SISTEMI AUTOORGANIZZATI

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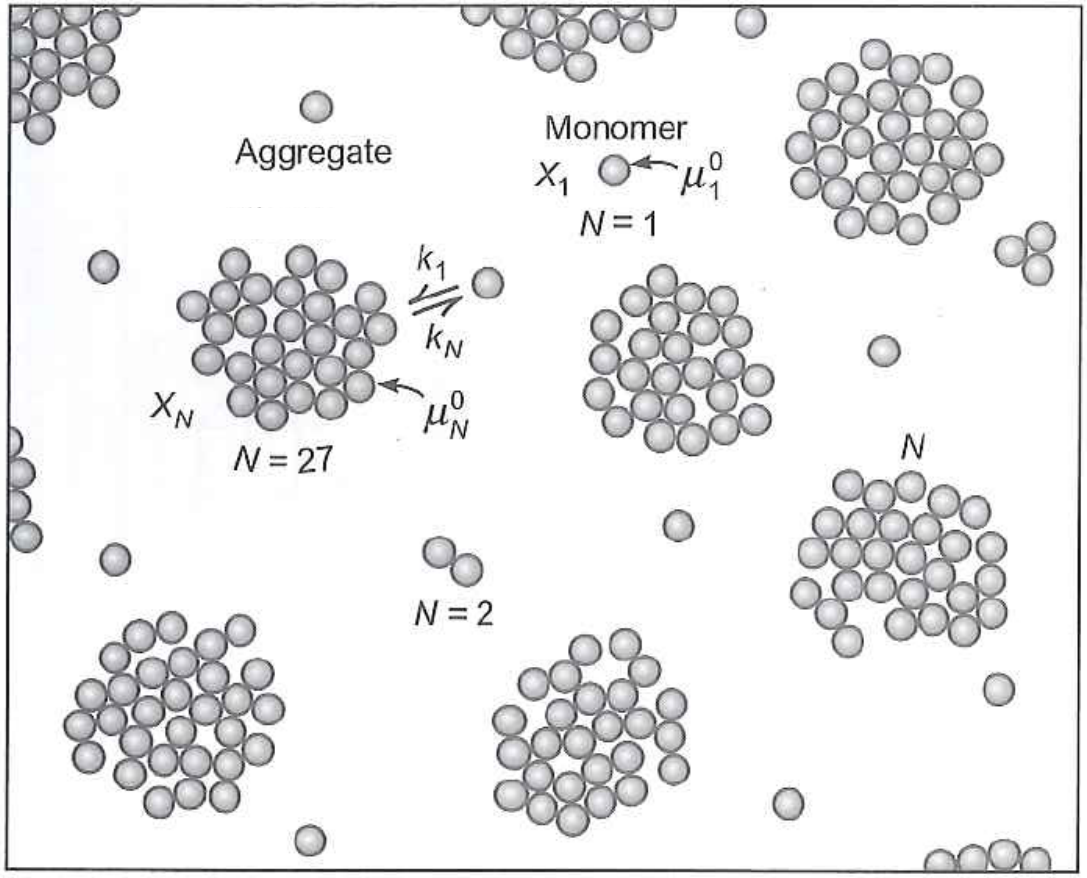
Self-assembly

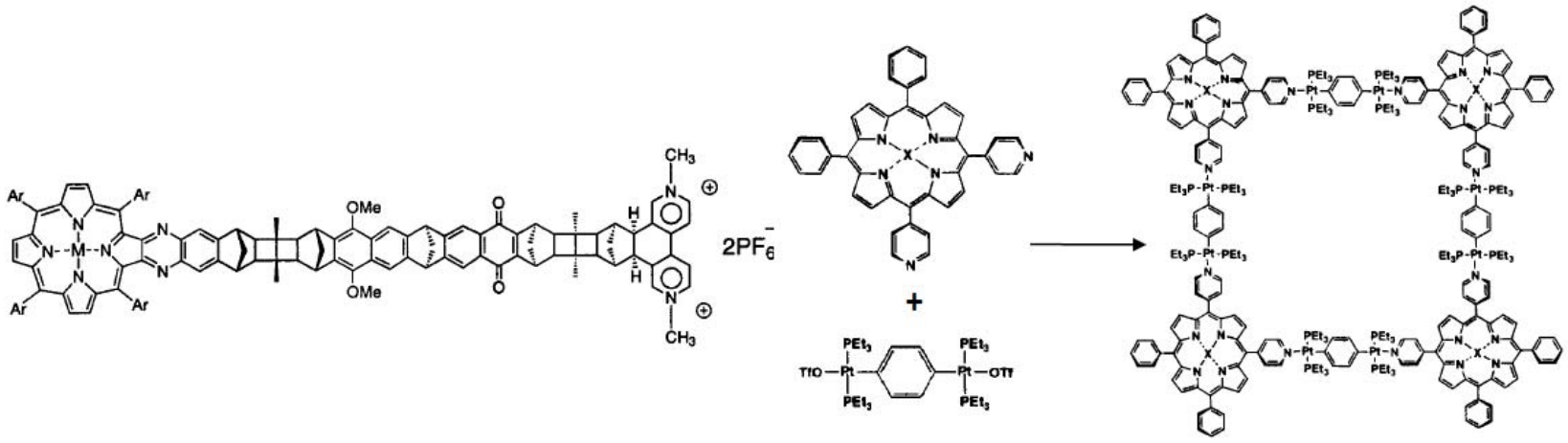
Molecules that want to stay togheter



Self-assembly: individual molecules group together, driven by intermolecular forces to form associated structures

Self-assembly

Molecules that want to stay togheter



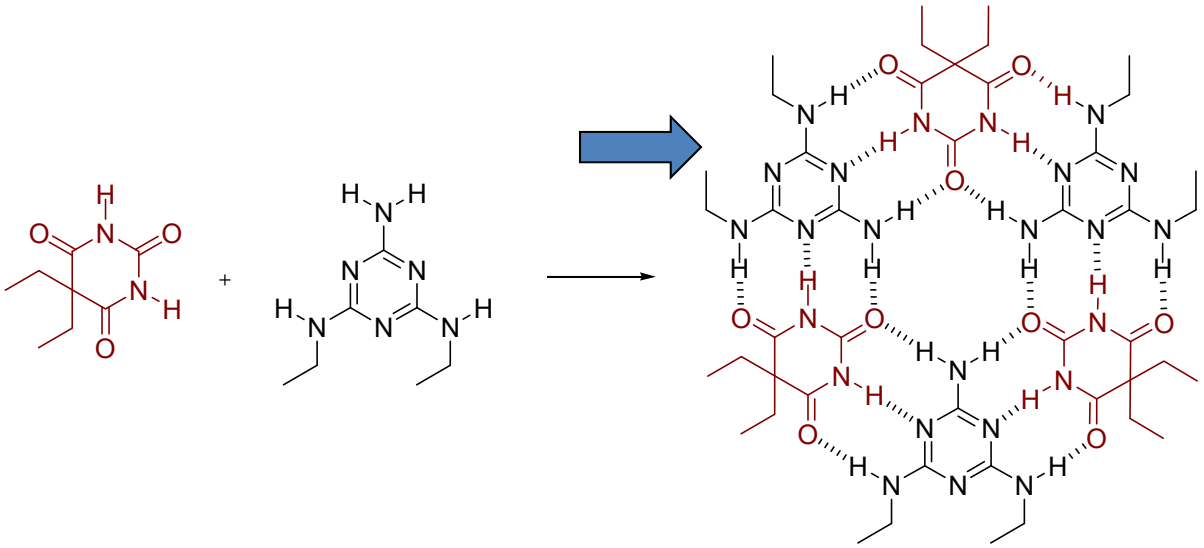
Paddon-Row *et al.*
Chem.Eur.J. **1999**, *5*, 2518

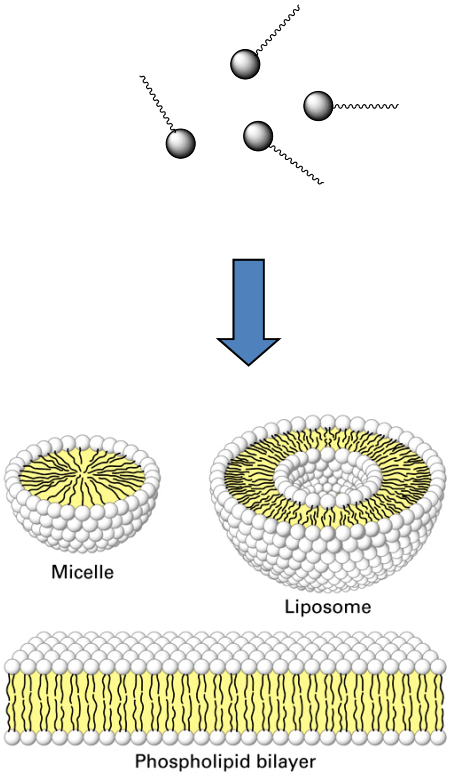
Stang *et al.*
JACS **1999**, *121*, 2741

Characteristics

building block	atom	molecule
target	molecules	assemblies
bond type	covalent	ionic, hydrophobic, metal-coordination, H-bond
bond energy	35-135 kcal/mol	2 - 20 kcal/mol
kinetic stability	high	low (dynamic structures !!!)

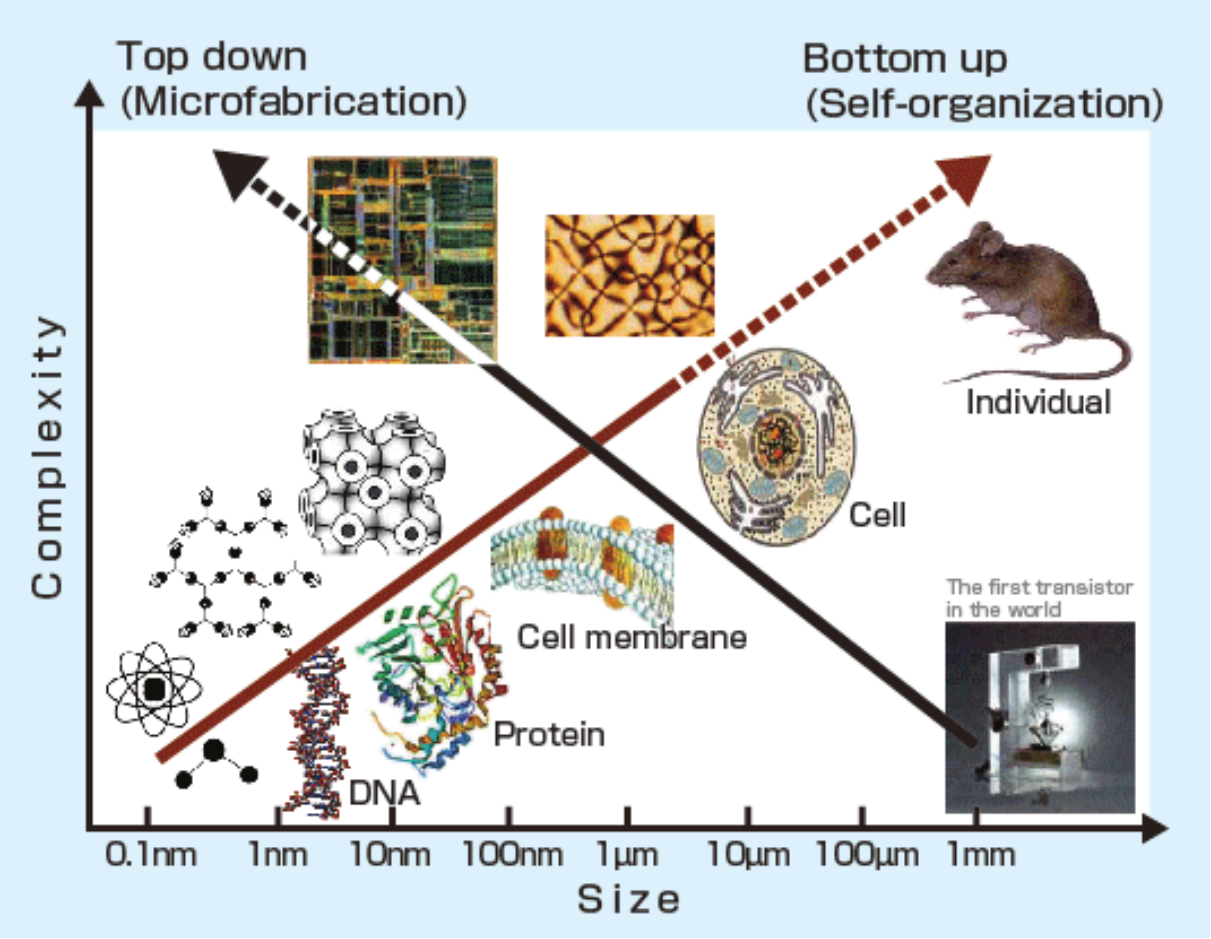
Bottom-up





CHIMICA SUPRAMOLECOLARE

Top-down vs Bottom-up



Self-assembly

Thermodynamic principles

$$\mu = \mu_1^0 + kTlnX_1 = \mu_2^0 + \frac{1}{2}kTln\frac{1}{2}X_2 = \mu_3^0 + \frac{1}{3}kTln\frac{1}{3}X_3 = \cdots$$

$$\mu = \mu_N = \mu_N^0 + \frac{kT}{N}ln\left(\frac{X_N}{N}\right) \qquad N = 1, 2, 3, \ldots$$

