Microencapsulation Technologies and Delivery Systems in Food and Pharmaceutical Industries

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HEALTH · NUTRITION · MATERIALS

DSM’s Major Markets

Human Nutrition
& Health

Animal Nutrition
& Health

Personal Care

Pharmaceuticals

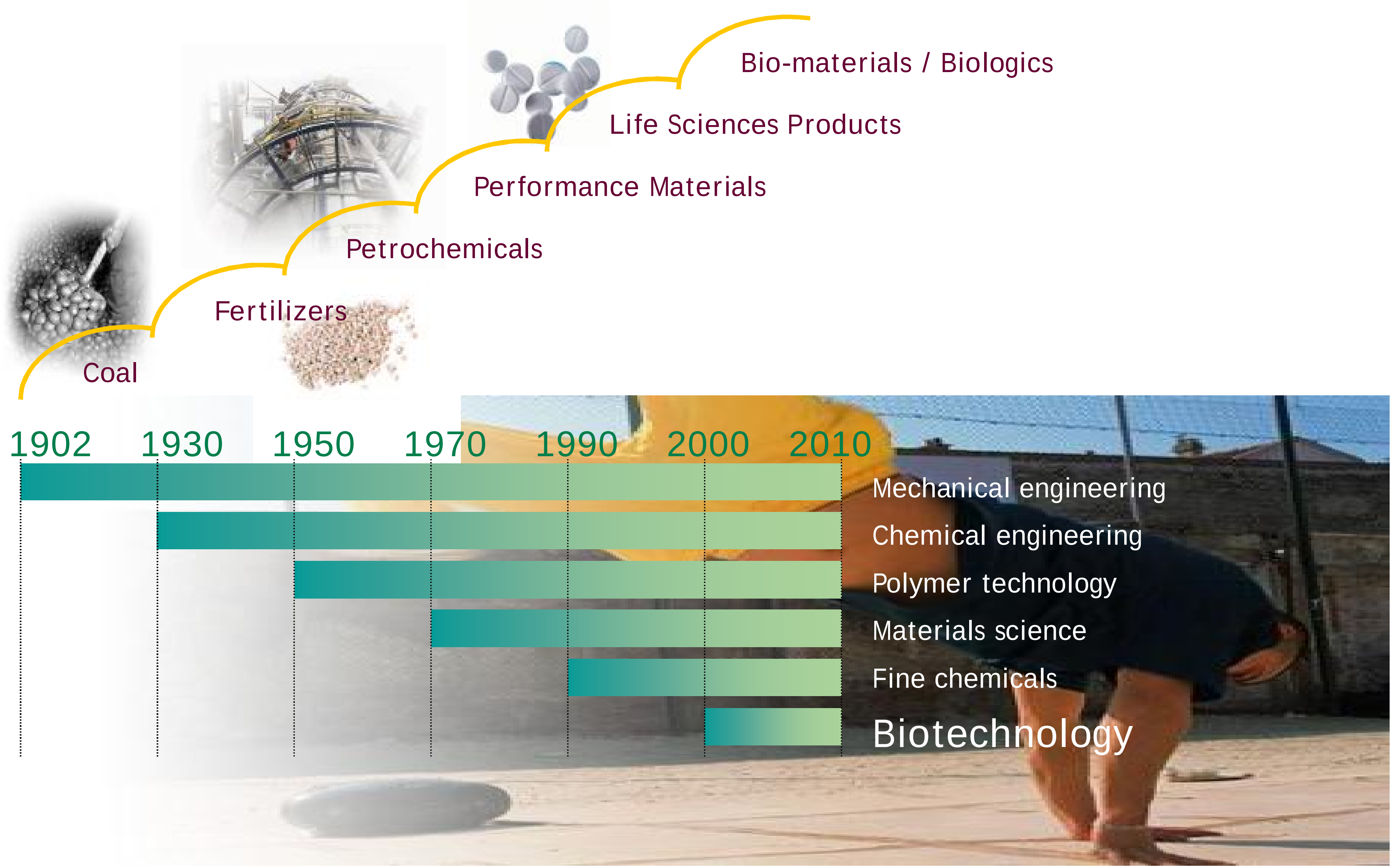
Metal, building
and construction

Automotive and
Transport

Electrics and
Electronics

Textiles

DSM: Over 100 Years of Successful Evolution



DSM Structure –
Clusters and Business Groups

DSM Managing Board

Nutrition

DSM Nutritional Products
- Human Nutrition & Health
- Animal Nutrition & Health
- Personal Care

DSM Food Specialties

Pharma

DSM Pharmaceutical Products

DSM Anti-Infectives

Performance Materials

DSM Engineering Plastics

DSM Dyneema

DSM Resins

Polymer Intermediates

DSM Fibre Intermediates

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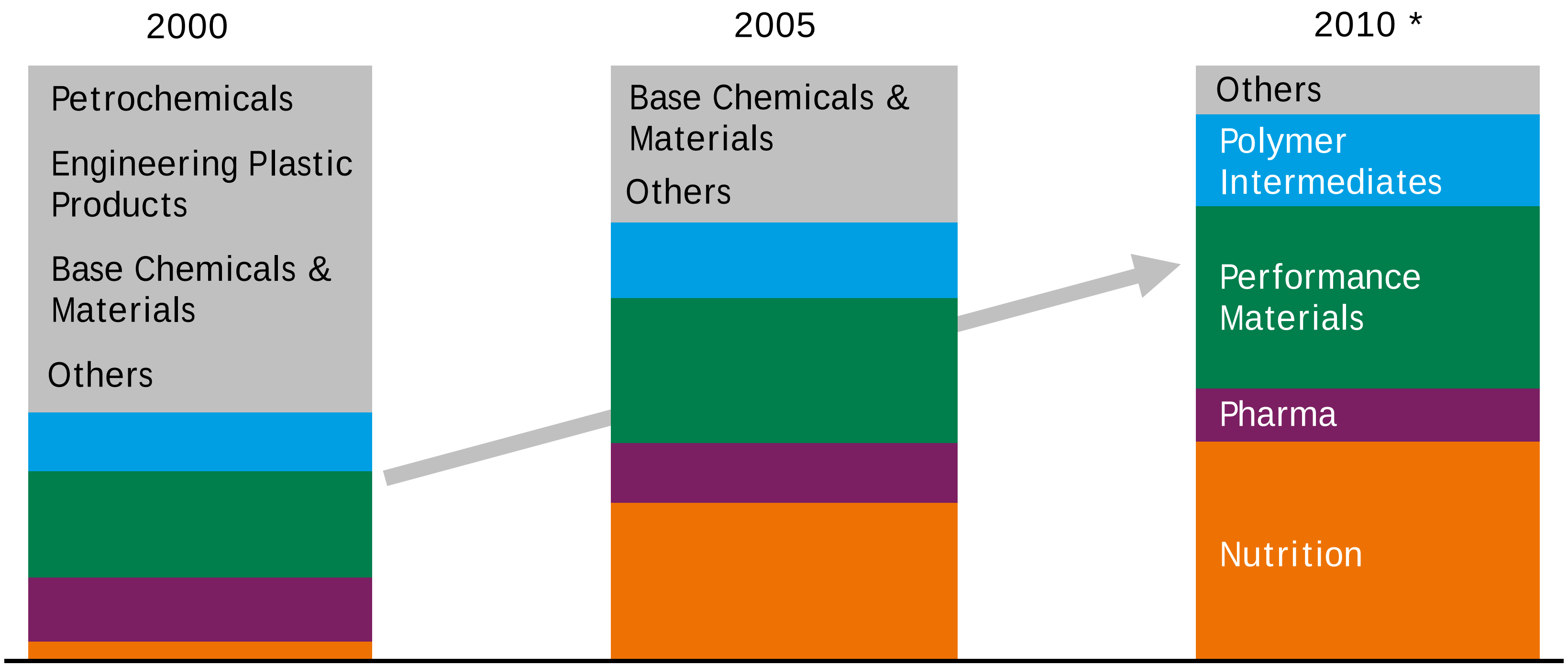
DSM: Transformation completed

- Breakdown DSM sales



* Excluding discontinued

DSM Nutritional Products (DNP)

Animal
Nutrition & Health

€ 1'540 mln*

Human
Nutrition & Health

€ 923 mln *

Personal Care

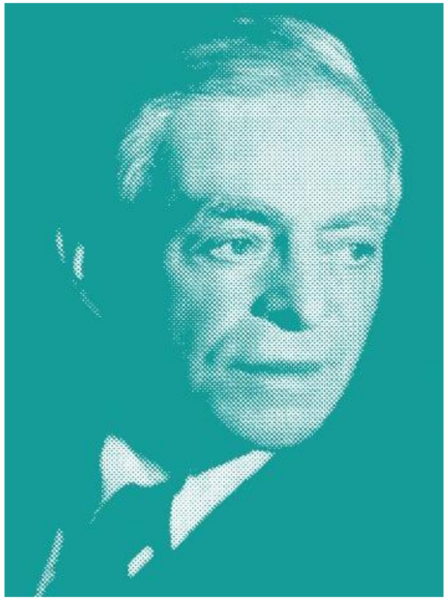
€ 158 mln *

- Net sales 2010

100 Years of Vitamins

- In **1912**, Polish-American scientist **Casimir Funk** coined the term "***vitamin***". He was the first scientist to suggest the existence of an entire family of organic substances essential for life.
- In 1916, American biochemist Elmer V McCollum introduced **large letters** in order to differentiate between vitamin A, B, C and D.
- Our knowledge of the biological function of vitamins on the molecular and cellular level has increased significantly. This understanding is reflected by the award of **20 Nobel Prizes** in this field between 1928 and 1967.
- The first production of a vitamin on a **technical scale** was achieved by Hoffmann-La Roche in 1934 for vitamin C. In the following year, all vitamins were to become available via chemical synthesis, fermentation or extraction from natural materials, which offered opportunities to **fortify diets or use as supplements**.

www.100yearsofvitamins.com



Vitamin	Alternative name	Discovery	Isolation	Structure	Synthesis
Vitamin A	Retinol	1910	1931	1931	1947
Provitamin A	β-Carotene	1831	1831	1931	1950
Vitamin D	Calciferol	1919	1932	1936	1959
Vitamin E	Tocopherol	1922	1936	1938	1938
Vitamin K	Phylloquinone	1929	1939	1939	1939
Vitamin B1	Thiamine	1897	1912	1936	1936
Vitamin B2	Riboflavin	1920	1933	1935	1935
Vitamin B3	Niacin	1936	1936	1937	1994
Vitamin B5	Pantothenic acid	1931	1938	1940	1940
Vitamin B6	Pyridoxine	1934	1938	1938	1939
Vitamin B7	Biotin	1931	1935	1942	1943
Vitamin B9	Folic acid	1941	1941	1946	1946
Vitamin B12	Cobalamins	1926	1948	1956	1972
Vitamin C	Ascorbic acid	1912	1928	1933	1933

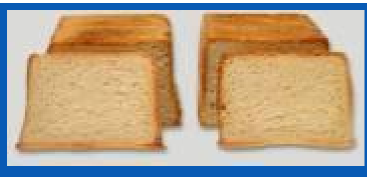
Food and Supplement Applications

Vitamins, Carotenoids and Health Ingredients

Staple foods

Sugar

Flour



Rice

Processed foods

Cereal bars

Margarine

Beverages

Nutritional supplements, e.g ...

