Curvature modifications ‘ECPP’

Cosurfactant

Cosolvent

Typical $H_2$ (at 25°C)

Fluid $H_2$ (at 25°C)

addition of Transcutol or ethanol

Typical $H_2$ (at 25°C)

free water

hydration water

TAG

GMO

Transcutol

Transcutol (at 1:1 GMO:Transcutol molecular ratio)

ethanol

ethanol (at 1:1 GMO:ethanol molecular ratio)
Effective Critical Packing Parameters

The use of third component
Cosurfactant/Cosolvent

Mathematical models, energy calculations, geometry considerations, vdw and hydrogen bonding interactions

- **Alcohols** molecules to compete with the hydration water at the head groups
- **Triglycerides** (TAG) to space the tails of the surfactant
- **Transcutol** to interact both with heads and tails
- **Phospholipids**

* Calculations by Dr Vesselin Kolev from Bulgaria
Discontinuous cubic mesophase

Elongated (tube-like) discontinuous mesophase of condensed micelles with cubic symmetry
Cryo-TEM images of $Q_L +$solubilizates (guest molecules)

- $Q_L +$ Pytosterols
- $Q_L +$ Na-DFC

Guest molecules disorder the structure
Guest molecules increase order
Fluid Hexagonal mesophases
(at room-temperature)
Characteristics of Reverse Hexagonal

Dense packing of cylindrical micelles, arranged in 2D hexagonal lattice.
Constructing $H_{II}$ Mesophase at 25°C

The concept: ECPP

Tricaprylin C8:C8:C8

Multiple mesophases with excess liquid

Glycerol monooleate

Amar-Yuli and Garti Colloids and Surfaces, B: (2005), 43(2), 72-82

How to modify the Hii° mesophases?
Less- and more-ordered $H_{II}$ Structures

- Oil/GMO ratio
- Water content
- Mixed surfactants
- Temperature

We can control:
- Diameter of tube
- Length of tubes
- Thickness of lipid layer
- Lattice parameter

Solubilization of bioactives

Small bioactives ✓
( nutraceuticals, aromas, antioxidants, pesticides)

Peptides ✓

Small proteins ✓

Enzymes ✓

Protein-based drugs ✓

DNA ✓

Lysozyme (LSZ)- Solubilization and stability

- Water (13%) cylinders diameter is 17Å, while LSZ (14KDa) Rg is 30Å.

  - In **water-rich** systems lattice parameter in the presence of LSZ decreases, but the channels diameter increased (GMO dehydration.)
  - In **water-poor** systems lattice parameter does not change but the channels shrink (volume restriction)

- LSZ interacts with the water and with the interfacial amphiphilic layer and is **intercalated within the water cylindrical channels**

<table>
<thead>
<tr>
<th>Water conc. (wt%)</th>
<th>Cylinders’ diameter (Å)</th>
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<tbody>
<tr>
<td>13</td>
<td>17</td>
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<td>16</td>
<td>22</td>
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<td>20</td>
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<td>23</td>
<td>29</td>
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</table>
Delivery of Bioactives

- **Dermal**
- **Transdermal**
  - Pigs skins (Franz cells) and rats skins
- **Trans membrane**
  - Caco-2 cells, Rats oral intake (drugs) and human oral (nutraceuticals)
Transport & Bioavailability

1. Drug molecule

2. Enhanced Release

3. Selective transport

4. Vehicles are not transported

5. Surfactant is not transported
Cumulative Na-DFC Penetration (pigs’ skin-Franz Cells)

**The problem:** low bioavailability

Study 1

\[
Q_t = V_r \cdot C_t + \sum_{i=0}^{t-1} V_s \cdot C_i
\]

\[
\frac{Q_t}{S} = \left[ \mu g / cm^2 \right]
\]

Linear increase of cumulative Na-DFC penetration—**Fick’s law of diffusion control**

1% DFC in QL
Dose 1 mg of DFC.
Lotion-transdermal
Plasma levels of diclofenac sodium salt
(rats’ skin)

Plasma levels (ng/ml)
- Voltaren Emulgel
- Our technology

![Graph showing plasma levels over time](image)

Time (hours)
0 1 2 4 6 8
Transdermal delivery of cyclosporin A (rats skins)

The problem: Low bioavailability

The cyclosporin A penetration from our mesophases is:

Higher than from solvents and their mixtures

27-40 times higher than from competing systems available today.