μ_N is the mean chemical potential of a molecule in an aggregate of N molecules, μ_0 is the standard part of the chemical potential, X_N is the concentration (activity) of molecules in aggregates with number N.

$$X_N = N\left(X_1 e^{\frac{\mu_1^0 - \mu_N^0}{kT}}\right)^N \qquad C = X_1 + X_2 + X_3 + \cdots = \sum_{N=1}^{\infty} X_N$$

Where N = 1 (isolate monomer in solution) has been chosen as reference state, X are mole fractions and can never exceed unity.

Self-assembly

Conditions to form an aggregate

If the interaction of a molecule is similar in the aggregate or in the free state

$$\mu_1^0 = \mu_2^0 = \mu_3^0 = \ldots = \mu_N^0$$

$$X_N = N\left(X_1 e^{\frac{\mu_1^0 - \mu_N^0}{kT}}\right)^N \qquad X_N = NX_1^N$$

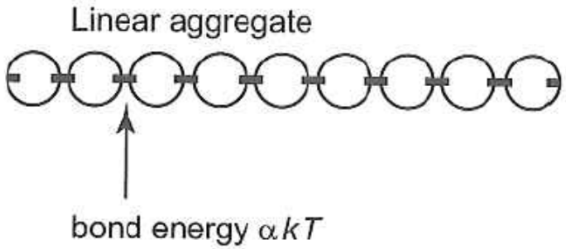
since $X_1 < 1$, then $X_N << X_1$: aggregates don't form.

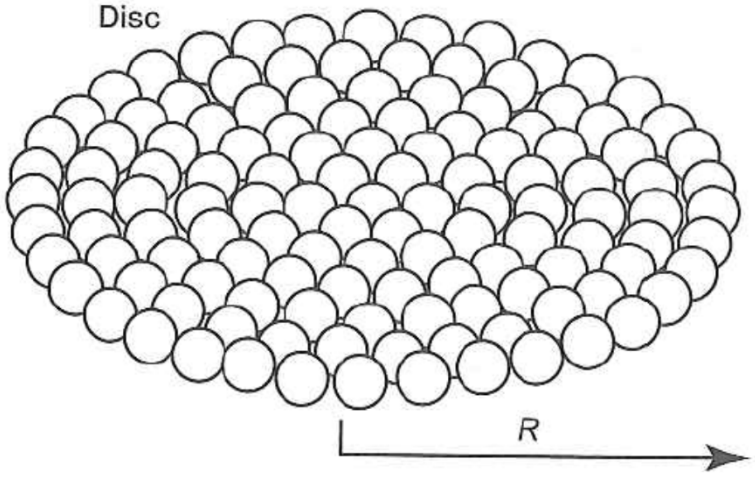
To allow aggregates formation is necessary that

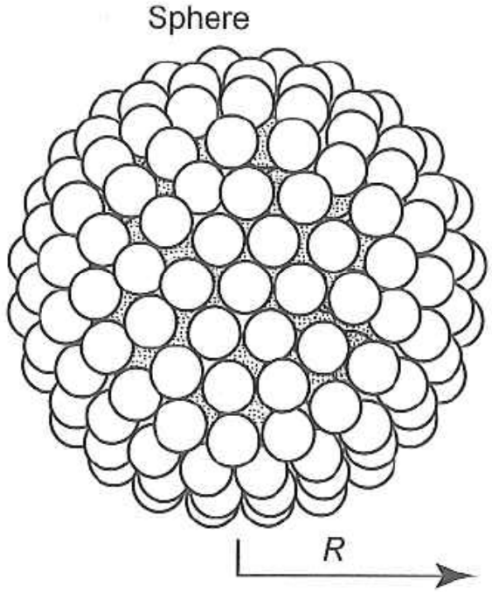
$$\mu_N^0 < \mu_1^0$$

Self-assembly

Effect of dimensionality







Self-assembly

Effect of dimensionality

The total aggregate energy is $N\mu_N^0$. If $-\alpha kT$ is the monomer-monomer interaction energy in the aggregate:

$$N\mu_N^0 = -(\mathrm{N}-1)\alpha kT$$

$$\mu_N^0 = \mu_\infty^0 + \frac{\alpha kT}{N}$$

In the case of a spherical aggregate, since N is proportional to volume (R^3) and unbounded molecules to the surface (R^2) and thus to $N^{2/3}$

$$\mu_N^0 = \mu_\infty^0 + \frac{\alpha kT}{N^{\frac{1}{3}}}$$

$$\mu_N^0 = \mu_\infty^0 + \frac{\alpha kT}{N^p}$$

Self-assembly

Critical micelle concentration (CMC)

Given the general form of μ_N^0, can we predict the aggregate formation?:

$$X_N = N\left(X_1 e^{\frac{\mu_1^0 - \mu_N^0}{kT}}\right)^N \qquad \mu_N^0 = \mu_\infty^0 + \frac{\alpha kT}{N^p}$$

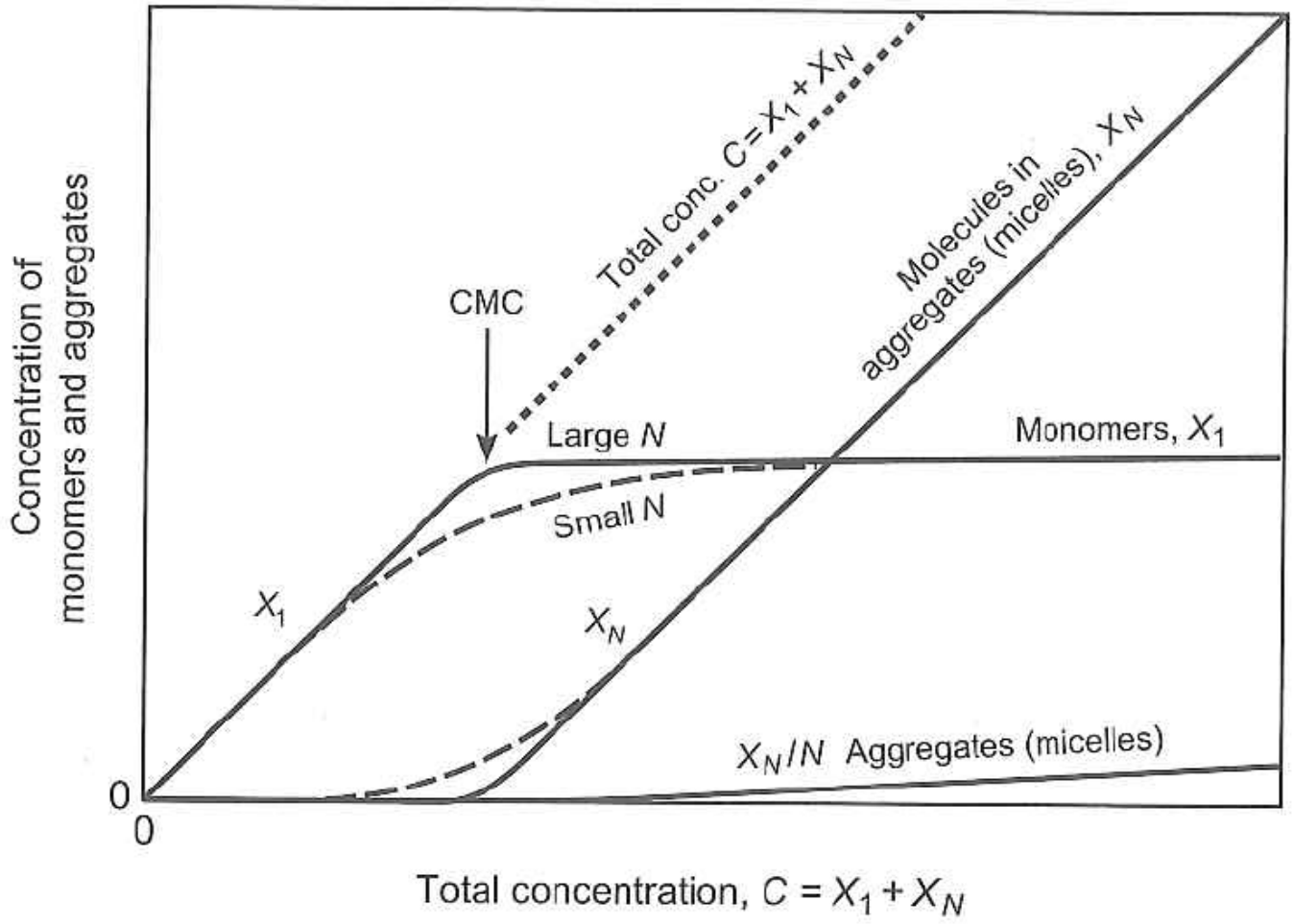
$$X_N = N\left(X_1 e^{\alpha\left(1-\frac{1}{N^p}\right)}\right)^N \approx N(X_1 e^{\alpha})^N$$

When X_1 is very small, $X_1 e^{\alpha}$ is <1 and $X_1 > X_2 > X_3 > \ldots$, hence no aggregates form.
When X_1 approaches $e^{-\alpha}$ it cannot increase further since X_N would exceed unity, aggregates start to form.

$$X_1(crit.) = CMC \approx e^{-\alpha}$$

Self-assembly

Critical micelle concentration (CMC)



Self-assembly

Phase separation versus micellization

For spherical aggregates (p = 1/3)

$$X_N = N\left(X_1 e^{\alpha\left(1-\frac{1}{N^p}\right)}\right)^N = N(X_1 e^{\alpha})^N e^{-\alpha N^{\frac{2}{3}}}$$

Above the CMC $X_1 e^{\alpha} \approx 1$, hence:

$$X_N \approx N e^{-\alpha N^{\frac{2}{3}}}$$

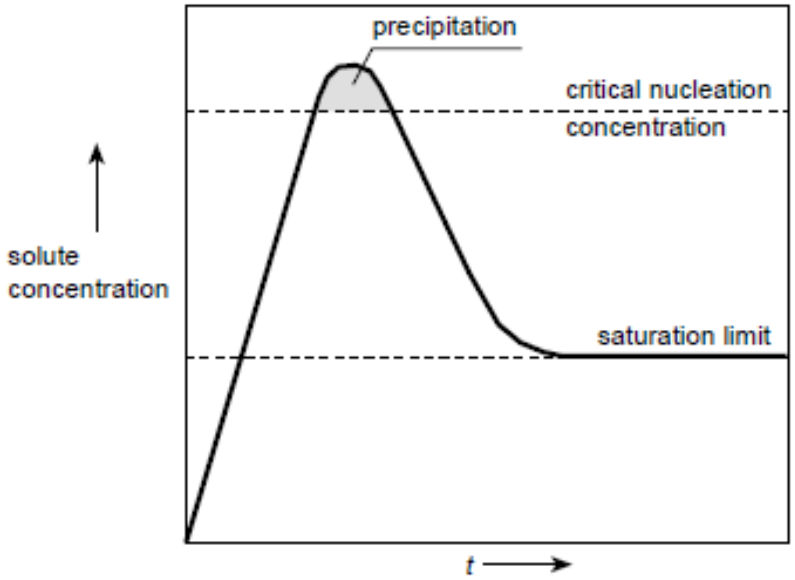
For any resonable a value, (usually greater than 1), concentration of aggregates drops very rapidly and no aggregates larger than 4-5 units form in appreciable concentration.