Tablets

Feed

Pellets

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Differentiation through the Value Chain

Pure Actives — 15% of revenues

Forms / **Premix** — 85% of revenues

Pure Actives

- Vitamins
- Carotenoids
- Enzymes
- Nutritional ingredients
- Functional Foods
  - *Chemistry*
  - *Fermentation*
- Personal care ingredients

Forms

- Stability / Shelf Life
- Delivery / Solubility
- Bio-availability
- Powder / Flow Properties
  - *Spray drying*
  - *Encapsulation*
  - *Absorption*

Premix

- Custom Formulation
- Dilution

Logistics
Sourcing
Blending

Quality, Reliability, Traceability, Sustainability

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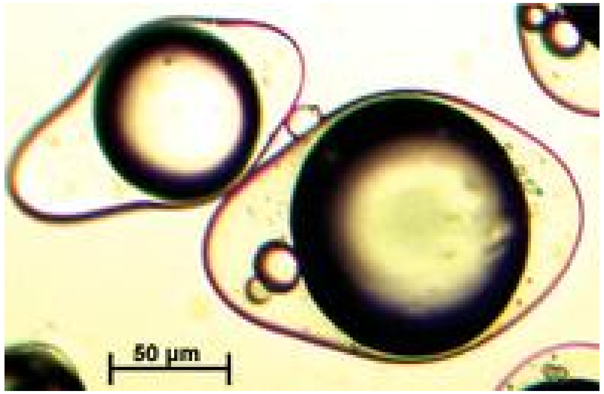
Encapsulation...

w/o/w double emulsion[1]



Microencapsulated o/w flavor oil emulsion[1]

- ....may be defined as a process to entrap one substance within another substance, thereby producing particles with diameters of a few nanometers to a few millimeters.
- Encapsulates might also be defined by their particle size:
  - Nanocapsules: < 0.2 µm
  - Microcapsules: 0.2 – 5000 µm
  - Macrocapsules: > 5000 µm

[1] www.bayertechnology.com

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BENEFITS	POSSIBLE DRAWBACKS
Superior handling of the active agent Conversion of liquid active agent into a powder (dust-free, free-flowing, neutral smell…)	**Additional costs** Max. cost in food industry for functional ingredients: €0.1/kg
Improved stability in the final product and during processing Less evaporation of volatile active agent and/or no degradation or reaction with other components in the food product such as oxygen or water	**Stability challenges of encapsulates during processing and storage of the food product**
Improved safety Reduced flammability of volatiles like aroma, no concentrated volatile oil handling	**Increased complexity of production process and/or supply chain**
Creation of visible and textural effects	**Undesirable customer notice of the encapsulates in food products**
Adjustable properties of active components Particle size, structure, oil- or water-soluble, color	
Off-taste masking	
Controlled release Release the core material at the right time	

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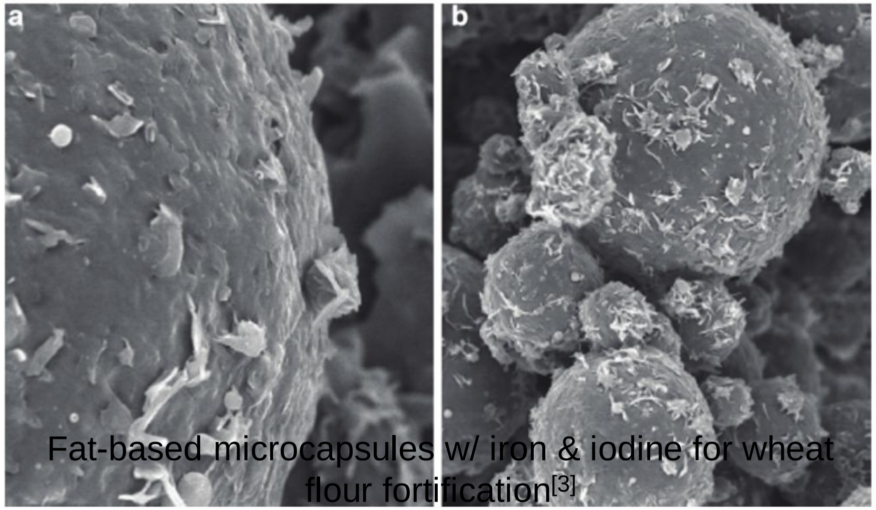
Micronutrients & Food Fortification

- Vitamin A: instable in the presence of oxygen and oxidizing agents
- Carotenoids: sensitive to heat, oxidation, light, insoluble in water, bioavailablility
- Iron: sensory changes, interaction with food components that lower Fe bioavailability
- Fortification of staple foods like cereal flours, rice, salt, sugar…

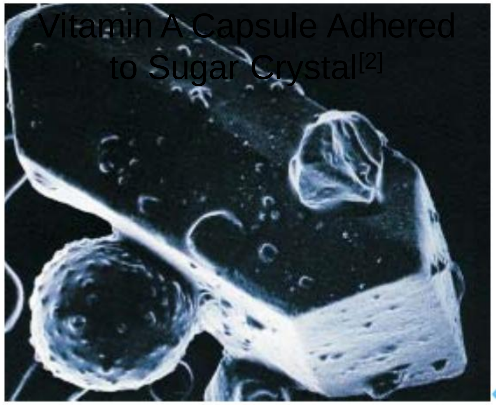

[1]


[1]


[2]



Fat-based microcapsules w/ iron & iodine for wheat flour fortification[3]

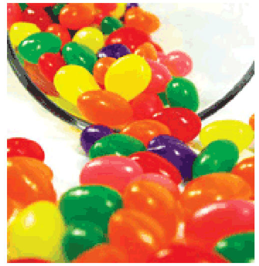

Vitamin A Capsule Adhered to Sugar Crystal[2]

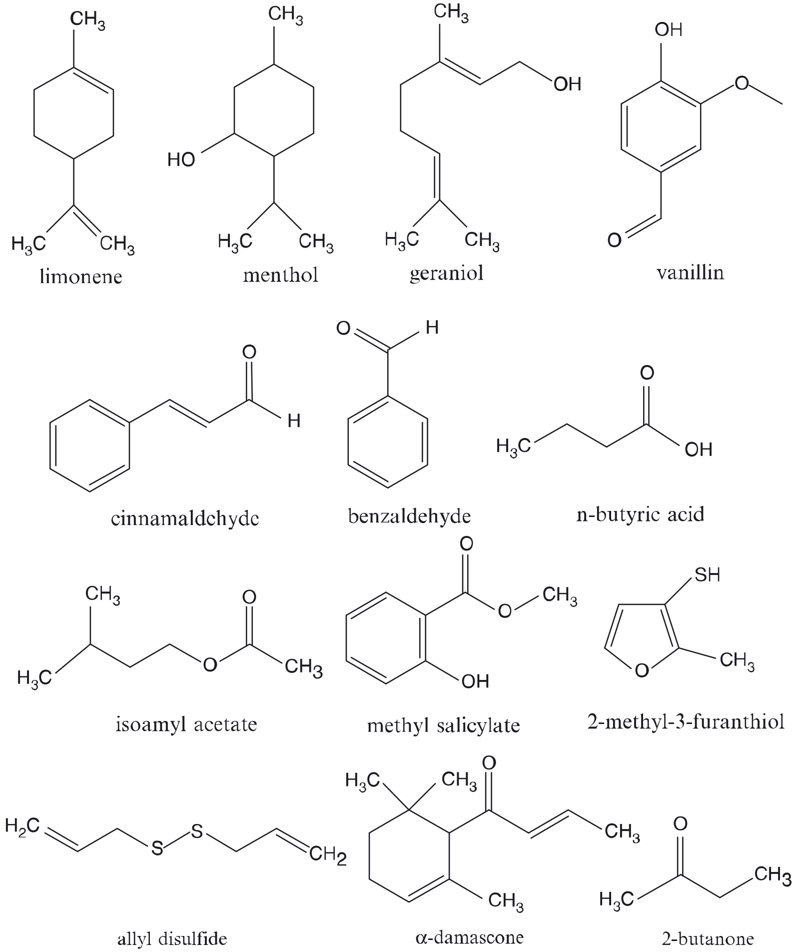
[1] www.buhlergroup.com, [2] www.dsm.com

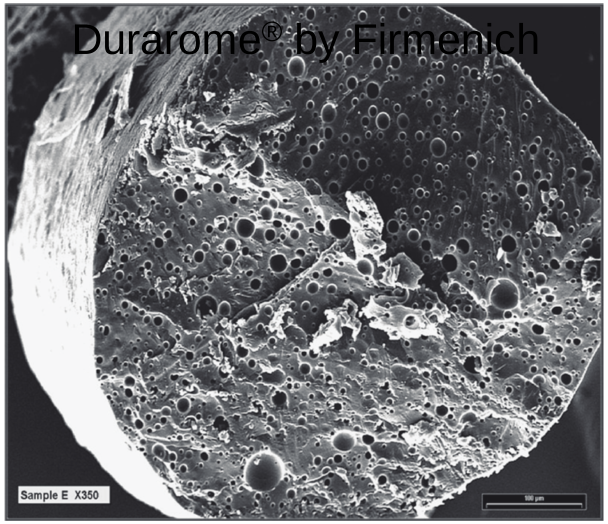
[3] Encapsulation Technologies for Active Food Ingredients and Food Processing. Eds. N.J. Zuidam and V.A. Nedovic, Springer (2010).