*in collaboration with Prof Hesson Chang, KIST, Korea

Membrane piercing agents (Franz cells)

Pore-forming agents

A

B

C

D

E

F

G

H

I

J

K

L

M

N

O

P

Q

R

S

T

U

V

W

X

Y

Z

Release (µg/cm²)

- no RALA
- +0.7% RALA
- +1.4% RALA

Diclofenac concentration (µg/cm²)

Permeation coefficients

Kp (µg/hr·cm²)/1000

RALA concentration (vol%)

0

0.7

1.4

'On demand' release

Stimuli-responsive nano carriers

* by concentration change
* by temperature
* by shear or pressure
* by adding PC and polyarginine
* by membrane piercing agents
Temperature-Dependence Release (Trans-4-decenal)

18% WT85-15 (12.3% oil)

Optical Microscope

- 25.0°C
- 30.1°C
- 35.0°C
- 36.0°C
- 36.6°C
- * 38.0°C
- 38.3°C
- 38.8°C
- * 39.7°C

Mesophase degradation causes triggered release
Effect of Shear on Viscosity Profile and Transformation

First oriented with the planes parallel to the shear plane

Shear triggers the release (On-demand release)

Fusion zone between intermediate structures (stalk structure)

- Two pores in the vicinity to the central are only in the upper layer.
- The pores appear between the bilayer and probably before the complete fusion.
- Central pore is dipper than the two other holes.
LDS Technologies

Lyotropic Delivery Systems

Innovative Solutions for Drug Delivery
**LDS Proprietary Technologies**

- **NSSL**
  - Nano Sized Self-assembled Liquid dilutable vehicles

- **M-LLC**
  - Modified Lyotropic Liquid Crystals Mesophases- LDS
LDS main mission is to resolve the problem of intake of insoluble, poorly stable and poorly permeable therapeutic compounds via oral, transdermal or ocular administration routes.
Fluorescein staining:

After 7 days - improvement in inflammation signs.
After 14 days no additional improvement was detected.
After stopping treatment an additional 7 days (total 21 days) a paracentral corneal erosion accrued.

An impressive improvement was observed after 2 weeks of treatment.
Oral intake

Digestion
Drugs taken in gut

Absorption
Drug absorbed into the circulation

Metabolism
Drugs are delivered to and metabolised in body tissues

Elimination
Metabolic end products and unabsorbed metabolites are excreted

Bioavailability of drugs

Health Benefits
Dispersed QL phase- Micellosomes (Soft Particles)

- Stabilized with casein

- Bar = 100nm.
**Micellesomes - soft particles**

**Advantages:**
- Minimum shear is applied
- No need of heat
- More than 6 wt% particles can be dispersed in water
- Small particles (330 nm)
- Less defects
- Dispersibility in sugar-solutions
- Low content of stabilizer
- Polymeric surfactants- more options!!

Water + 1 wt% stabilizer

6-8 wt%
**Preparation of modified hexosomes**

Homogenization for ~10min, 9000 rpm, at room temperature.

95 wt% of water contain 0.2 – 1 wt% of F-127

**Cryo-TEM Images of Hexosomes**

- GMO/tricaprylin/water system (0.4 wt% of F-127)
- GMO/tricaprylin/histin/water system (1 wt% of F-127)
Mixtures of Bioactives
Lycopene and Phytosterols in Micellesomes

2.5% phytosterols
+100ppm lycopene

2.5% phytosterols
+200ppm lycopene

2.5% phytosterols
+400ppm lycopene

Mixtures of bioactives enhance order in the micellesomes
Model of the transport across

- Tight junction
- LLC
- Microvilli
- Cell monolayer
- Drug
Take home messages:

Novel liquid architectures can be constructed for food applications.