What happens? A phase transition occurs to a separate phase, or an aggregate of infinite size. This always occur for p < 1 (not for linear aggregates and rods).

Nanoparticles growth: precipitates

"chemical growth of bulk or nanometer-sized materials inevitably involves the process of precipitation of a solid phase from solution"

Chem. Rev., 2005, 105, 1025



Nanoparticles growth

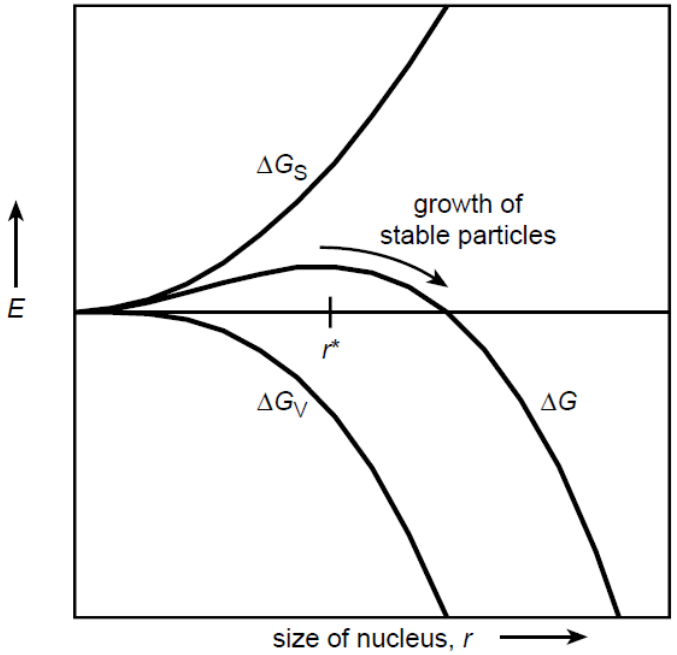
$$\Delta G = -\frac{4}{V}\pi r^3 k_B T \ln(S) + 4\pi r^2 \gamma$$

Free energy variation for the formation of a spherical particle

Molecular volume of the building block

Saturation ratio (bulk solution/infinite cristal surface)

Surface tension



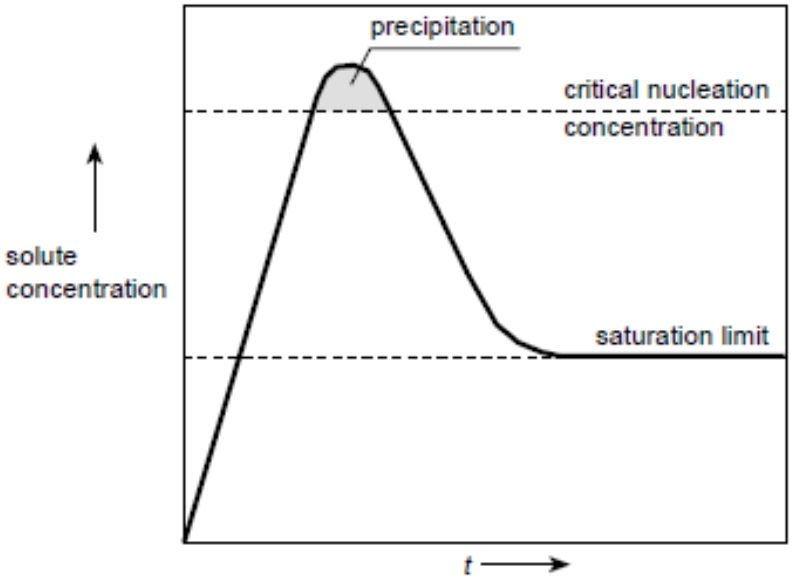
r > r* → growth

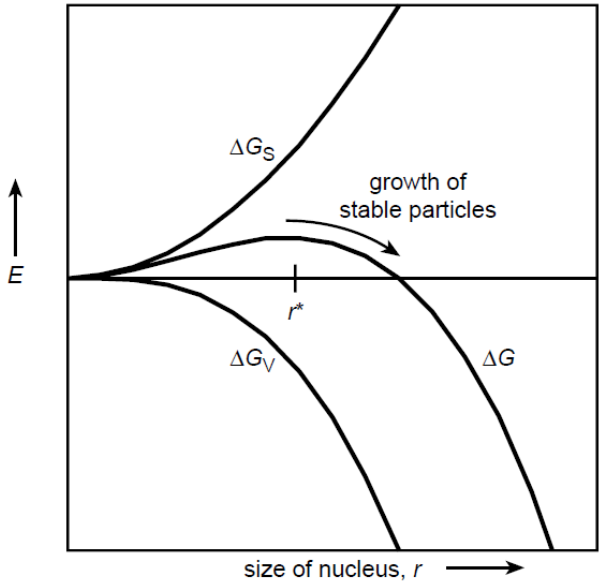
r < r* → dissolution

Smaller particles grow more rapidly than larger ones → **focusing**

Nanoparticles growth

SHORT TIMES

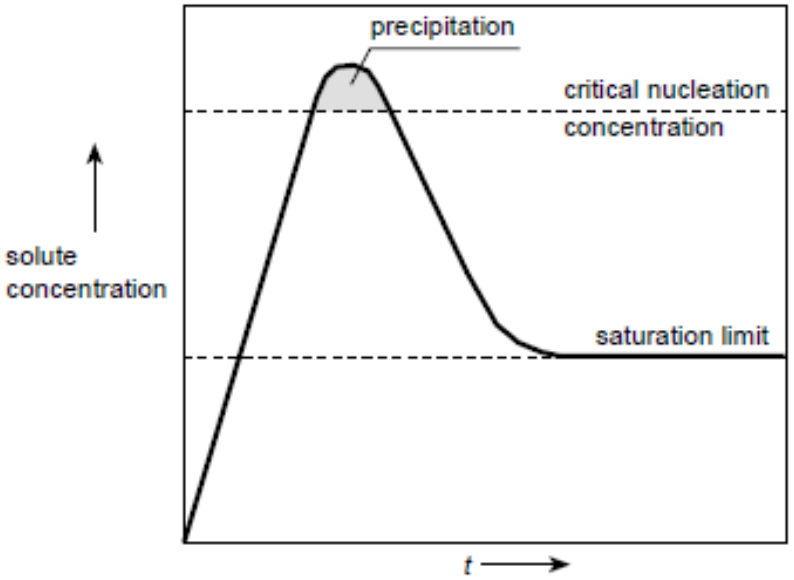


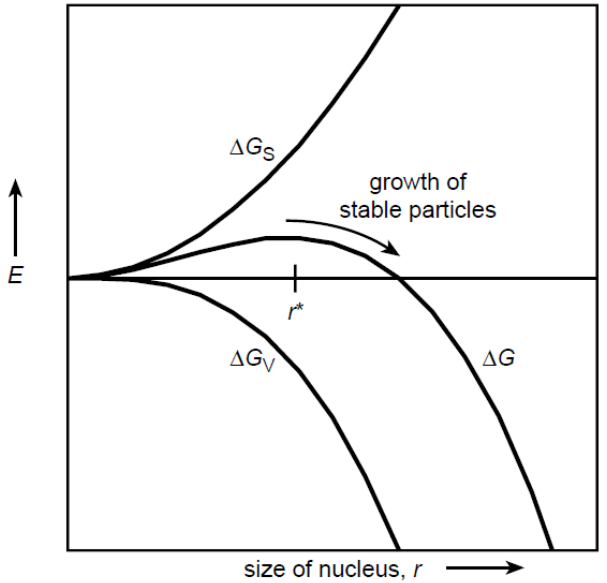


1. Concentration raises above critical nucleation concentration (cnc): nucleation **starts**.
2. Nucleation causes concentration to decrease below cnc: nucleation stops, growth goes on by molecular surface addition.
3. Smaller particles grow more rapidly than larger → size focusing
4. Concentration reaches the saturation limit → growth stops