Aromas and Flavors

- Volatile and odorous organic molecules
- Low MW
- Hydrocarbons, alcohols, aldehydes, ketones, esters, acids, sulphides etc.
- Mostly lipophilic
- 20 – 25% of all flavors are estimated to be sold in encapsulated form
- 2 – 2.5 billion US$ in 2008



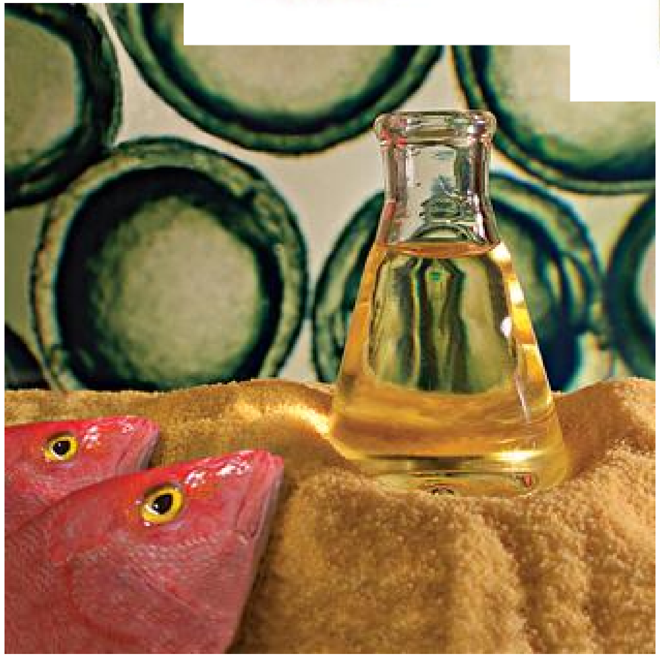


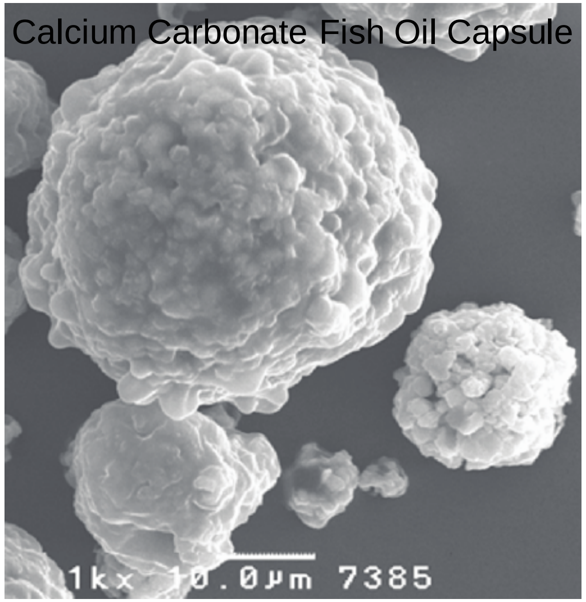


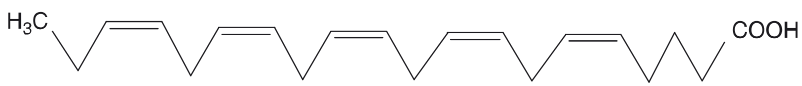
Encapsulation Technologies for Active Food Ingredients and Food Processing. Eds. N.J. Zuidam and V.A. Nedovic, Springer (2010).

Fish Oil

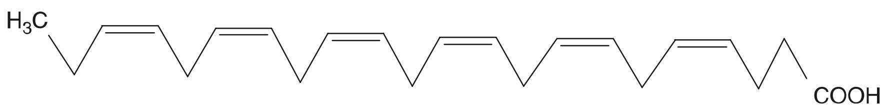
- Medicinal use since 1780s
- Long-chain polyunsaturated fatty acids
- Omega-3 fatty acids EPA and DHA in marine products and algae
- Very sensitive to lipid oxidation
- Off-smells, off-tastes







eicosapentaenoic acid EPA (20:5ω-3)



docosahexaenoic acid DHA (22:6ω-3)

Encapsulation Technologies for Active Food Ingredients and Food Processing.
Eds. N.J. Zuidam and V.A. Nedovic, Springer (2010).

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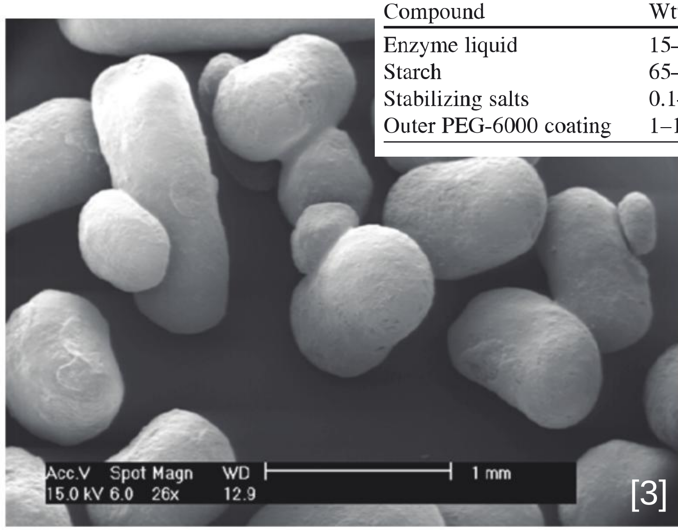
Enzymes, Probiotics

- Enzymes: stability, allergies to powdered proteins
- Probiotics: stability, protect probiotic bacterial cells during processing, storage and degradation in the gastrointestinal tract

Compound	Wt%
Enzyme liquid	15–30
Starch	65–80
Stabilizing salts	0.1–5
Outer PEG-6000 coating	1–10



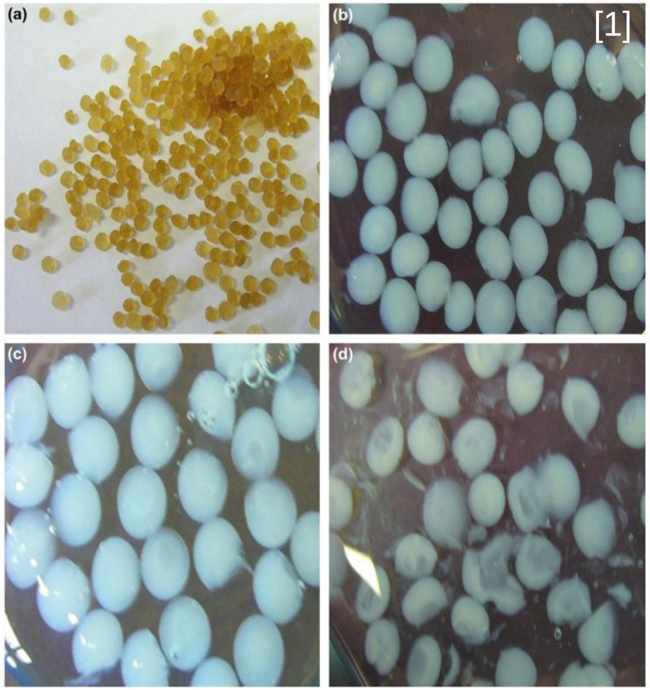


Fig. 1. Photographs showing the disintegration mechanism (swelling and burst effect) of whey protein isolate–alginate–chitosan–calcium chloride microcapsules incubated in simulated gastrointestinal fluids; simulated gastric fluid (SGF, pH 1.2), and simulated intestinal fluid (SIF, pH 7.4) at 37 °C: (a) dried microcapsules; (b) microcapsules incubated in SGF for 2 h; (c) microcapsules incubated in SIF for 2 h; (d) microcapsules incubated in SIF for 8 h (Unpublished).

[1] Anal and King, *Trends Food Sci. Techn.* **18**, 240-251 (2007).
[2] Sohail et al., *Int. J. Food Microbiol.* **145**, 162-168 (2011).

[3] Encapsulation Technologies for Active Food Ingredients and Food Processing. Eds. N.J. Zuidam and V.A. Nedovic, Springer (2010).

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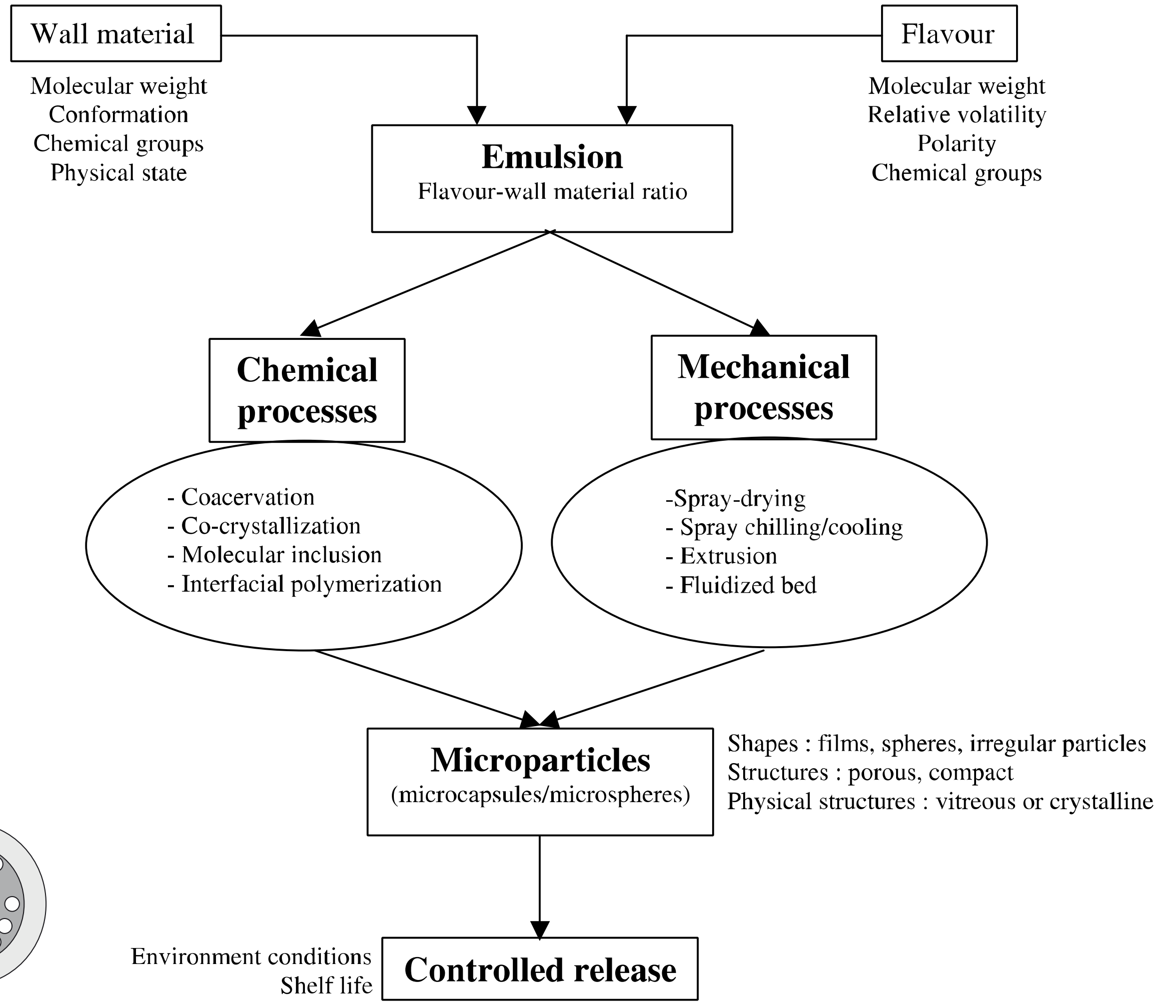
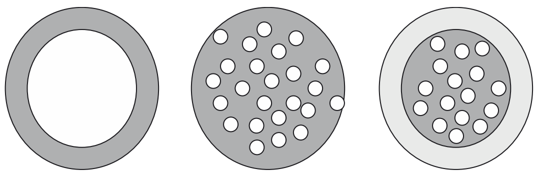
The Encapsulation Process