- Solubilization, functionality, and bioavailability

- Environmental Protection (physical and chemical enzymatic)

- Nano Reactors for Regioselective ‘Active Matter’

- Triggered Release

- Interfacial Crystallization
Encapsulation of Dendrimers in W/O Microemulsion for Improved Drug Delivery

I. Nir, D. Libster, A. Karsch-Bluman, A. Aserin, N. Garti

Casali Institute of Applied Chemistry
Department of Chemistry
The Hebrew University of Jerusalem
Jerusalem, Israel
Targeted release
DENDRIMERS- DRUG - LLC
Solubilization of bioactives into dendrimers

- Adriamycin (ADR)
- Fullerene
- Rose Bengal (RB)
- Protoporphyrin IX (PPIX)
- Methotrexate (MTX)
- Gold nanoparticle (Au)
PART 3- Cosolubilization of drug and dendrimers
Microemulsions based on AOT as Surfactant

AOT:

Water=20wt%  

The water core radius in Å:

\[ R_{wp} = (1.25W + 2.7) \]

\[ W = \text{water/AOT molecular ratio} \]

In our study: \[ R_{wp} = 3.1 \text{ Å} \]

Why we used AOT-based microemulsion?

- Well defined structure: spherical water droplets with defined diameter determined just by the water/AOT ratio

- Only three components system: cosurfactant is not needed
Summary - take home messages...

QL and HII and the corresponding Micellosomes and Hexosome are:

- Versatile systems for enhancing drug absorption, protecting unstable drugs, increasing circulation times, controlling release...

- Highly suited for water soluble and water insoluble bioactives as well as amphiphilic and polypeptide drugs

- Manufacturable in small and large quantities and prepared from GRAS ingredients

- Structures are available as colloidal dispersions or as liquid/solid precursor

- QL and HII are platform vehicles for transdermal application

- Micellosomes and Hexosomes are platforms for oral transmembrane applications

- Release can be controlled (on-demand) by various physical controls
Maillard Reaction Products in W/O ME

Reaction in Water

\[ \text{D-Glucose} + \text{HS-CH(OH)-CH(NH}_2\text{-COOH}} \rightarrow \text{FFT} \]

A, Furfurylthiol

Reaction in W/O ME

B- 2-(2-furanyl)-Thiazolidine

C- N-(mercaptovinyl)-2(2-furanyl)-Thiazolidine
Effect of surfactant/oil ratio on conversion and rate

On demand triggered reaction

Reaction rate and regioselectivity depend on water mobility and location of reactants in the microemulsion

The reactivity depends on:
- management of water (free or bound)
- competitive binding - The water can bind to various ME ingredients.
- reactivity decreases as the binding effect is enhanced
Polymorphism and Habit

Powdered "crude" sample

Solubilization of bioactive within NSSL droplets

SAXS

DSC

PS

CH

T/q
Changes in Crystal Habits

82-0%

R-lim-EtOH

82-20%

82-30%

82-40%

82-90%
Emulsions & Double Emulsions

Stabilized by Proteins and Modified Hydrocolloids Complexes
Stabilization of the Outer Interface

‘charged complexes’- ‘pseudo coacervates’

new concept!!

WPI/Xanthan gum

Modified xanthan

WPI conc. (wt%)

Xanthan gum conc. (wt%)

protein hydrocolloid

mixing (ionic strength, pH, ratio)

complex incompatibility

one phase system two phase system

one phase system two phase system
The charge-charge conjugated complexes
Two types of Double emulsions - 4.5%wt (4:0.5) Protein/Xanthan gum

W/O/W (W/MCT/W)

O/W/O (MCT/W/MCT)

Creaming and floculation Test (centrifugation at 3000 rpm for 10 hours)

WPI/XG complex

No creaming
No flocculation
No coalescence
Double emulsions prepared with BSA/modified gum Arabic (3/1 wt ratio)

- Type A: Primary continuous phase
- Type B: Type C: Final continuous phase

Droplets 3-5 microns

Single compartment DE

Stepwise & very slow release with lag time
Stabilization of the Inner Interface

Emulsified Microemulsions (EME)

replace the inner phase of the DE by microemulsions

new concept!!