Nanoparticles growth

LONG TIMES

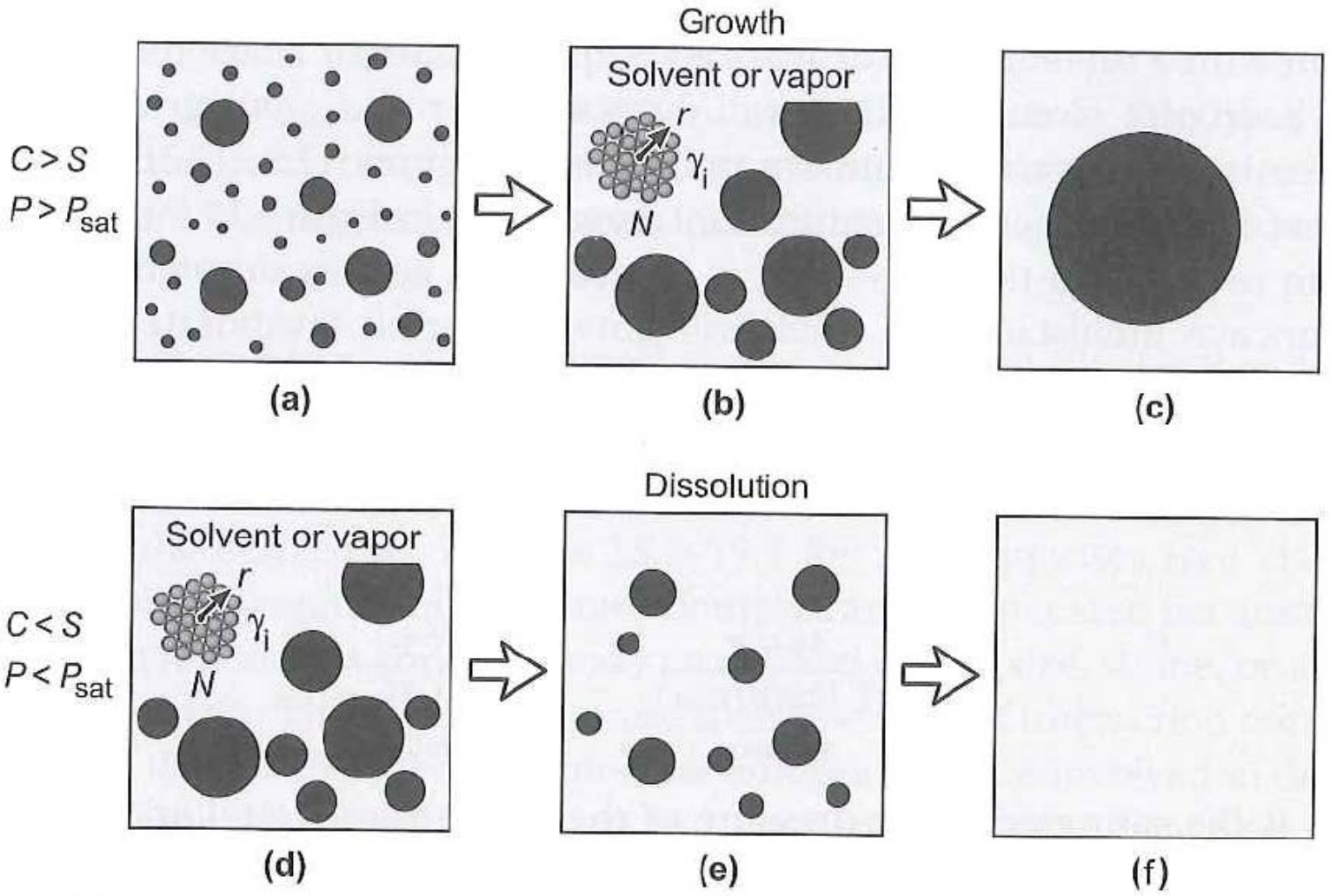




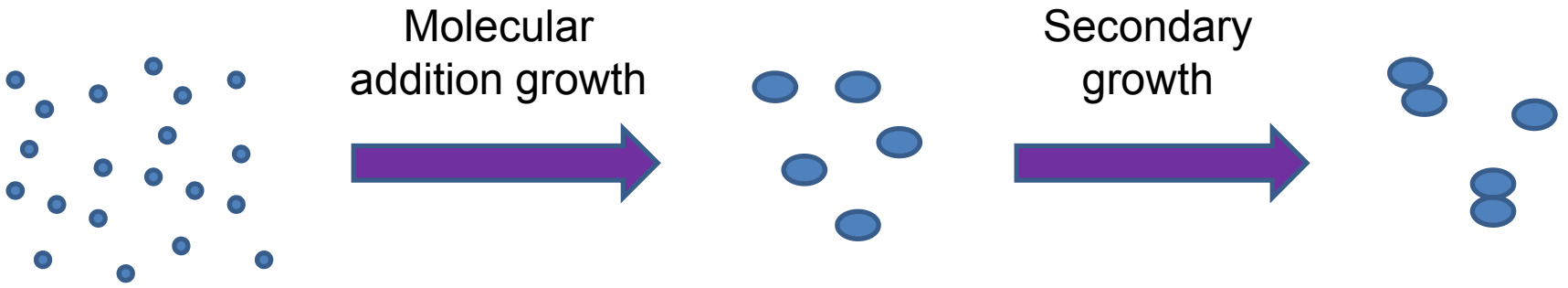
1. Bulk concentration has decreased: S decreases and r* increases
2. The smaller nanoparticles are now unstable, if the reaction is reversible, they can dissolve
3. Smaller particles dissolve more slowly than larger ones → size defocusing (Ostwald)
4. If long reaction times are allowed, r < r* nanoparticles dissolve → focusing (Ostwald)

Self-assembly

Ostwald ripening



Nanoparticles growth: secondary growth



1. After their formation, small aggregates start collapsing to form larger ones
2. Growth by aggregation is faster than molecular addition
3. Aggregation stops when nanoparticles reach colloidal stability

Surface stabilization

All the nanoparticles tend to aggregate: aggregation decreases the total surface and hence the second term of the equation (related to surface tension)

$$\Delta G = -\frac{4}{V}\pi r^3 k_B T \ln(S) + 4\pi r^2 \gamma$$

Free energy variation for the formation of a spherical particle

Molecular volume of the building block

Saturation ratio (bulk solution/infinite cristal surface)

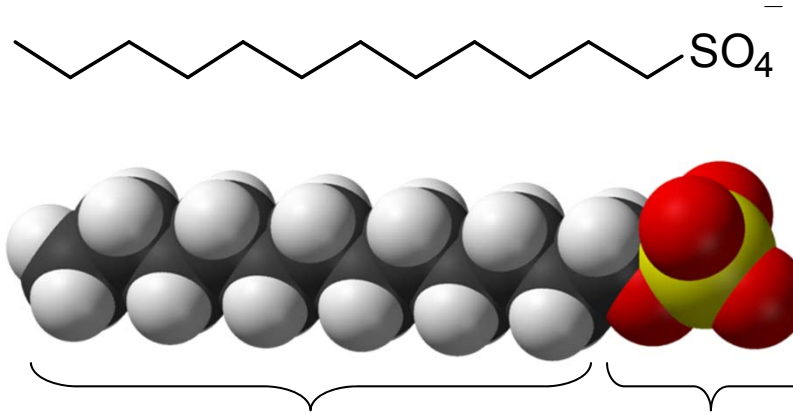
Surface tension

Surface tension is **decreased** by:

- **Electrostatic repulsion** (surface charge)
- **Steric repulsion**

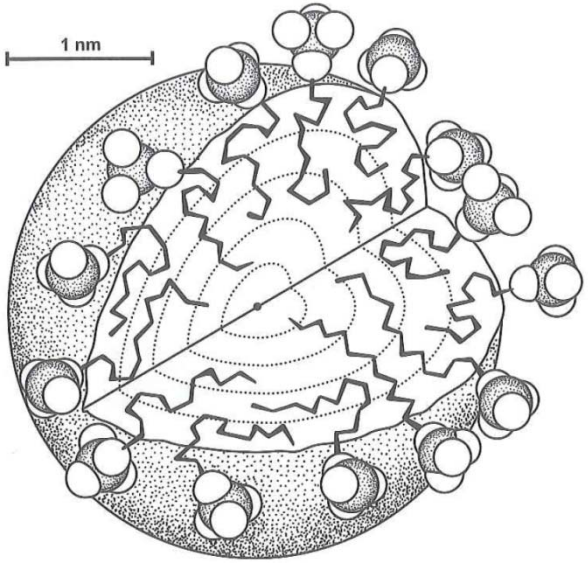
Stabilizing agents can be added to the nanoparticles in order to prevent aggregation: **surfactants**

Tensioattivi

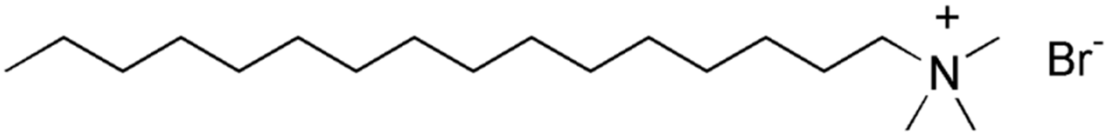


(Sodio) DodecilSolfato (SDS)

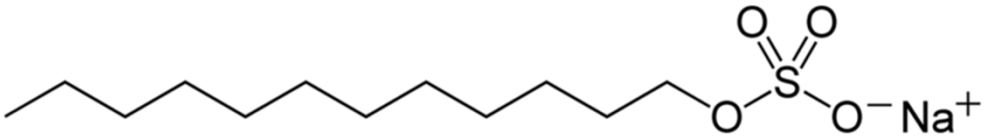
TENSIOATTIVO



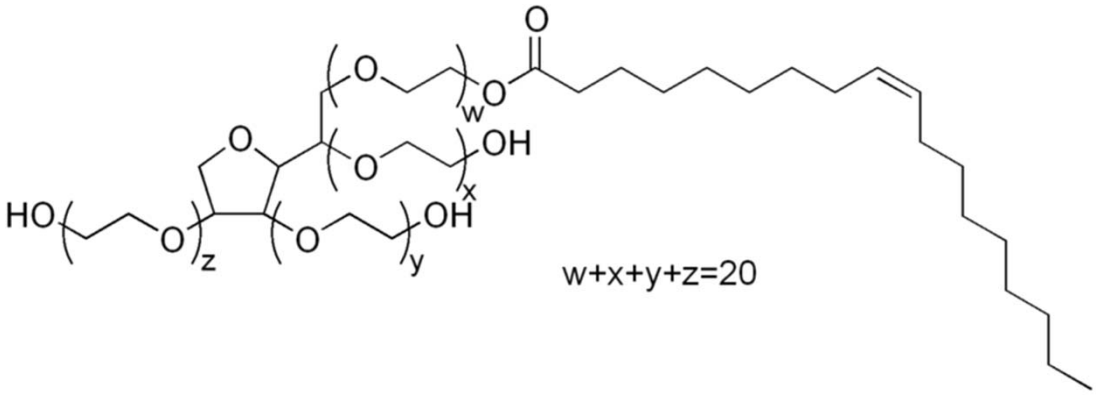
Tensioattivi



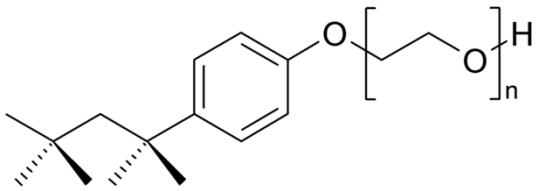
CTABr (cmc =$8 \cdot 10^{-4}$ M)



SDS (cmc =$8 \cdot 10^{-3}$ M)



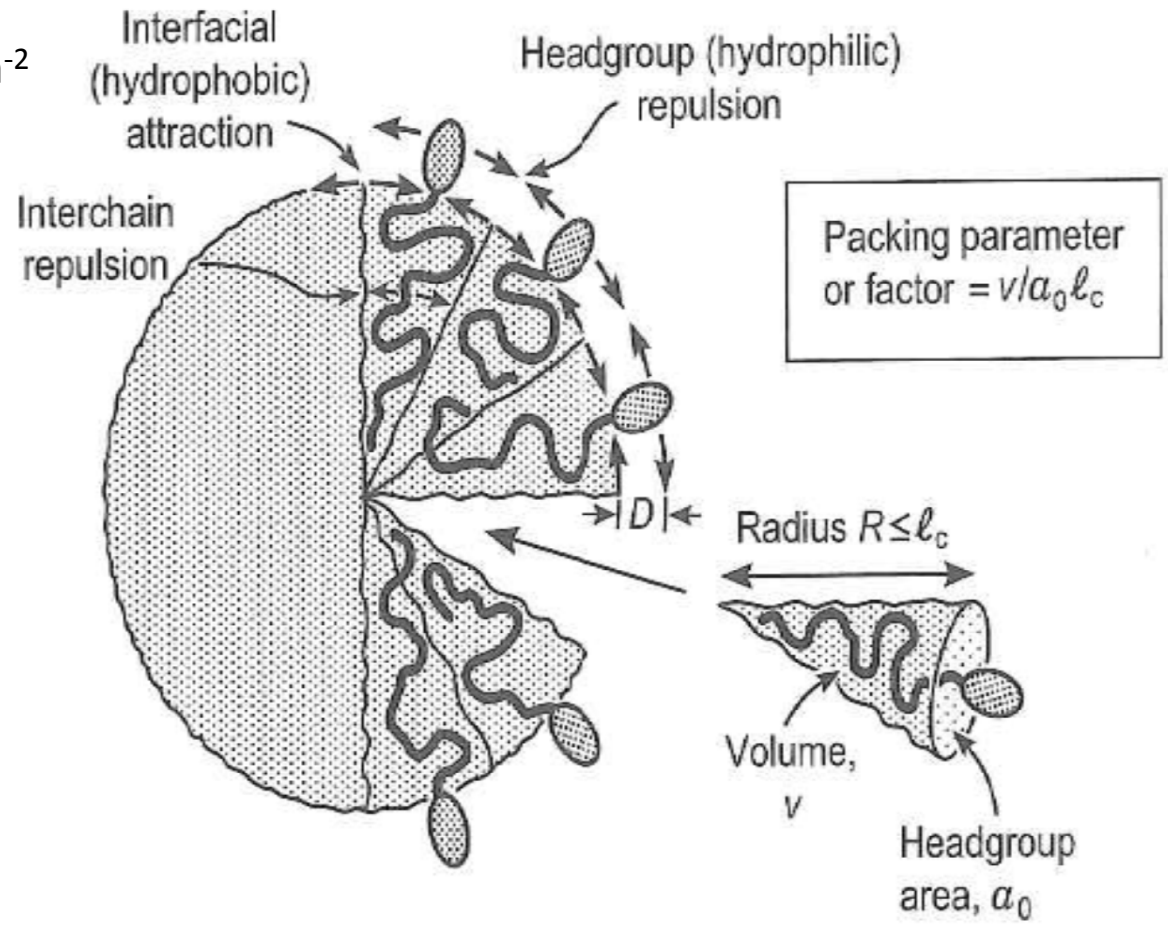
Tween 80 (cmc =$1.2 \cdot 10^{-5}$ M)