1. **Formation of the inner phase**
   droplets of the active in gas, liquid or powder form



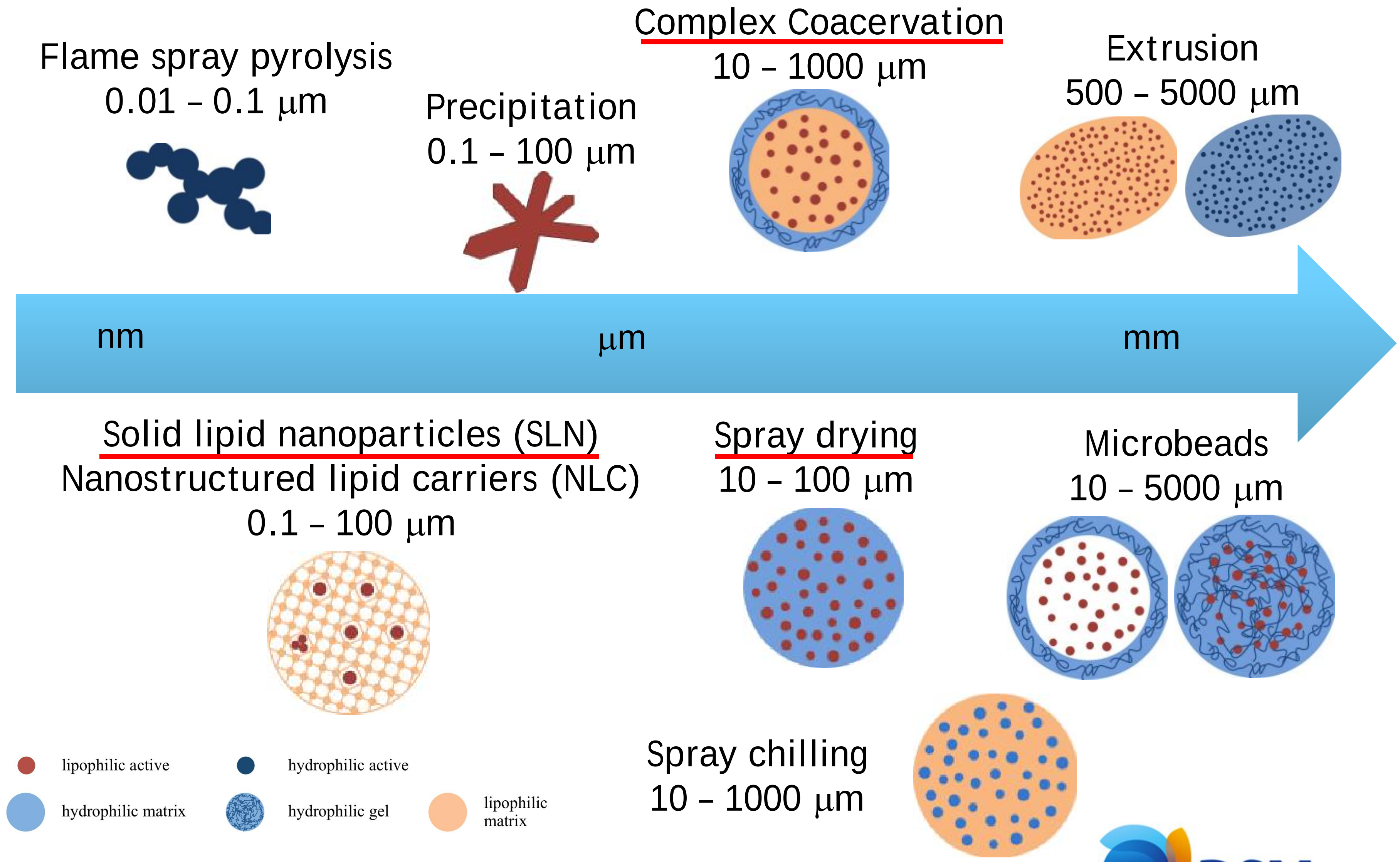
1. **Formation of (dry) microencapsules**
   droplets are surrounded by carrier material in a gas or liquid phase via different physico-chemical processes



reservoir type   matrix type   coated matrix type

Madene et al., *Int. J. Food Sci. Techn.* **41**, 1-21 (2006).
Encapsulation Technologies for Active Food Ingredients and Food Processing. Eds. N.J. Zuidam and V.A. Nedovic, Springer (2010).

Common Formulation Technologies (Food)



Teleki, A., A. Hitzfeld and M. Eggersdorfer, "100 years of vitamins: the science of formulation is the key to functionality", *KONA Powder and Particle Journal* in press (2012).

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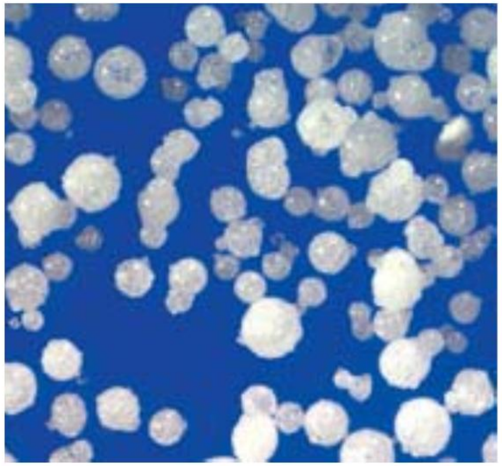
Spray Drying Technology

- 1932: first spray-dried flavor powder by the English company A. Boake, Roberts & Co., Ltd.
- Today one of the most important process to produce dry flavors from liquids throughout the food and beverage industries.



Powders

Agglomerates

www.niro.com

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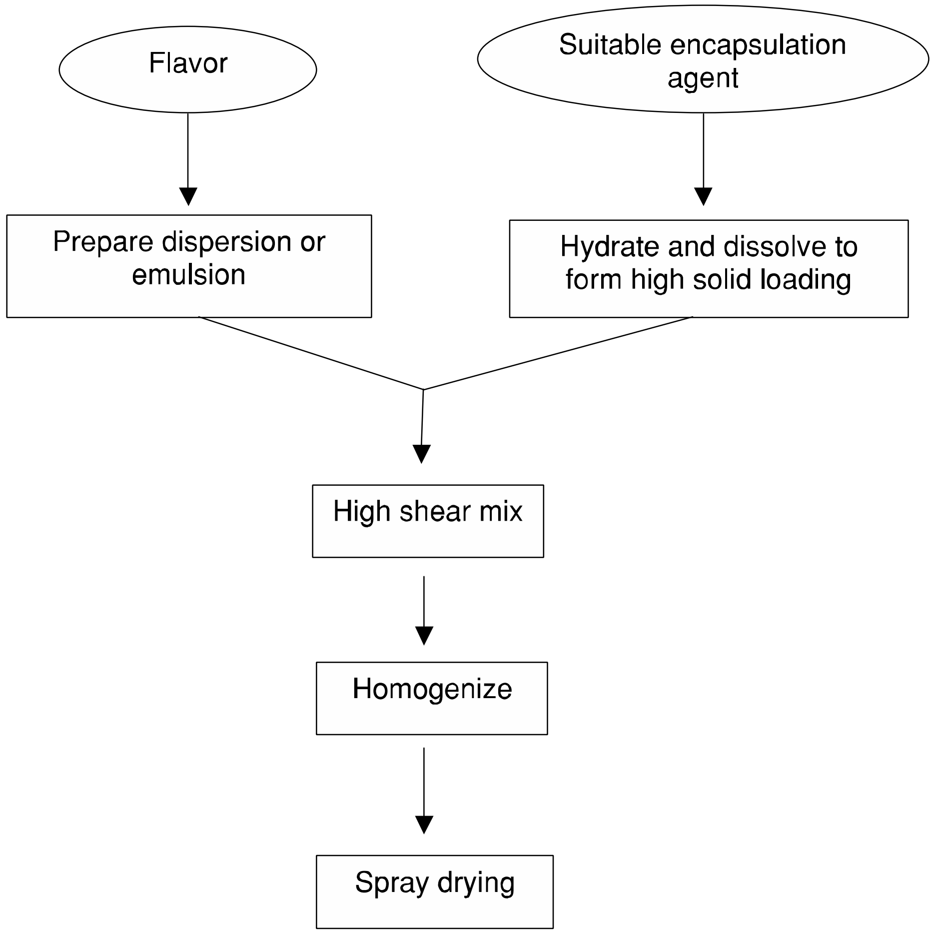
Spray Drying Process for Flavor Encapsulation

1. Preparation of the dispersion or emulsion to be processed
2. Homogenization of the dispersion
3. Atomization of the mass into the drying chamber



Barbosa-Canovas et al., *"Food powders. Physical properties, processing and functionality."* Kluwer Academic/Plenum Publishers (2005).

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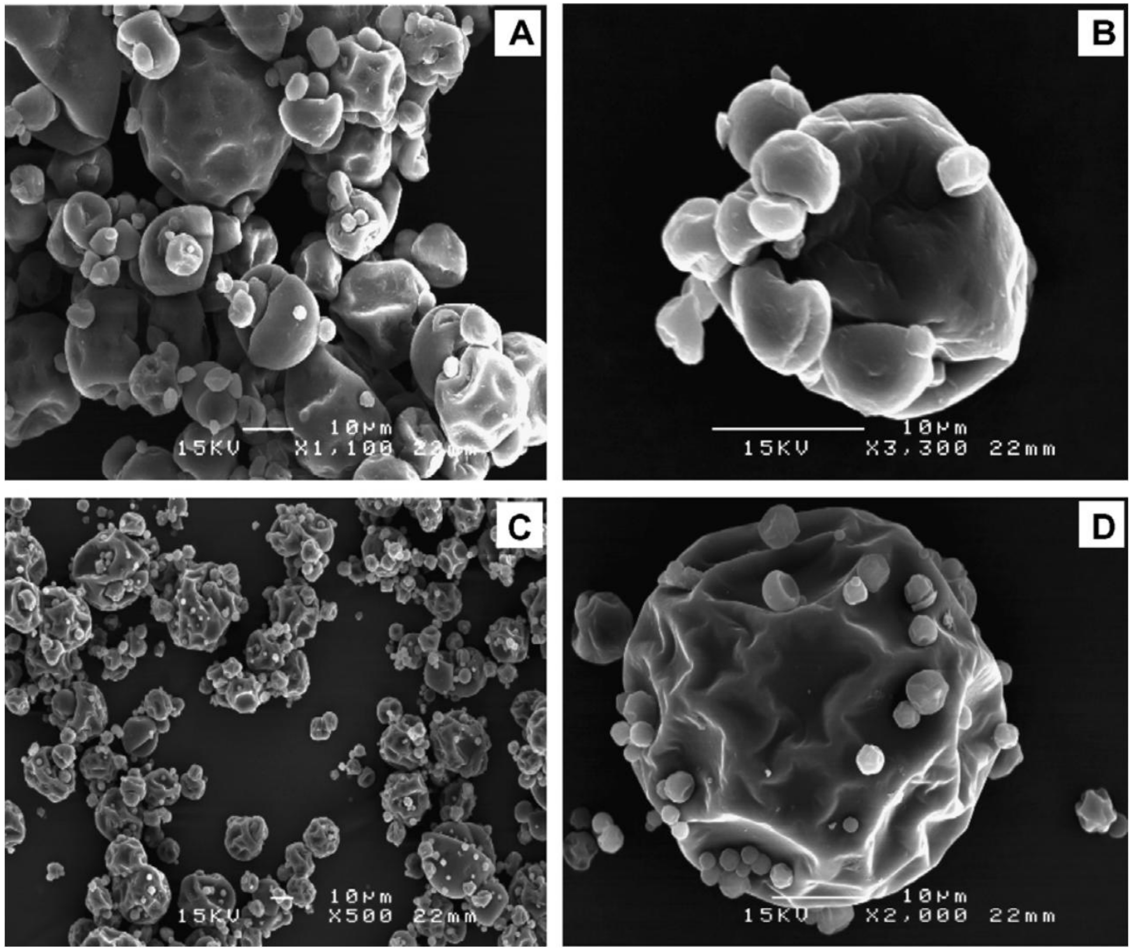
Spray Dried Fish Oil Microcapsules



