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® by Dior

…..to learn from history for future innovative products
CAPTURE
THE VICTORY OF SCIENCE OVER TIME.

COMPLEXE LIPOSOMES

Christian Dior
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
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Development of lipid nanoparticle concept

Traditional Carriers
- Polymeric nanoparticles
  - polymer (solid)
- Liquid lipid (o/w emulsion)
  - liquid lipid (=oil)

Lipid Nanoparticles
- First generation
  - SLN
  - solid lipid
- Second generation
  - NLC
  - solid lipid blend

Surfactant/stabilizer layer

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The Solubility People

No. 9
Definitions

**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**

- **NLC:** Compritol ATO 888 10% stabilized with Miranol C32
- **Emulsion:** 10% Miglyol, 1.5% Tween 80

Problems of “old” SLN

formation of “perfect” crystalline structure during storage (β modification) \(\Rightarrow\) drug expulsion

- drug in imperfections
- drug between FA chains

days \(\Rightarrow\) months

Drug!
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)
Production

Principle: High pressure homogenization

1. Melt lipid (>40 °C) & dissolve active compound

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

3. Homogenize pre-emulsion at >40°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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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® Neoral vs
one of the volunteers
Oral cyclosporine - blood profiles

![Graph showing plasma concentration over time for Sandimmun Optoral and cyclosporine loaded SLN.](image)
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 26th 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

- NLC 30% approx. 200nm
- NLC 30% approx. 600nm
- Andriol Testocaps

smaller size (200 nm) is more effective
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How work NLC in cosmetic creams and lotions?

Cream

Oil droplets

NLC

water

Skin
Situation on damaged skin

Lipid film on skin
thin film
damaged areas of lipid film

Reduced protection, moisture loss, distorted cell function
Action of NLC in creams

Rehydration

Re-inforce!

Repair!

NLC film

Skin
Film formation on skin - principle mechanism

Occlusion effect

large lipid microparticles

H₂O evaporation

2 µm

skin

200 nm

tightly packed layer of lipid-nanoparticles

Top view:

large pores

small "capillary pores"
Occlusion effect
Cream vs. Cream with Nanopearls®

Occlusion factor of a commercial o/w cream (left) and a cream with incorporated Nanopearls® (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® 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: heat, light

synergistic effect: sunscreen in NLC
Protection by incorporation of TiO$_2$ in NLC

**Potential Problem:** TiO$_2$ might penetrate into skin, side effects

**Solution:** Firm encapsulation of TiO$_2$ into NLC should avoid/ minimize potential penetration into the skin.

![Diagram showing NLC with encapsulated titanium dioxide particles](image)
## Summary: Performance & Effects on Skin

- Adhesiveness to skin
- Film formation, repair of stratum corneum
- Occlusion effect
- Skin hydration $\uparrow$
- Wrinkle depth $\downarrow$
- Increased / modulated penetration of actives
- UV protection system

$\Rightarrow$ 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
NANOREPAIR Q10
DAS GEHEIMNIS VON ANTI-AGING

Dr. RIMPLER
Welcome to the future!
Measurement of skin hydration: Corneometer

- Not invasive method
- Measuring time: 1 sec
- Principle: capacity changes
- Capacity changes are dependent upon the water content in stratum corneum ($\varepsilon = 78$ at 32 °C)

MPA5 with Corneometer 825 (Courage and Khazaka, Köln)
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
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
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
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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)
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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?