Triton X-100 (cmc =$3 \cdot 10^{-4}$ M)

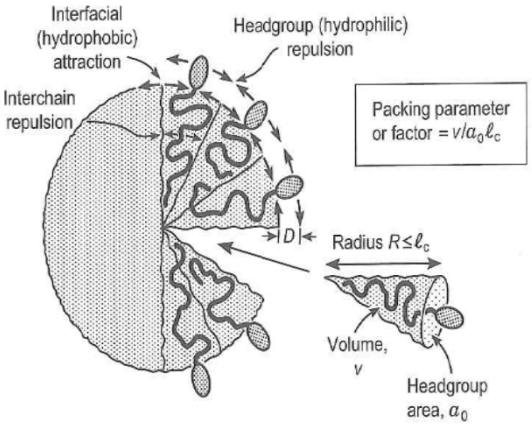
Micelles

20-50 mJ m^{-2}



Micelles

Optimal headgroup area



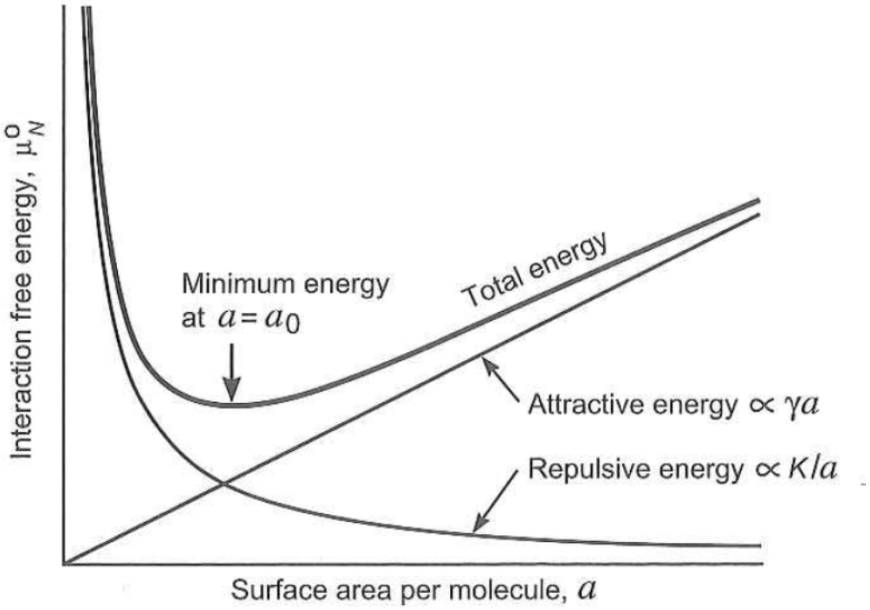
$$\mu_N^0 = \gamma a + \frac{K}{a}$$

Repulsive contribution

Attractive contribution

$$\mu_N^0(min) = 2\gamma a_0 \qquad a_0 = \sqrt{\frac{K}{\gamma}}$$

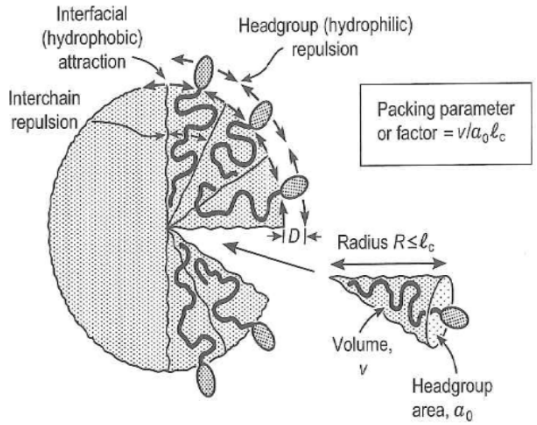
$$\mu_N^0 = 2\gamma a_0 + \frac{\gamma}{a}(a - a_0)^2$$



Micelles

Spherical micelles

To have a spherical micelle a_0 must be sufficiently large and v sufficiently small to allow the micelle radius to not exceed l_c. For a spherical micelle of radius R and mean aggregation number M we have:



$$M = \frac{4\pi R^2}{a_0} = \frac{4\pi R^3}{3v}$$

$$R = \frac{3v}{a_0}$$

$$\frac{v}{a_0 l_c} < \frac{1}{3}$$

$$l_c < l_{max} \approx (0.154 + 0.1265n)\ nm$$

$$v \approx (27.4 + 26.9n) \times 10^{-3}\ nm^3$$

$$SDS, M = 74$$

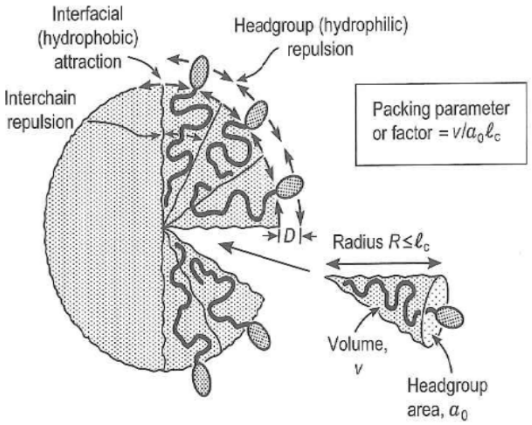
$$v \approx 0.352\ nm^3$$

$$R = 1.84\ nm \qquad a_o = 0.57\ nm^2$$

$$l_c = 1.67\ nm \qquad \frac{v}{a_0 l_c} = 0.37$$

Micelles

Packing parameter



NORMAL STRUCTURES

Larger, more hydrated headgroups
Lower ionic strength, Larger D/ℓ_C
Lower pH (cationics), higher pH (anionics)
Lower temperature (non-ionics)

INVERTED STRUCTURES

Smaller, less hydrated headgroups
Higher ionic strength, Smaller D/ℓ_C
Higher pH (cationics), Lower pH (anionics)
Higher temperature (non-ionics)

LARGER a_0 | SMALLER a_0

$V/a_0\ell_C$	1/3	1/2	1.0	2	3
HLB	40	20	10	2	1

SMALLER V, LARGER ℓ_C | LARGER V, SHORTER ℓ_C

Single, saturated chains
Shorter chains, larger D/ℓ_C
Less oil-penetration
Higher MW oil

Branched, unsaturated chains
Double-chains, Higher temperature
Greater oil-penetration
Co-surfactant addition

Self-assembly

Linear aggregates

For linear aggregates (p = 1)

$$X_N = N\left(X_1 e^{\alpha\left(1-\frac{1}{N^p}\right)}\right)^N = N(X_1 e^{\alpha})^N e^{-\alpha}$$

Above the CMC $X_1 e^{\alpha} \approx 1$, hence:

$$X_N \approx N e^{-\alpha}$$

The concentration of molecules in the aggregates is proportional to the aggregate size with no phase separation. Only for very large N the $(X_1 e^{\alpha})^N$ term begins to dominate, bringing the X_N concentration to 0 for very large X_1 concentration. The distribution is hence highly polydisperse.

$$N_{max} = M = \sqrt{C e^{\alpha}}$$ ← Strong dependence from α

Micelles

Nonspherical aggregates

Surfactant and lipids with smaller headgroup area don't respect the relationship:

$$\frac{v}{a_0 l_c} < \frac{1}{3}$$

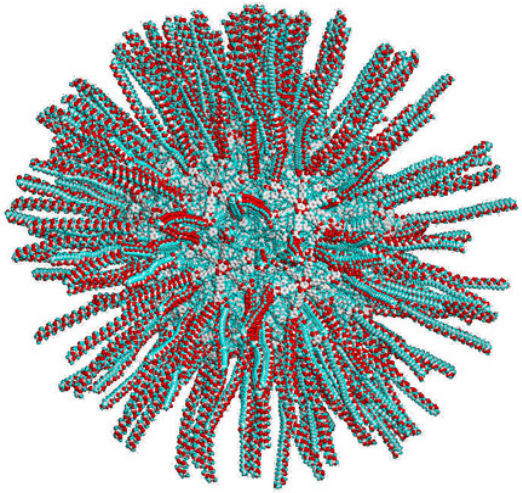
And cannot pack into spherical micelles but form cylindircal micelles that respect the linear aggregates rules.

$$N_{max} = M = \sqrt{Ce^{\alpha}}$$

Since aggregation number is higly sensitive to a, change in enviromental conditions strongly affect cilindical micelles.

For SDS, M ~ 60 in water and M ~ 1000 in 0.6 M NaCl.

Aggregati di tensioattivi: micelle



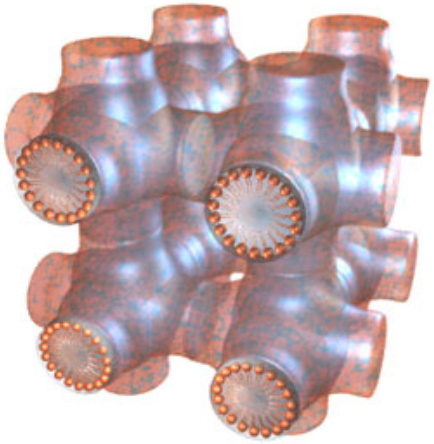
Micella sferica

Micella cilindrica

Le micelle hanno un diametro tra 5 e 20 nm ed un **numero di aggregazione** medio pari a 50-100.

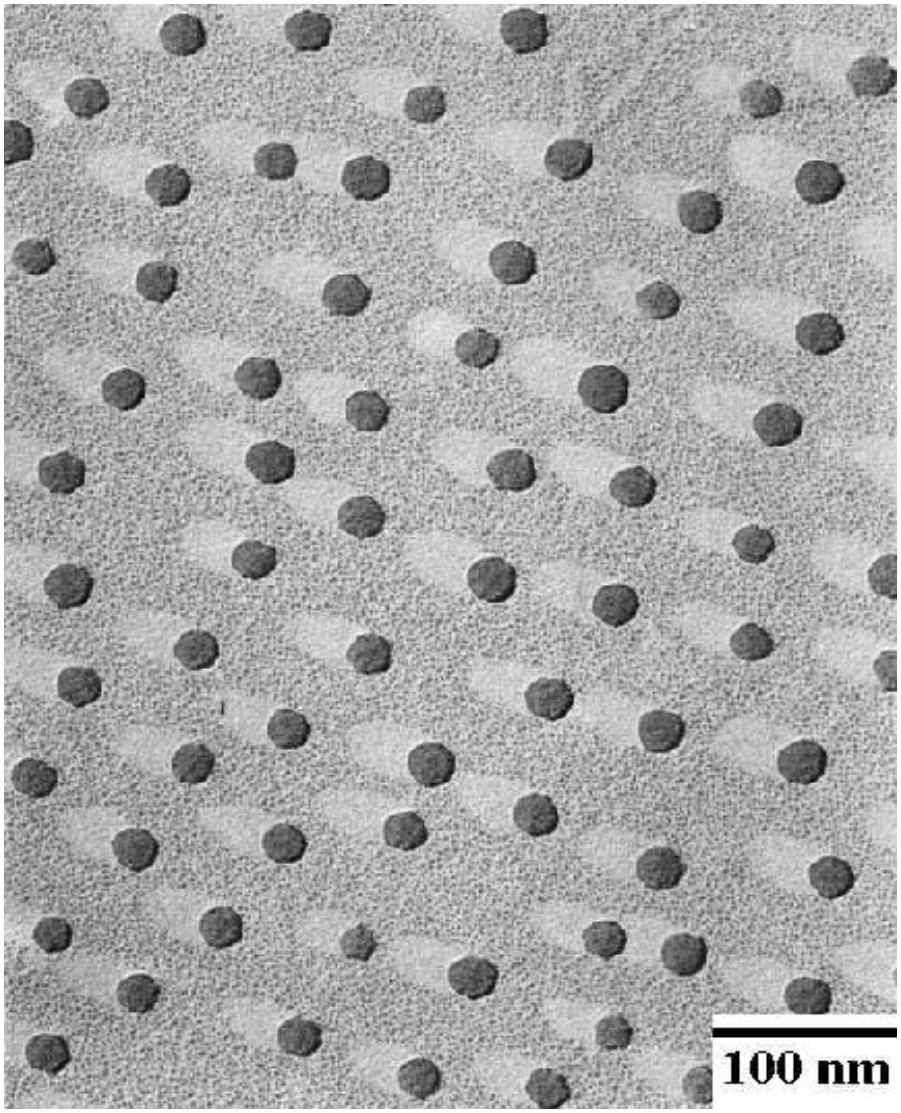
All'aumentare della concentrazione sono possibili morfologie diverse.