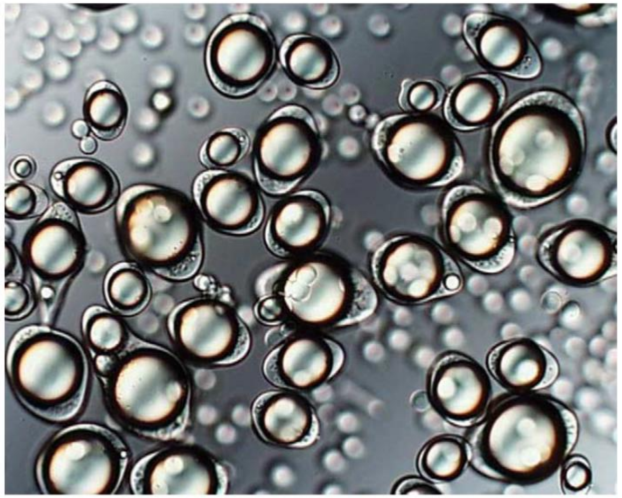
with whey protein concentrate

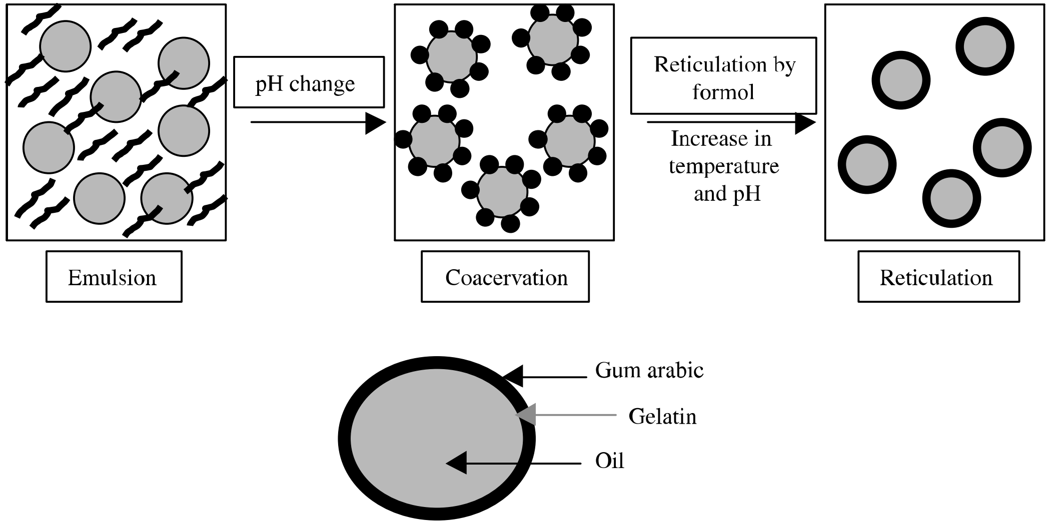
with modified food starch

Jafari et al., *Food Research International* **41**, 172-183 (2008).

Complex Coacervation

- Complex coacervation between oppositely charges proteins and polysaccharides
- Developed in the 1950s, one of the oldest techniques of encapsulation
- Submicron sized encapsulated particles
- High payload (85-90%)
- Efficient but expensive
- Difficult to find food-approved coating materials





Gouin, *Trends Food Sci. Techn.* **15**, 330-347 (2004).
Madene et al. *Int. J. Food Sci. Techn.* **41**, 1-21 (2006).

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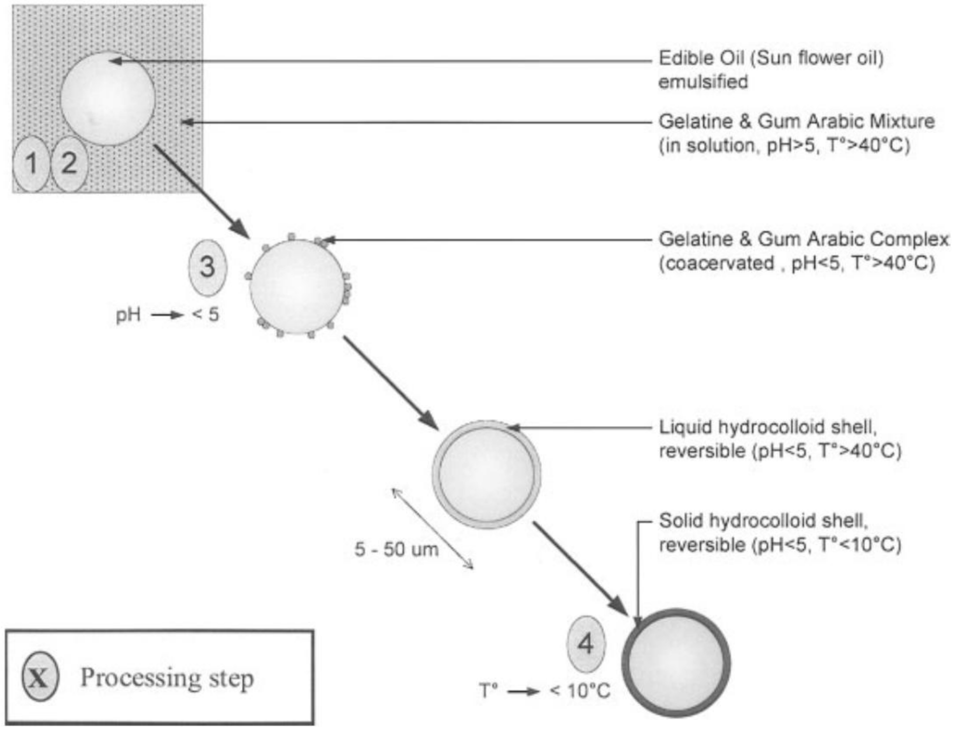
The Complex Coacervation Process

1. Polymer dissolution and hydration
   (at a pH at which coarcervation can not occur, above the gelling temperature of the polymer)
2. Emulsification
   (formation of the core: oil droplets in the water phase, emulsion is stabilized by the two polymers)
3. Coarcervation
   (formation of the shell: lower pH, polymers interact via electrostatic interactions and form a polymer complex, fluid coarcervate phase distributes over entire oil surface, lowering of temperature below the gelation temperature of gelatin creates the solidified polymer shell)
4. Hardening
   (crosslinking agent like glutaraldehyde to strengthen wall material)
5. Washing/separation stage



Lemetter et al., *AIChE J.* **55**, 1487-1496 (2009).

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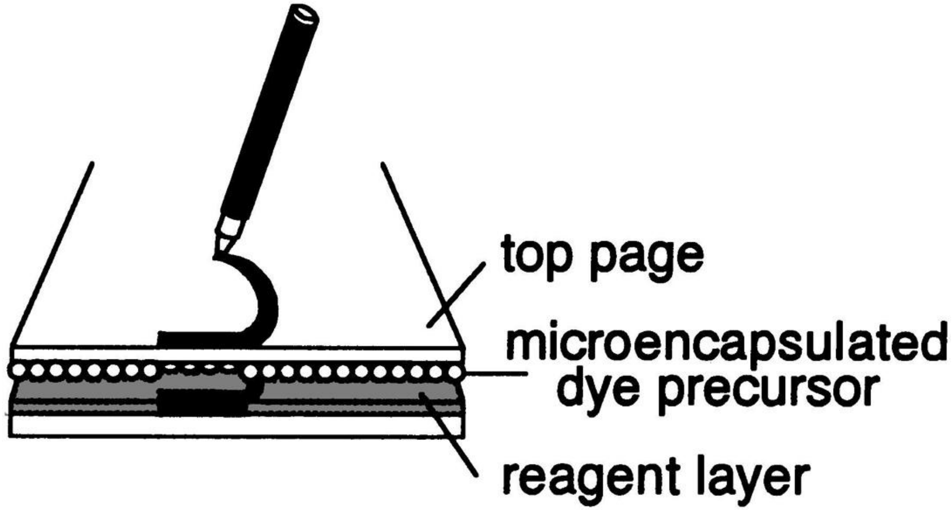
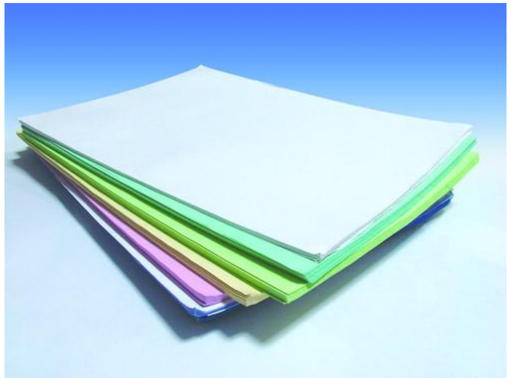
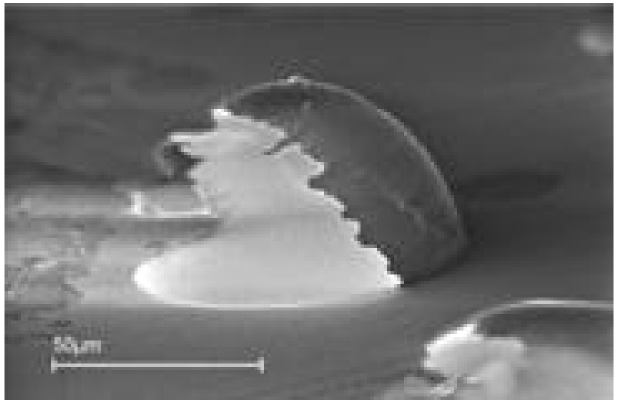
Carbonless Copy Paper





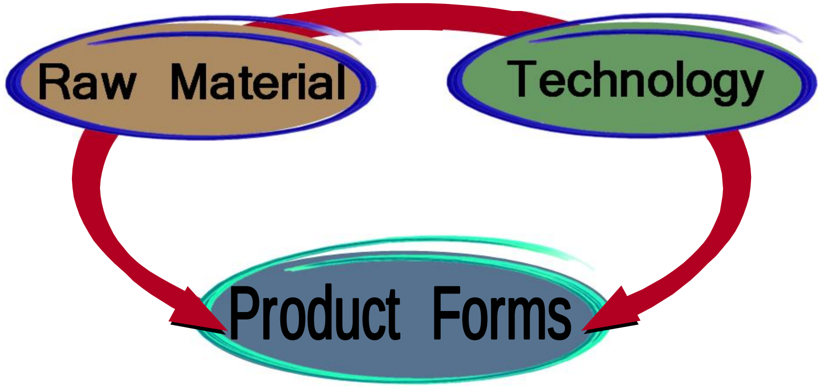


www.swri.org

1. Top page undercoated with microencapsulated dye precursor (3 – 8 μm)
2. Pressure of the pen causes microcapsule to break
3. Dye precursor reacts with reagent coated on top of lower sheet
4. Reaction leads to colored product

White, M.A., *Chemistry Everyday for Everyone* **75**, 1119-1120 (1998).

