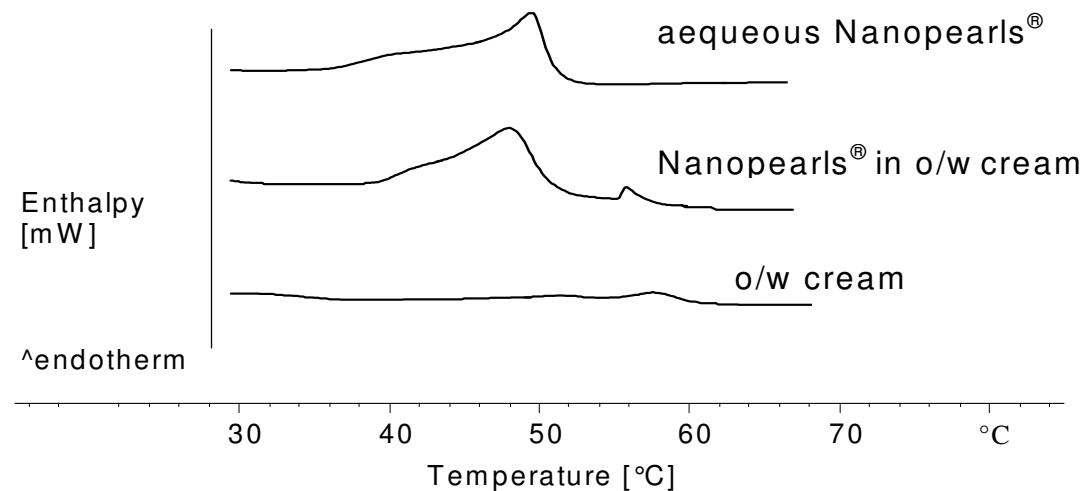
1. physical stability in o/w systems
2. quantitative analysis difficult
3. chemical stability of labile actives

### **Advantages of NLC:**

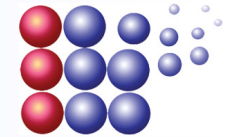
1. high physical stability due to solid state of particle matrix
2. physical stability easy to prove (DSC)
3. chemical stabilisation of actives due to solid character



## Physical stability: Incorporation into cream



Melting peaks of Nanopearls® aqueous dispersion and after its incorporation into an o/w cream  
(reference: DSC thermogram of cream - no melting event).



## Chemical stability of incorporated actives

### Nanoemulsions and Liposomes:

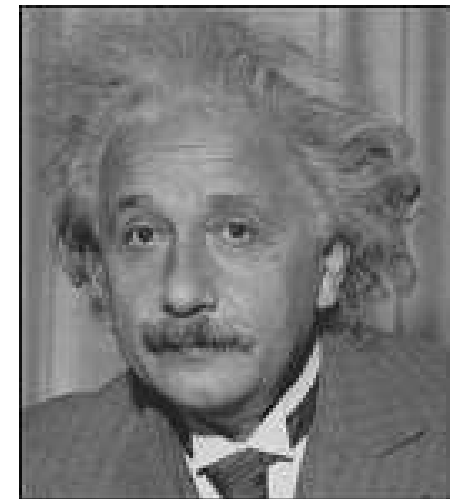
#### Limited protection of actives because:

- lipophilic actives are in exchange with water due to fluid character of oil droplet / liposome bilayer
- hydrophilic actives in liposome core diffuse through bilayer in outer water phase

### NLC:

#### Enhanced protection of actives:

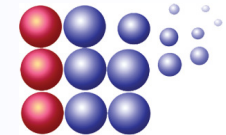
- solid state minimizes exchange of actives with water phase (diffusional law by Einstein)



# Content

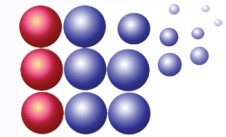
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- ➔ **Summary**





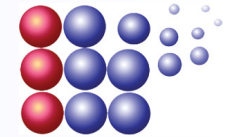
## Summary Pharmaceuticals

- NLC can be made with regulatory accepted excipients
- NLC are produced with production technology already available in pharmaceutical industry
- Make-ability of technology proven by cosmetics products on the market
- primary delivery routes:
  - dermal application
  - oral administration (poorly soluble drugs)



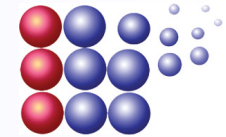
## Summary Cosmetics/Consumer Care

- unloaded NLC have own skin effects
- loaded NLC increase chemical stability & “bioactivity” of actives
- NLC can easily be incorporated into creams, etc.
- physical stability high, easy to prove quantitatively
- extremely short time from invention to market (6 years)
- Products: > 40 in about 4 years  
(including La Prairie /Beiersdorf group)



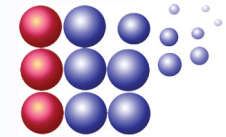
## Perspectives for Nutraceuticals

- increase bioavailability of poorly soluble plant actives
- increase bioavailability of actives like coenzyme Q10 (nano Q10 is 100% available!)
- delivery of unsaturated fatty acids (incl. fish oil NLC)
- NLC for delivery of lipophilic vitamins in a diet
- NLC as physically stable taste enhancer?



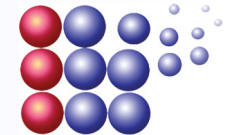
## NLC Product Examples





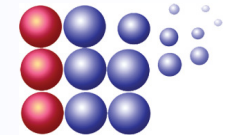
## Summary – SLN/NLC in general

- ➔ Lipid nanoparticles can be made with regulatory **accepted excipients** (lipids, surfactants)
- ➔ they are produced with **production technology** already **available in pharmaceutical industry**
- ➔ **Make-ability of technology proven by cosmetics products on the market**
- ➔ **primary delivery routes:**
  - **dermal application**
  - **oral administration (poorly soluble drugs)**
  - **intravenous (replacement of liposomes !)**



## Summary – NLC for oral delivery

- ➔ NLC proved effective in BA enhancement of the drugs cyclosporine, fenofibrate, T and TU
- ➔ **fenofibrate**: competitive products to exclusive nanocrystal products are possible by using NLC as alternative technology
- ➔ **especially for TU:**
  - a competitive product to Andriol seems feasible: same BA, but only 1 tablet (NLC – lipid 1)
  - higher BA with NLC also possible by optimizing NLC - lipid 2: smaller particle size



## Summary – perspectives for Nutraceuticals

- ➔ increase bioavailability of poorly soluble plant actives (e.g. rutin, hesperidin etc....)
- ➔ increase bioavailability of actives like coenzyme Q10 (nano Q10 is 100% available!)
- ➔ delivery of unsaturated fatty acids
  - incl. fish oil NLC
- ➔ NLC for delivery of lipophilic vitamins in a diet
- ➔ NLC as physically stable taste enhancer?