struttura tubolare ad impaccamento esagonale

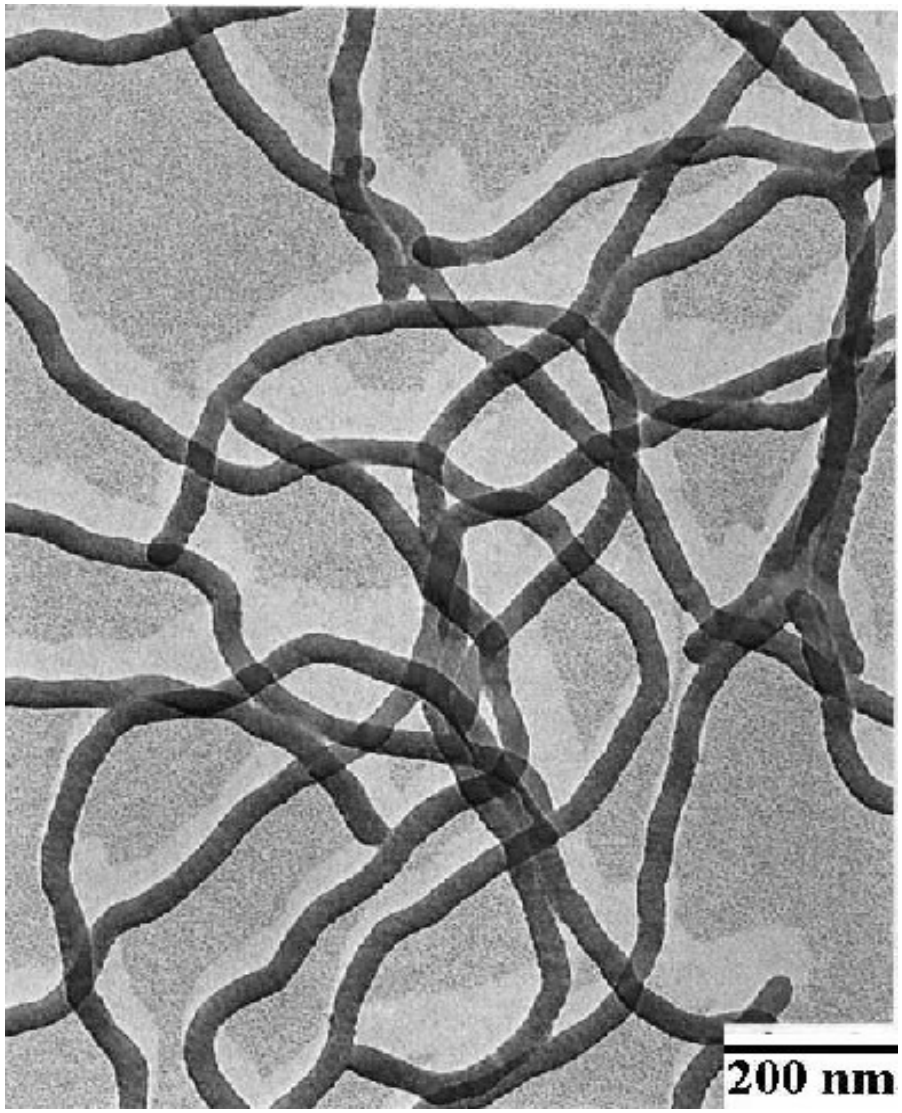


struttura tubolare ramificata

Aggregati di tensioattivi: micelle



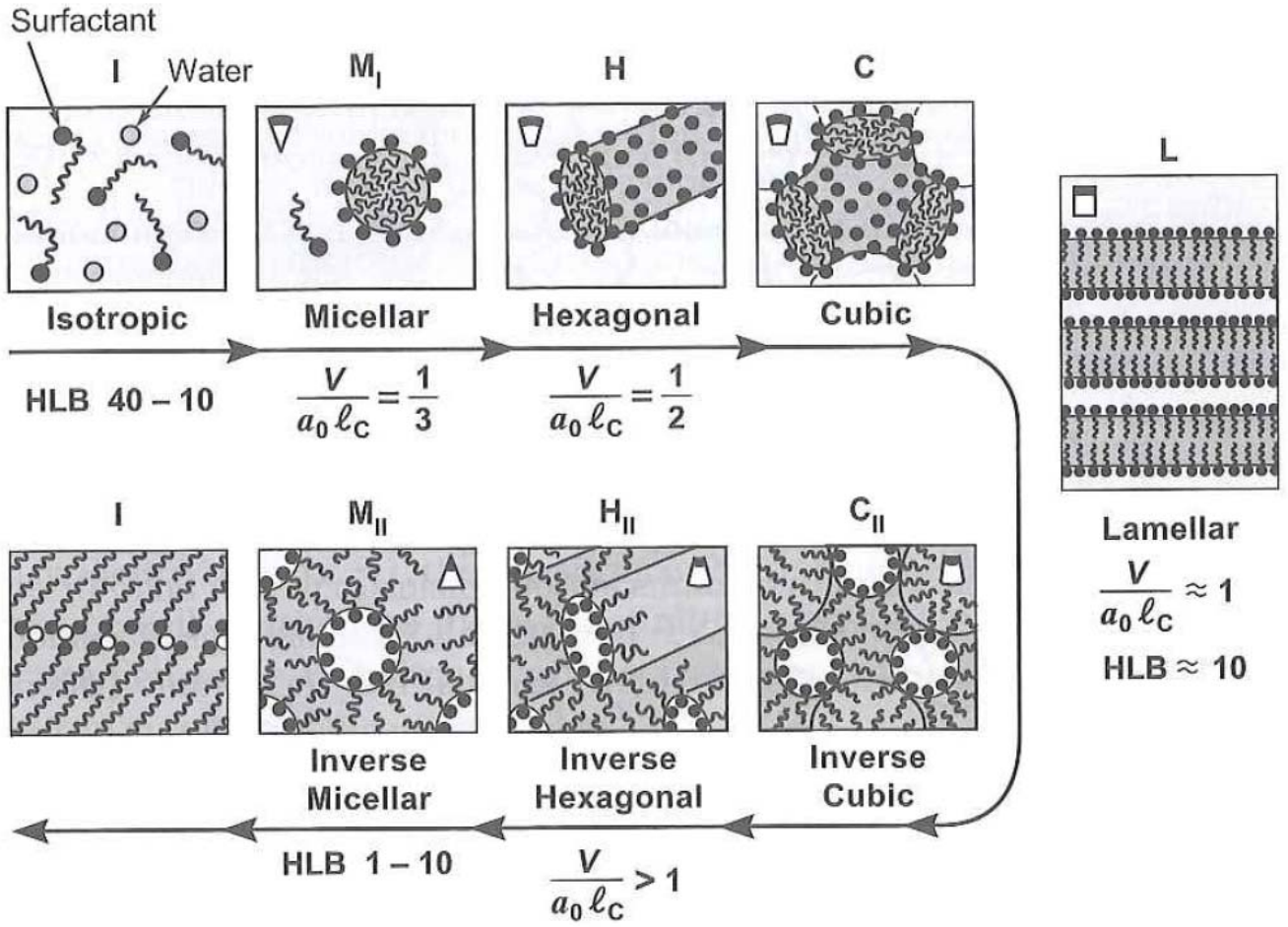
Spherical micelles of PS-PAA amphiphile



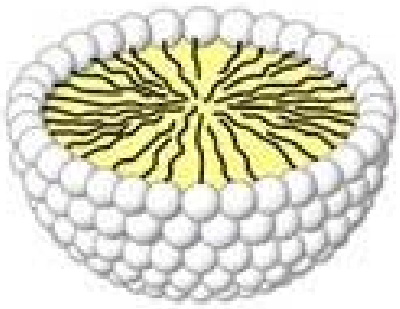
Cylindrical micelles of PS-PAA amphiphile