Importance of the Protective Colloid



Protective Colloid
determines main properties of form

Customer Perception	Performance in Application	Cost Position
- kosher/halal - no-BSE - animal-free - no GMO - no allergen labeling	- Phys. stability in beverages - Chem. stability in tablets - Chem. stability in feed	- Raw material costs - Processing costs

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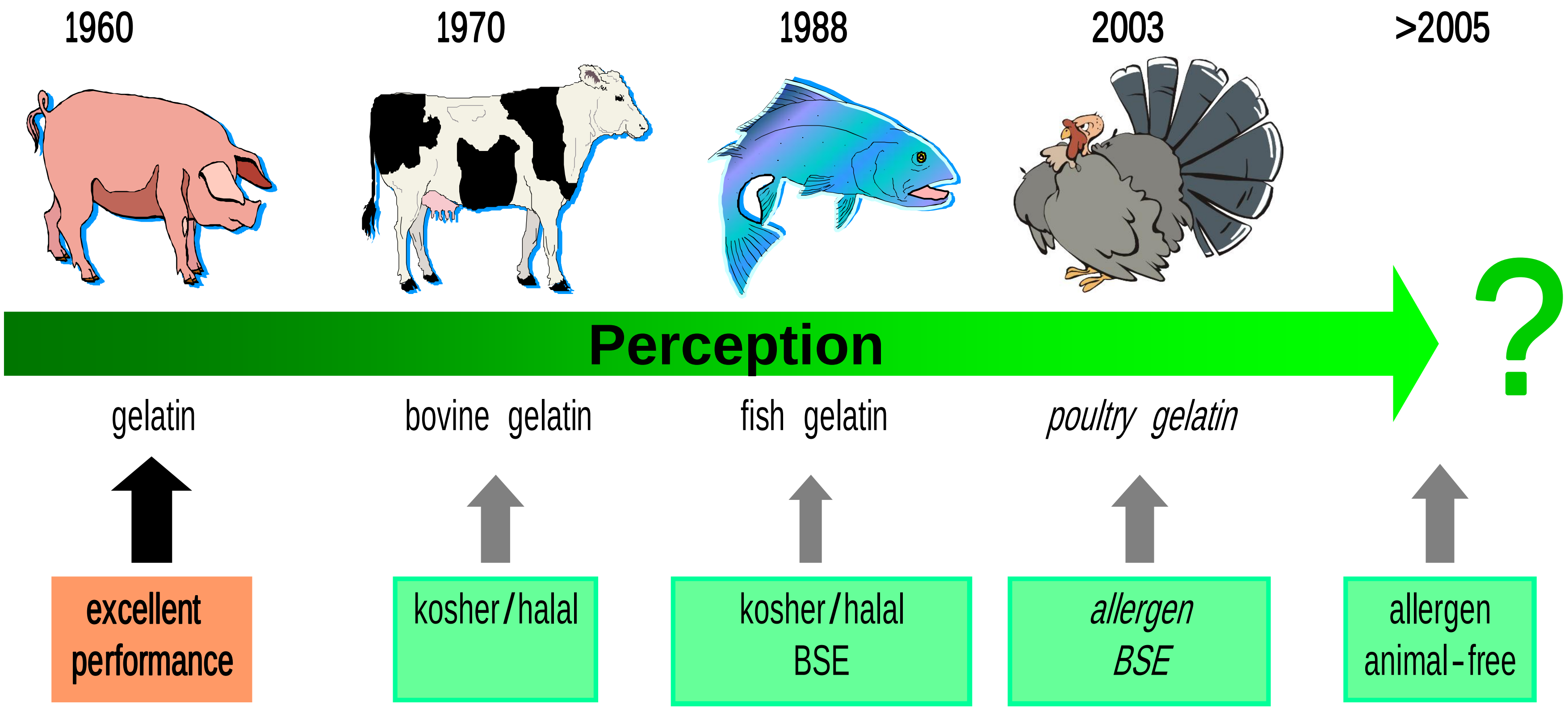
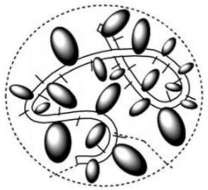
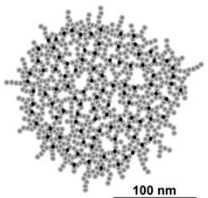
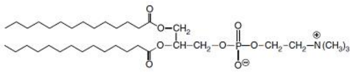
Development of New Protective Colloids for Forms



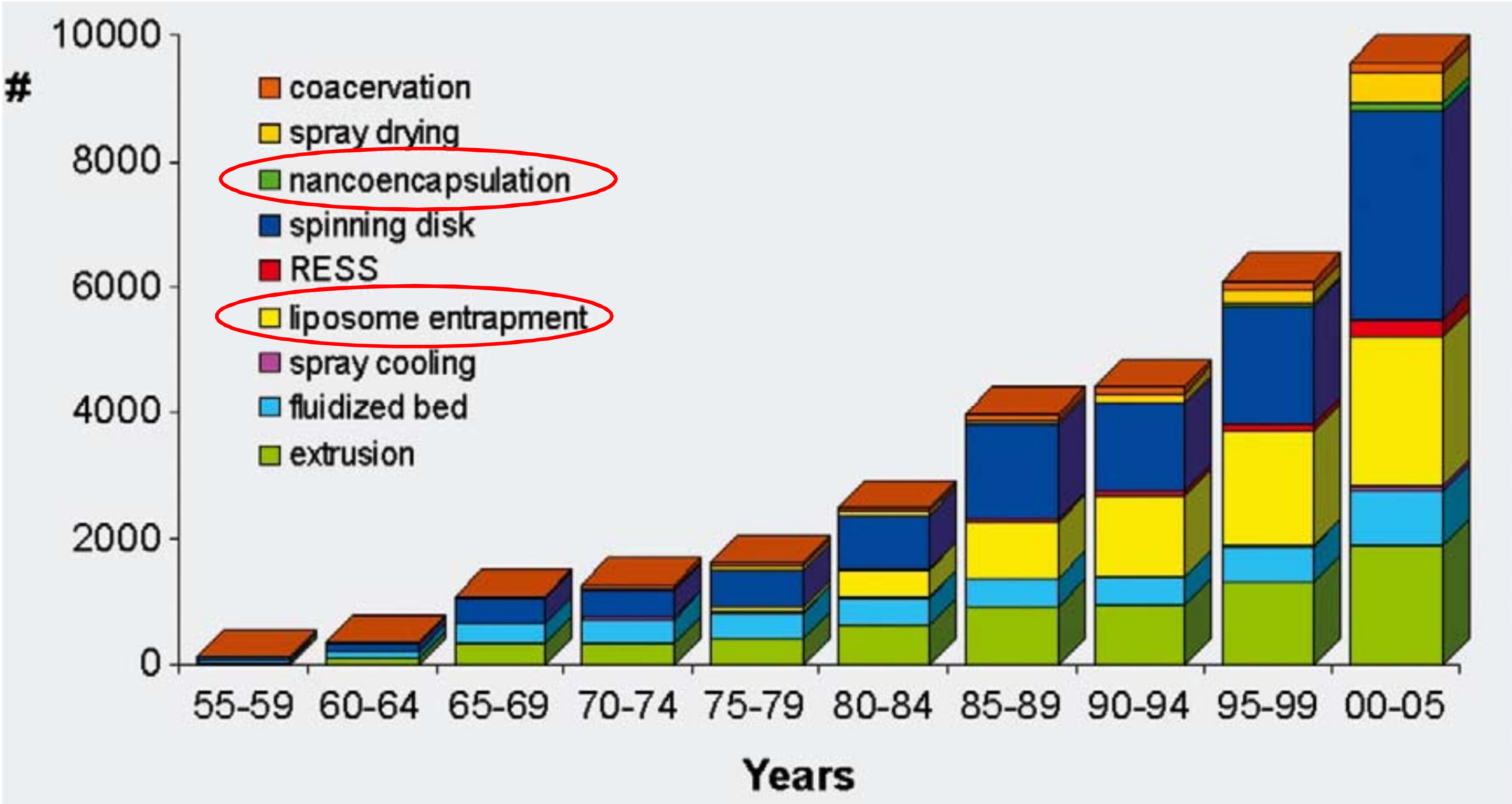
Commercially Most Relevant Materials for Microencapsulation in the Food Industry

	Animal	Plant	Marine	Microbial
Carbohydrate 	chitosan	*trees exudates:* gum arabic, gum karaya, gum ghatti, gum tragacanth *plants:* starch, cellulose *extracts:* guar gum, pectin, galactomannans *polysaccharides:* soluble soy polysaccharide, maltodextrins	carrageenan agar alginate	xanthan gellan dextran curdlan pullulan
Protein 	gelatin casein whey egg white lactoglobulin	gluten soy pea rice sorghum lupine zein		
Lipid 	fatty acids glycerides waxes phospholipids Shellac	fatty acids glycerides waxes phospholipids		

Teleki, A., A. Hitzfeld and M. Eggersdorfer, "100 years of vitamins: the science of formulation is the key to functionality", *KONA Powder and Particle Journal* in press (2012).