✓ The ‘core’ has a d-spacing of ca 65Å.
✓ Inner phase of ca 50 nm
Microstructure of EME - Stabilized by Biopolymer complexes (WPI/U63 pectin)

- Average droplets sizes of EME 100-300 nanometers.
- Full coverage of droplets by the complex !!!!

Dramatic improvement in the microstructure- no vesicles !!!!
Special thanks...
Advantages on Novel liquid vehicles

- Food grade components
- Low viscosity and transparent
- Thermodynamic stability
- Spontaneous formation (no hear)
- High solubilization capacities
- Progressive and full Dilution in aqueous phase
- Enhanced bioavailability
- Protection - oxidative stability
- Not sensitive to wide range of pHs
- Low cost– made of inexpensive ingredients
- Regioselectivity reactivity
- On-demand release or triggered reaction
Life History of a ‘Orchestrated Products’

Performance Food Challenge - 3rd generation R&D

Sensory Evaluation / Analytics

Nutrition

Q&AS

Raw Material (חומרי גולמים)
Ingredients Preparation (הכנה)
Processing (עיבוד)
Packaging (אריזה)
Storage

Home Preparation Eating

Body Effects

Use as combined Drivers

Integral Performance of Products
(Sensorial & Nutritional Functionalities, Quality & Safety, Cost
Efficient Production, Availability, Value-for-Money, Communication)

Life History of a Product
What can food R&D provide?

2nd Generation R&D

- Nutritional Values and Energy
  (at max. convenience and min. cost)

3rd Generation R&D

✓ Delight
✓ Nutrition with Health
✓ Prevent/Treat Diseases?
3rd Generation R&D - What is delight?

How to generate new concepts

(not in priority order)

'CHIEF'

- Convenience
- Health
- Indulgence
- Excitement
- Freshness

Multi dimensional thinking in R&D!!!
Garti’s ID:

- Director of the Graduate School of Applied Science
- Director of the Casali Institute of Applied Chemistry
- Manager of 32 Students, technicians, postdocs
- Consultant of multi national companies around the globe

**82 Patents**

- 50 review chapters, 6 books
- 380 publications
- Solubilization of Nutraceuticals in NSSL
- Generation *in-situ* of ‘signature’ flavors
- Crystallization of nanosized particles
- Enzymatic reactions in nanoreactors
- Protection against environmental chemical or enzymatic reactivity
- Cubic phases and cubosomes
- Hexagonal phases and Hexosomes
- New ‘microemulsion-like’ mesophases - QL
Industrial projects - ii

- Fire-resistant hydraulic fluids
- Solubilization of high-bromine-insoluble bactericides
- Enhance crystallinity in polymers-solubilization of nucleators
- Inorganic Nanoparticles from microemulsions (Al-oxide, boron)
- Environment protection by nanozised droplets
Advantages of Nano Structures

- Combination of small size, complex organizational patterns with performance
- High surface to volume ratios - composite materials, chemical reactions, drug delivery and energy storage
- Information technology devices with higher speed to information processing.
- High reactivity and regioselectivity of any molecular process
The needs

Science below the critical scale length of 100 nm

- Fabrication of materials and devices at the atomic/molecular scale
- A need for instrumentation to analyze nanostructures (STM, AFM, NFM- "eyes and fingers").
- Computational capabilities for sophisticated simulations in nanoscale dimensions

* (R. Feynman, 1959)
New Emerging Products by Nanotechnology

- Quantum size confinements
- Supramolecular nanostructure of self-assembled triblock copolymers
- Quantum corals
- Magnetotactic bacteria
- Nano pharmaceutical vehicles
- Super 3D high capacity storage of data-TVD devices