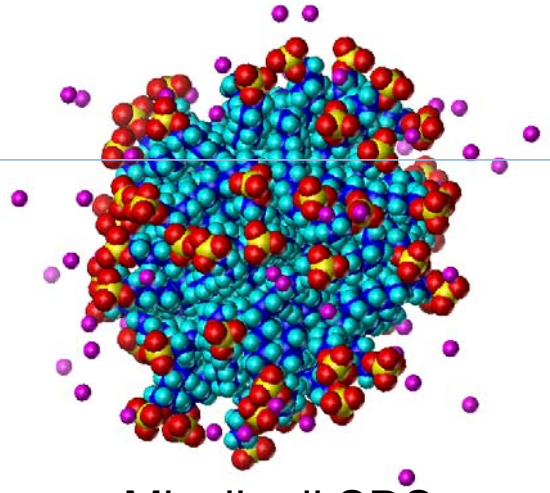
Micelles

Sperical micelles

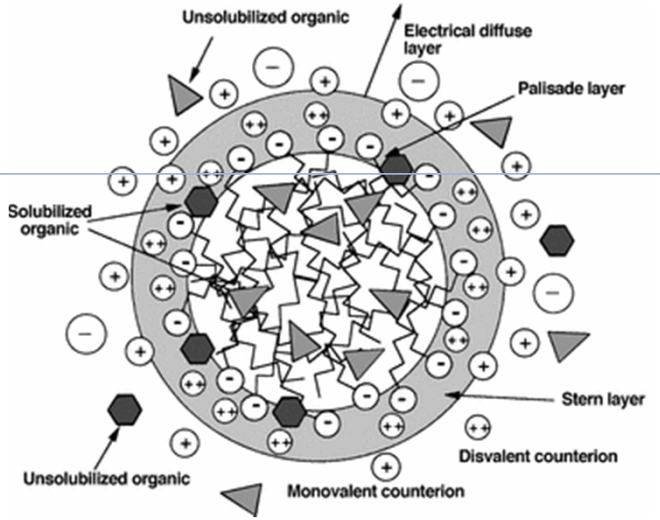


Aggregati di tensioattivi: micelle





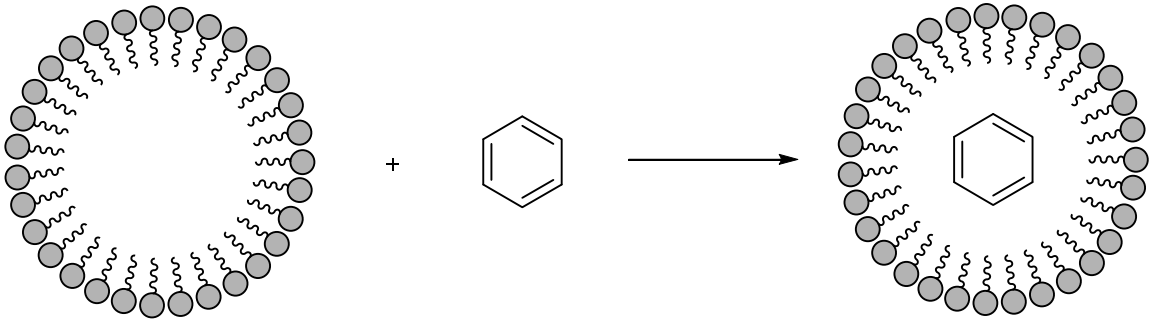
Micella di SDS



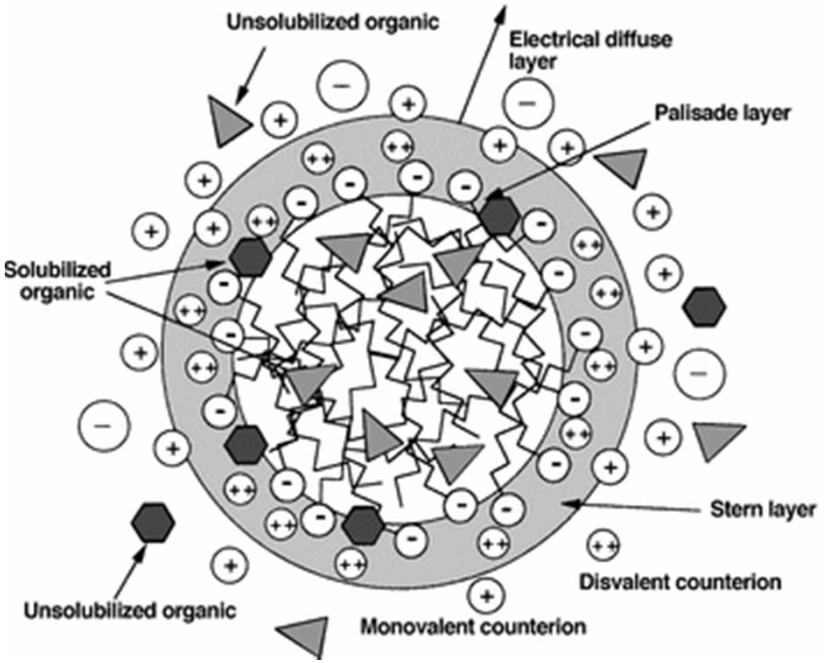
Normalmente, le micelle sono visualizzate come aggregati sferici (**Modello di Hartley**) in cui le teste polari sono esposte al solvente e mascherano le code idrofobiche. In realtà, la struttura delle micelle è dinamica, con un elevato grado di disordine.

Se il tensioattivo è ionico, la micella è circondata da una corona, detta **strato di Stern**, ricco di ioni di carica opposta a quella delle teste polari.

Micelle: solubilizzazione



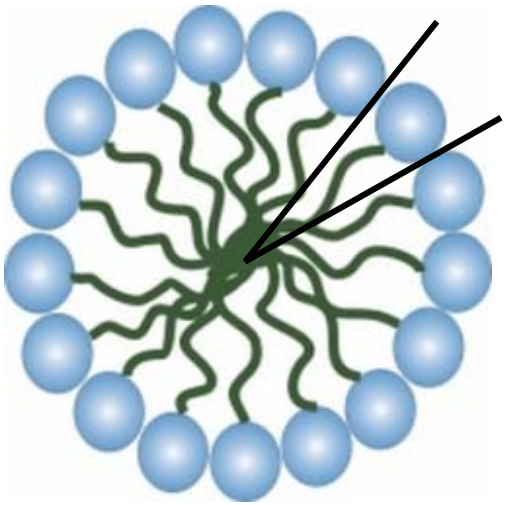
La capacità delle micelle di solubilizzare molecole organiche consente la detergenza



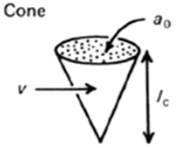
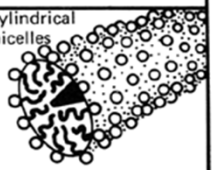
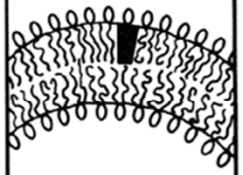
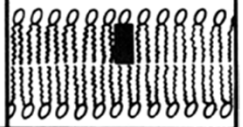
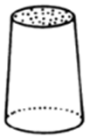
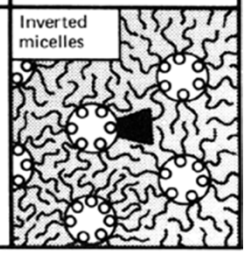
Micelle, controioni, molecole solubilizzate formano un sistema di grande complessità

Altre morfologie

L'impaccamento sferico richiede che il tensioattivo occupi un volume conico

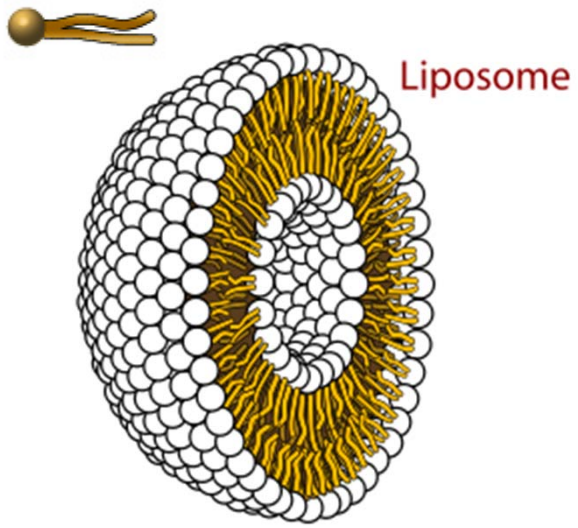


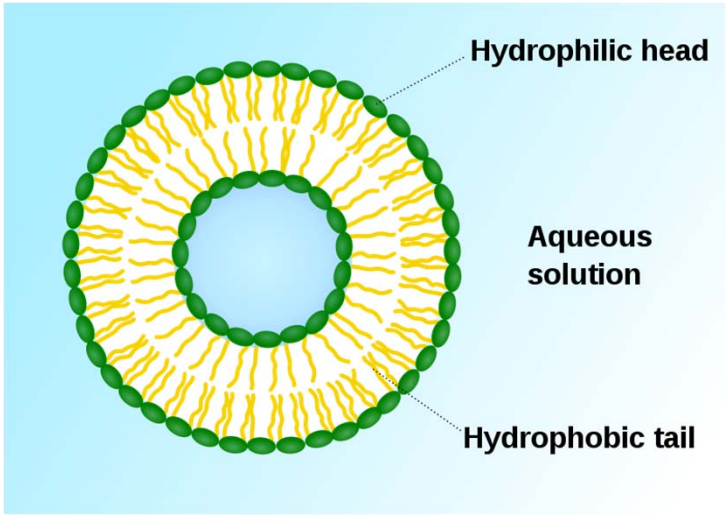
Se la forma è diversa, possono formarsi altre tipologie di aggregati

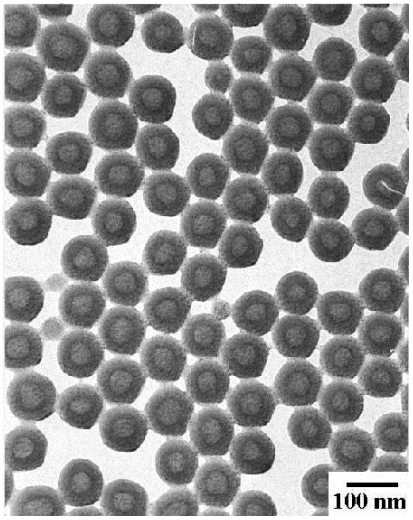
Lipid	Critical packing parameter $v/a_0 l_c$	Critical packing shape	Structures formed
Single-chained lipids (surfactants) with large head-group areas: *SDS in low salt*	$< 1/3$	Cone 	Spherical micelles 
Single-chained lipids with small head-group areas: *SDS and CTAB in high salt, nonionic lipids*	1/3-1/2	Truncated cone 	Cylindrical micelles 
Double-chained lipids with large head-group areas, fluid chains: *Phosphatidyl choline (lecithin), phosphatidyl serine, phosphatidyl glycerol, phosphatidyl inositol, phosphatidic acid, sphingomyelin, DGDG[a], dihexadecyl phosphate, dialkyl dimethyl ammonium salts*	1/2-1	Truncated cone 	Flexible bilayers, vesicles 
Double-chained lipids with small head-group areas, anionic lipids in high salt, saturated frozen chains: *phosphatidyl ethanolamine, phosphatidyl serine + Ca^{2+}*	~1	Cylinder 	Planar bilayers 
Double-chained lipids with small head-group areas, nonionic lipids, poly *(cis)* unsaturated chains, high *T*: *unsat. phosphatidyl ethanolamine, cardiolipin + Ca^{2+} phosphatidic acid + Ca^{2+} cholesterol, MGDG[b]*	> 1	Inverted truncated cone or wedge 	Inverted micelles 

[a] DGDG, digalactosyl diglyceride, diglucosyl diglyceride.
[b] MGDG, monogalactosyl diglyceride, monoglucosyl diglyceride.

Vescicole e doppi strati

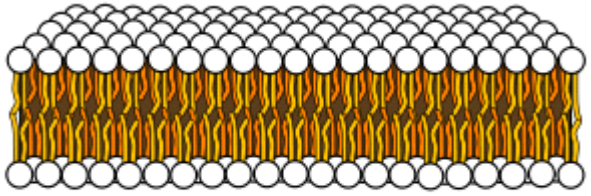






Vescicola/liposoma

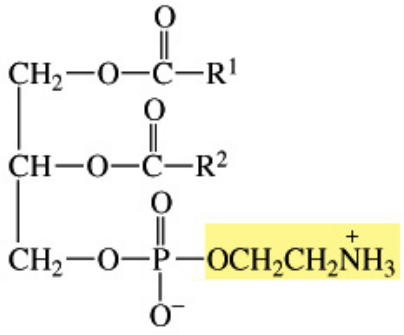
Amphiphiles with two hydrophobic tails have a *v* value about 2-fold the one of single tail anphiphiles, hence the:



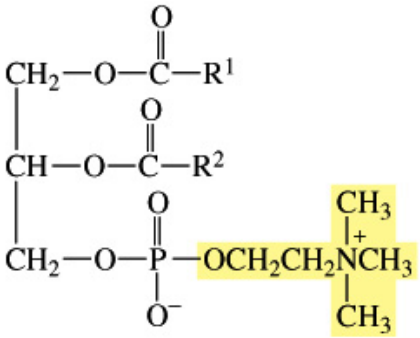
Doppio strato

Cylindrical structure of such amphiphiles nicely fits a bilayer packing.