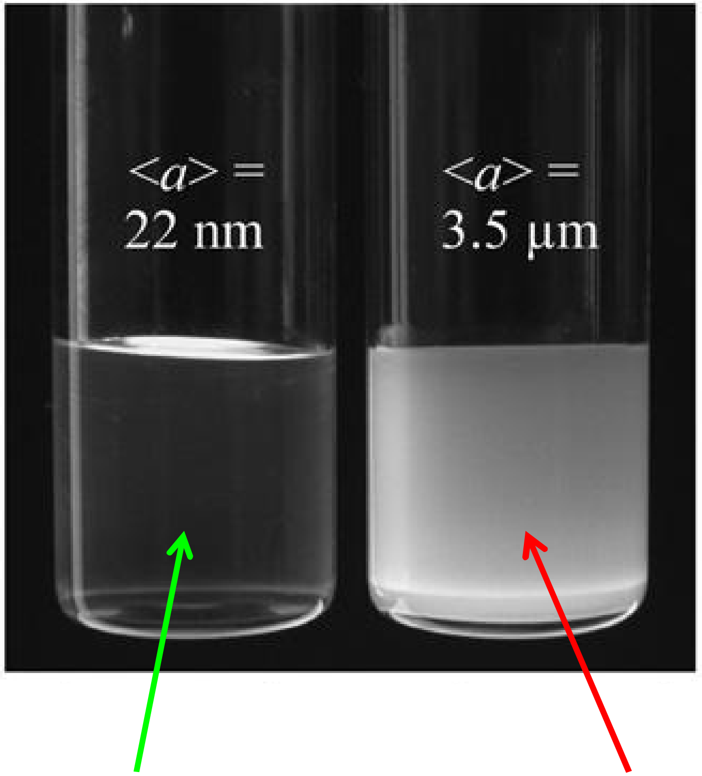
Future Trends in Microencapsulation Technologies

Published literature



Gouin, *Trends Food Sci. Techn.* **15**, 330-347 (2004).

Nanoemulsions



- Optically transparent (microscale emulsions scatter light)
- Potential to improve bioavailability of the core because of the increased surface area
- Improved shelf stability against gravitationally driven creaming, Brownian motion keeps droplets in motion

Mason et al. *J. Phys.: Condens. Matter* **18**, R635-R666 (2006).

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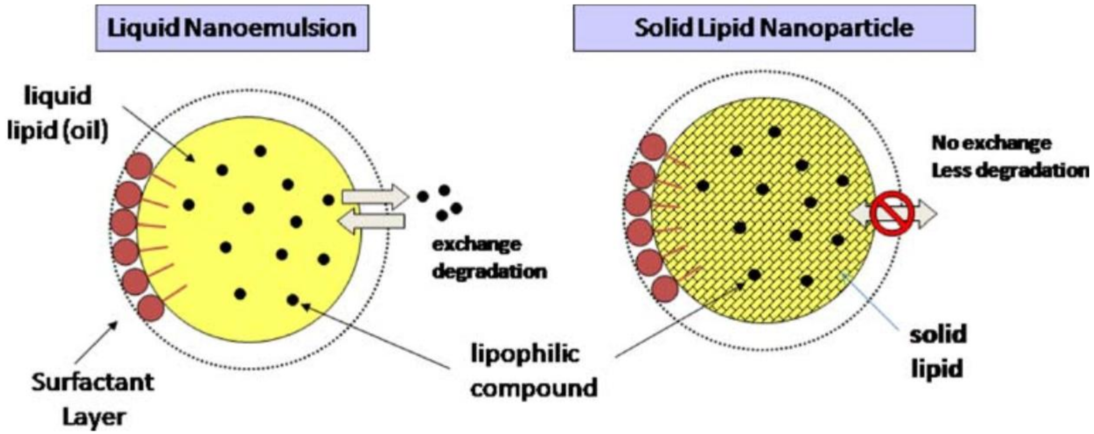
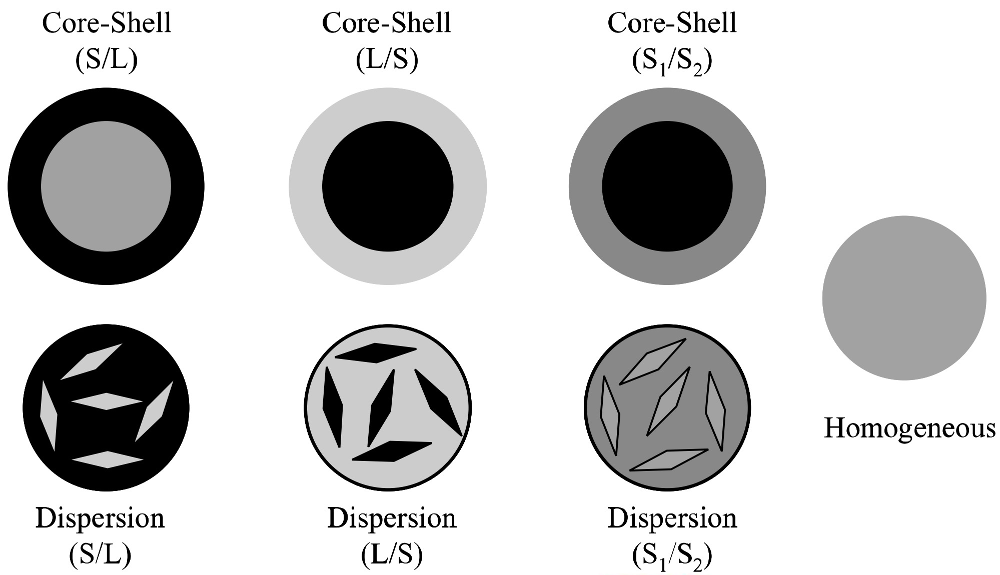
Solid Lipid Nanoparticles (SLN)

- Delivery of lipophilic actives
- Crystallized nanoemulsions
- Solid core of lipid-active ingredient mixtures
- Stabilized by a surfactant layer
- Composition of carrier lipid
  - Determines manufacturing method/conditions
  - Influences loading capacity (crystal structure)
  - SLN structure (crystallization temperatures lipid vs. active)
  - Common: triacylglycerides





Weiss et al., *Food Biophys.* **3**, 146-154 (2008).
McClements et al., *J. Food Sci.* **72**, R109-R124 (2007).

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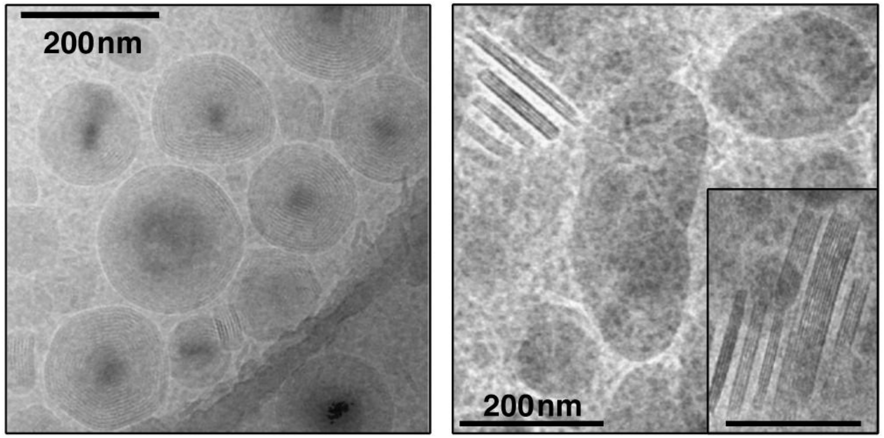
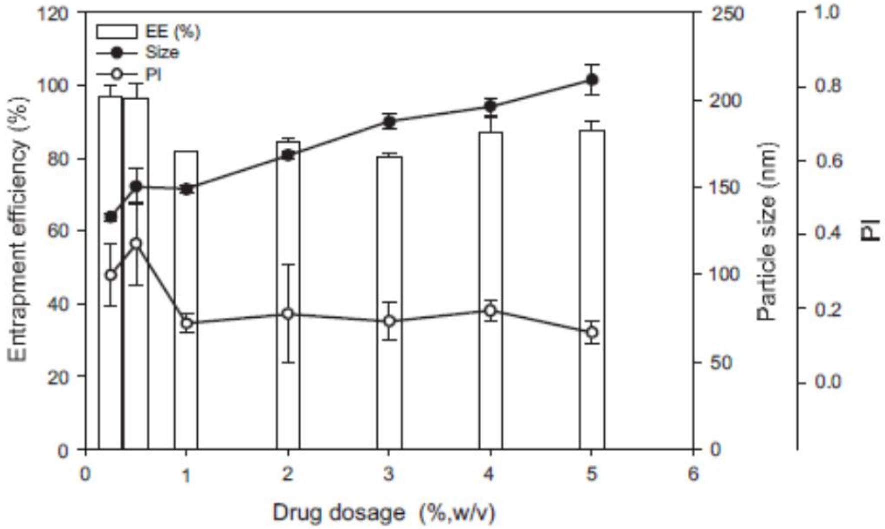
Drug Expulsion during Storage of SLN

- Highly crystalline lipid particles with a perfect lattice ➔ expulsion of the bioactive ingredient
- Synthesis of stable SLN requires delaying of the α to β polymorphic transition



Tristearin nanoparticles in the α- (left) and β-modification (right) induced by different thermal treatment of the nanosuspensions.



Vitamin K_1-loaded SLN.

Mueller et al., *Adv. Drug Del. Rev.* **54**, S131-S155 (2002).
Bunjes, *Curr. Op. Coll. Interf. Sci.* **16**, 405-411 (2011).
Liu et al., *Drug Dev. Ind. Pharm.* **36**, 751-761 (2010).

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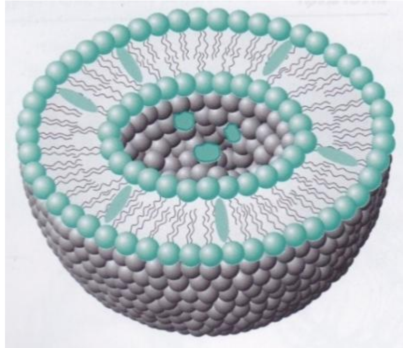
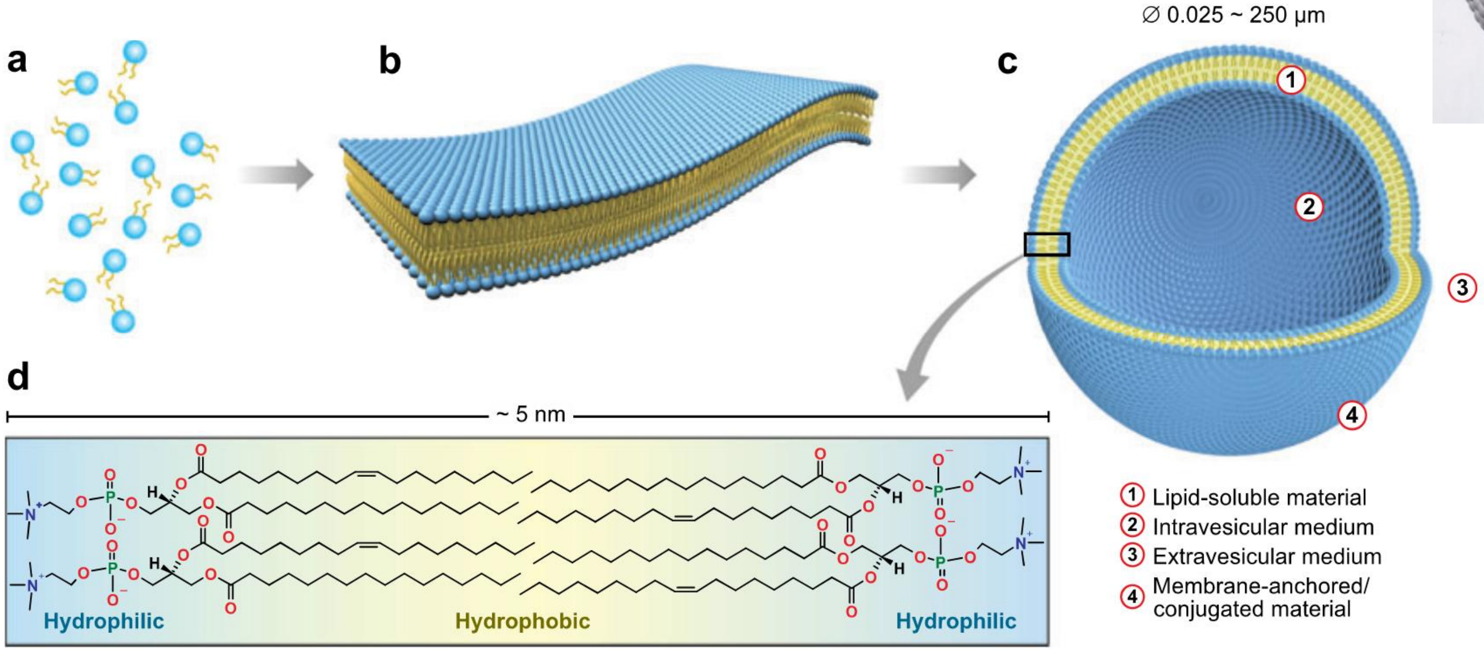
Liposome Entrapment



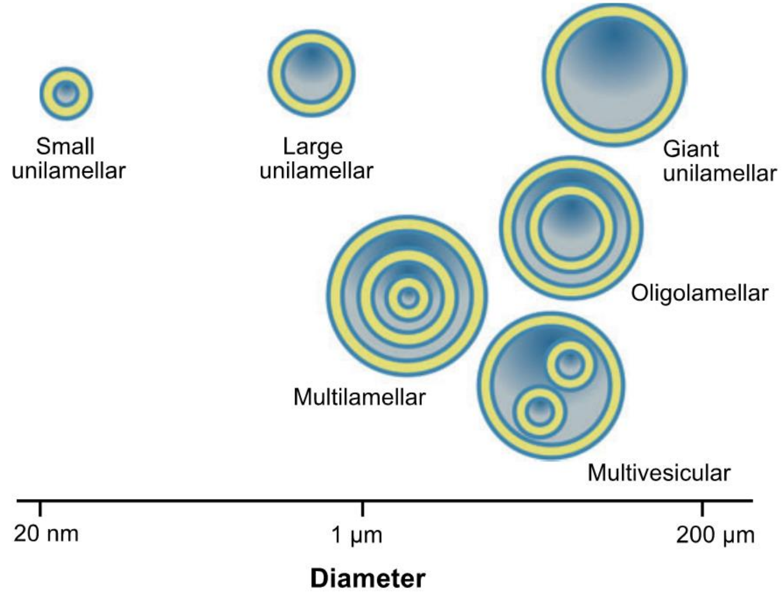


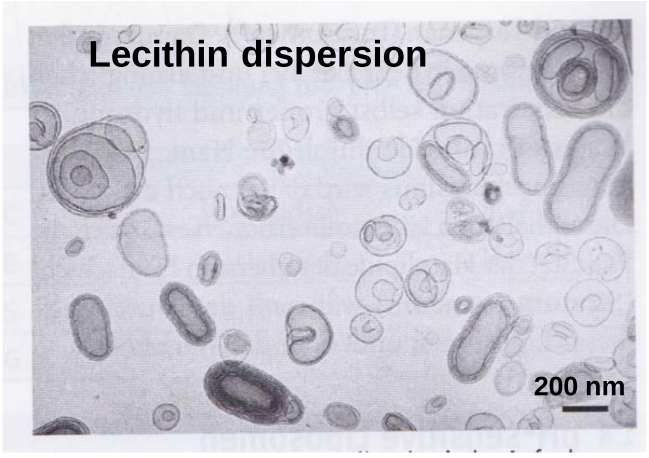
- Interaction between amphiphilic compound (mainly phospholipids) and water molecules:
  - Polar head groups are subjected to the aqueous phases of the inner and outer media
  - Hydrophobic hydrocarbon tails are associated into the bilayer
- Spherical core shell structures are formed

Jesorka and Orwar. *Annu. Rev. Anal. Chem.* **1**, 801-832 (2008).

Classification Scheme for Liposomes

- Small unilamellar
  - < 50 nm, one lipid bilayer
  - High membrane curvature, curvature elastic energy, unstable
  - Small inner volume
- Large unilamellar
  - > 50 nm, one lipid bilayer
  - Good stability
  - Models for biological membranes
  - High encapsulation efficiency
  - Simple production methods
- Large multilamellar
  - 100 nm up to several μm
  - Models to measure permeability of different ions through membranes
  - Retarded release of hydrophilic molecules





Innovative Arneiformen, Mader and Weidenauer, Wissenschaftliche Verlagsgesellschaft Stuttgart (2010).
Jesorka and Orwar. *Annu. Rev. Anal. Chem.* **1**, 801-832 (2008).

Cryo-TEM Images of Liposomes

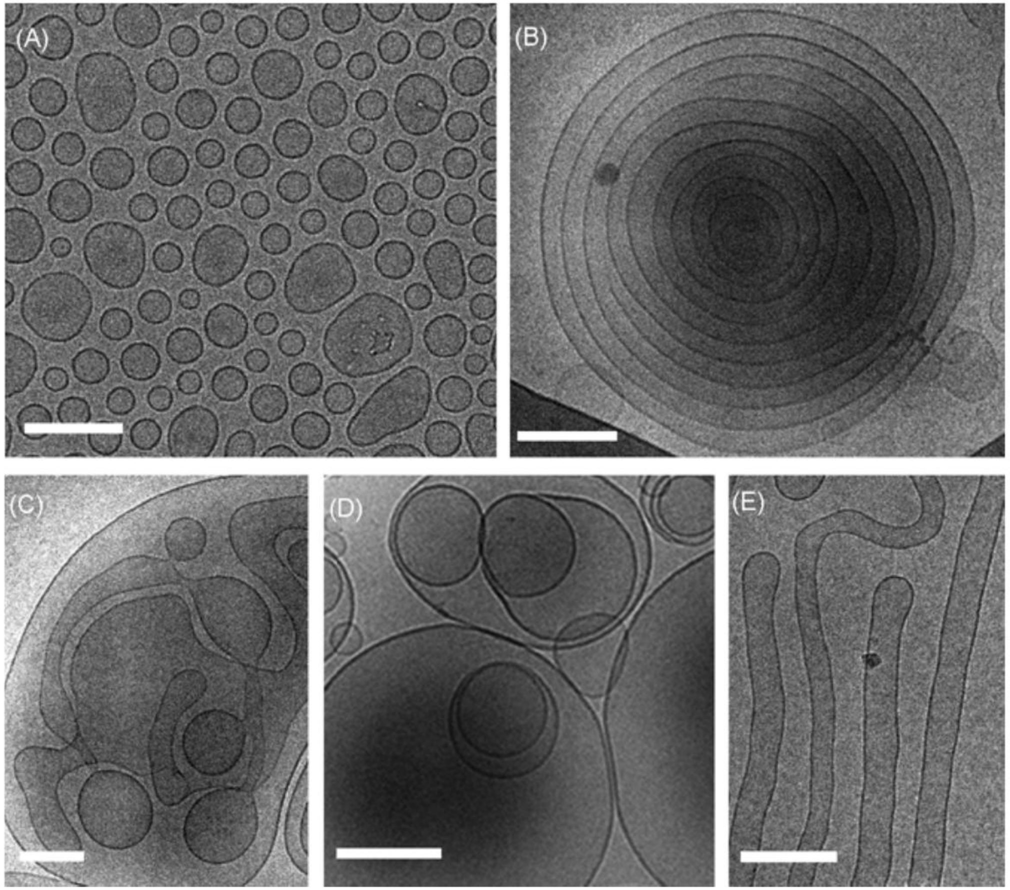


Fig. 8.2 Direct-imaging cryo-TEM images of liposomes: (A) small unilamellar vesicles, (B) multilamellar vesicles composed of concentric bilayers, (C, D) multivesicular vesicles and (E) tubular vesicles. The vesicles shown in (A) form in the MO/ethanol/water system. All the structures shown in panels B to E form spontaneously in binary phosphatidylserine/water solutions. Bars equal 100 nm in all panels.

Delivery and controlled release of bioactives in food and nutraceuticals, Ed. N. Garti, Woodhead Publishing (2008).

Applications of Liposomes

- Among the first nanotechnology drug delivery systems (1960s)
  - 1980: cell-specific targeting of liposomes
  - 1987: long-circulating liposome
  - 1995: Doxil (doxorubicin liposome) for treatment of AIDS-associated cancer

DOXIL® (doxorubicin HCl liposome injection)

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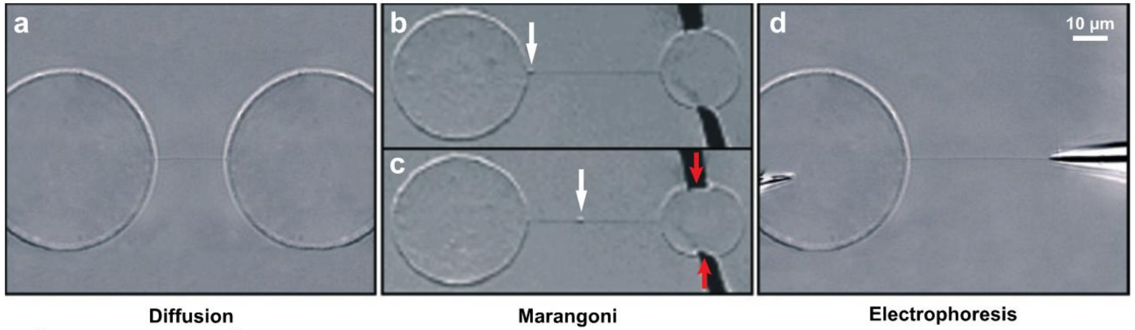
- Analytical sciences
  - Liquid chromatography
  - Capillary electrophoresis
  - Immunoassays
  - Biosensors



Giant unilamellar vesicles connected by a lipid nanotube
a) Concentration gradient
b,c) Tension gradient
d) Applying an electric field

- Advanced, pharmaceutical drug carrier
  - Release on demand (temperature, pH)
  - Antibody-tagged immuno-liposomes
  - Entrap and deliver genetic material
  - Transdermal delivery applications
- Food industry: starting to be explored

Jesorka and Orwar. *Annu. Rev. Anal. Chem.* **1**, 801-832 (2008).

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