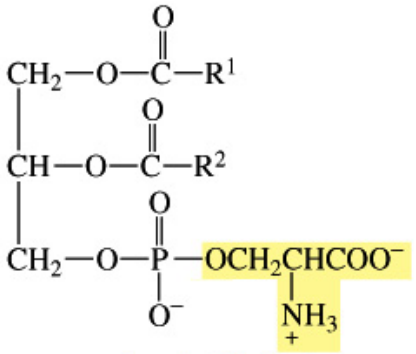
Tensioattivi bicoda



a phosphatidylethanolamine
a cephalin

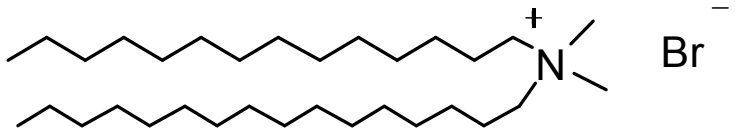


a phosphatidylcholine
a lecithin



a phosphatidylserine

Natural bilayer-forming amphiphiles (phospholipides)



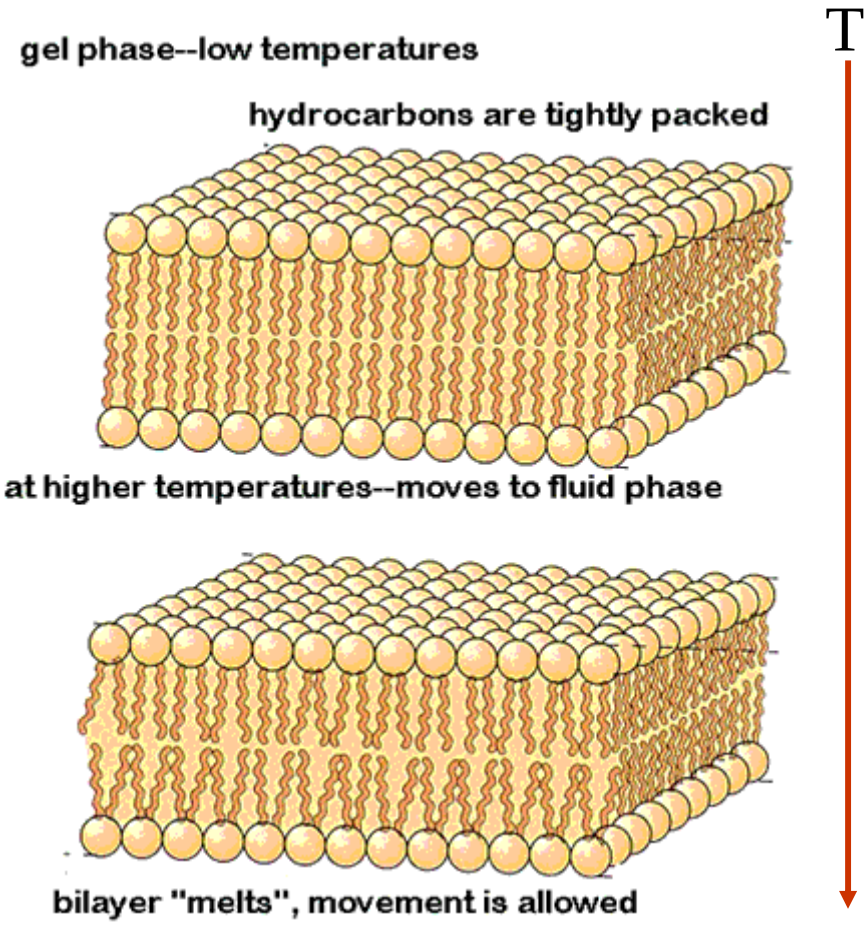
Synthetic bilayer-forming amphiphile

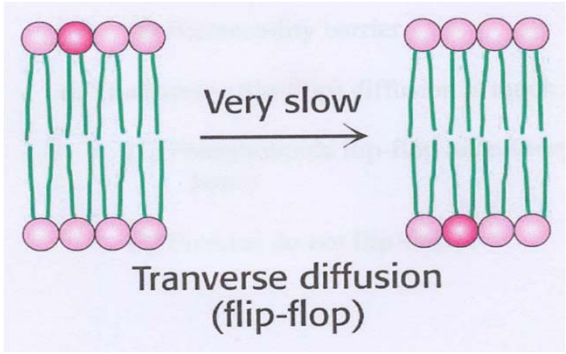
Doubling of the lipophilic chains affects not only packing:

- Amphipiles hydrophobicity is higher ⇨ lower CMC (CMC = $e^{-\alpha}$): mic. 10^{-2}-10^{-5}M, bl 10^{-6}-10^{-10}M
- Interaction energy is higher ⇨ higher residence time: mic. 10^{-4} s, bl 10^{4} s

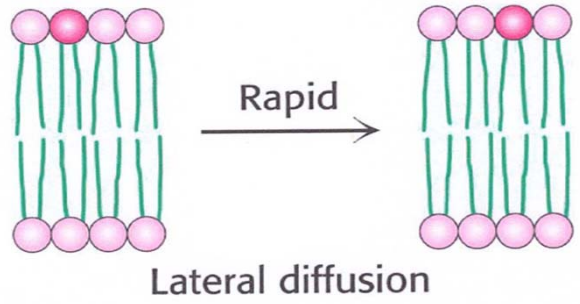
These features depend on the surfactant structure and not on the double layer one: residence time of a single tail surfactant in a bilayer is much shorter than that of double chain ones.

Liposomi





Il passaggio di un tensioattivo da una parte del doppio strato alla parte opposta è sempre molo lento. Il movimento dalla stessa parte dello strato è rapido.



A bassa T le catene idrocarburiche sono completamente estese ed impaccate (**fase gel**), ad alta T le catene diventano più mobili (fase fluida). La transizione avviene ad una determinata T detta di transizione di fase.

Liposomi

For a bilayer to curve, outer surfactants must pack into a truncated cone:

$$R_c \approx \frac{l_c}{1 - \frac{v}{a_0 l_c}}$$ Critical radius

$$N \approx 8\pi R^2 / a_0$$ Aggregation number

$$t \approx \frac{2v}{a_0}$$ thickness

PC (phosphatidiylcholine)

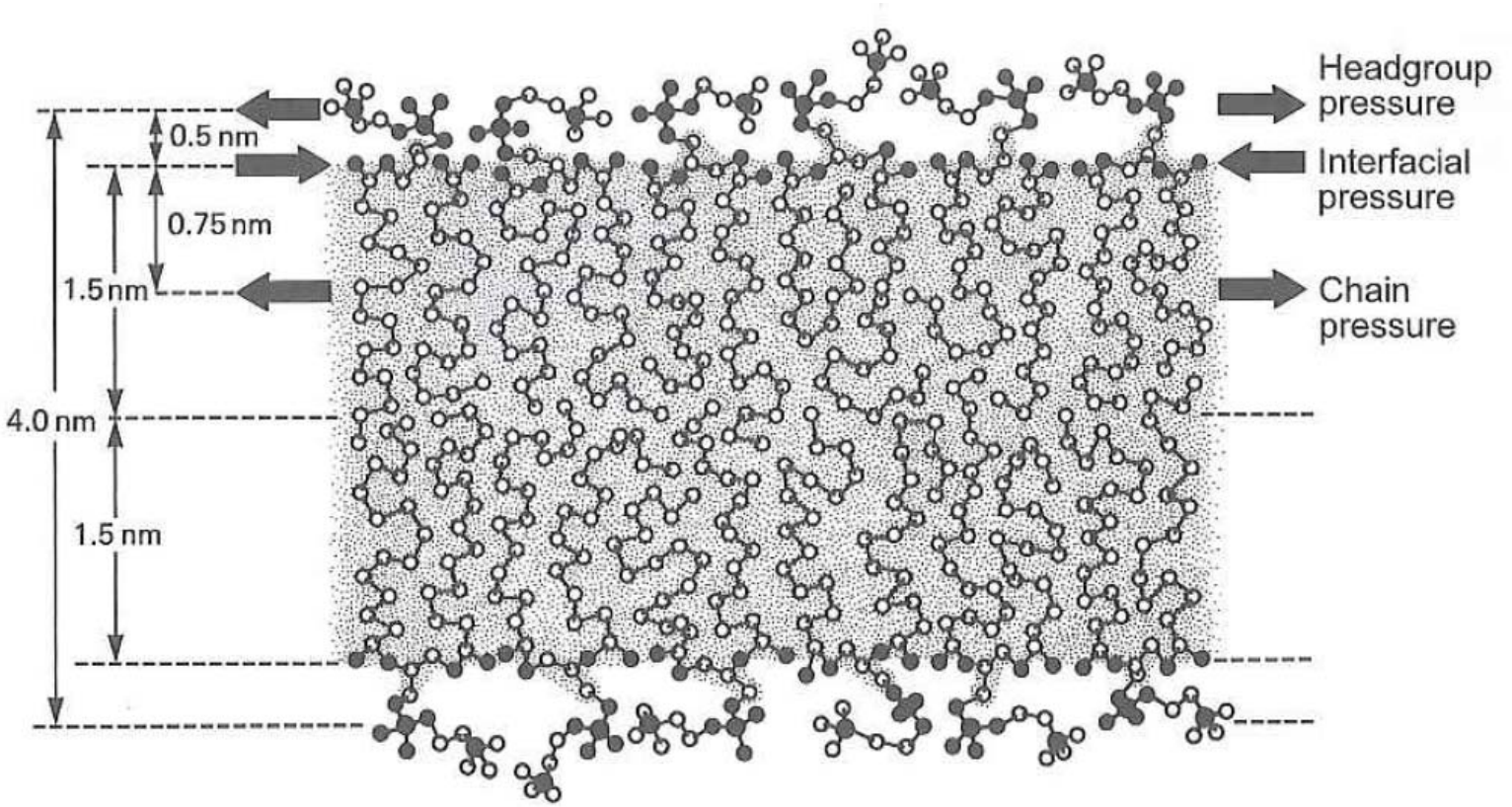
$$a_o \approx 0.717\ nm^2 \qquad v \approx 1.063\ nm^3$$

$$l_c \approx 1.75\ nm$$

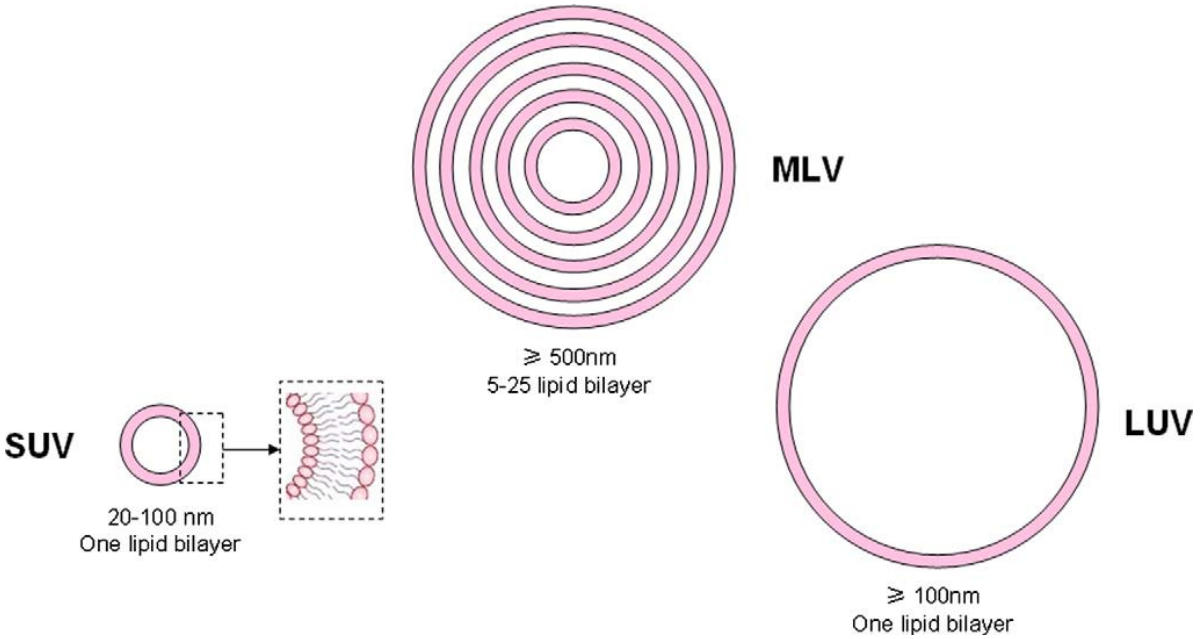
$$\frac{v}{a_0 l_c} \approx 0.85 \qquad R_c = 11\ nm$$

$$t \approx 3\ nm \qquad N \approx 3000$$

Liposomi

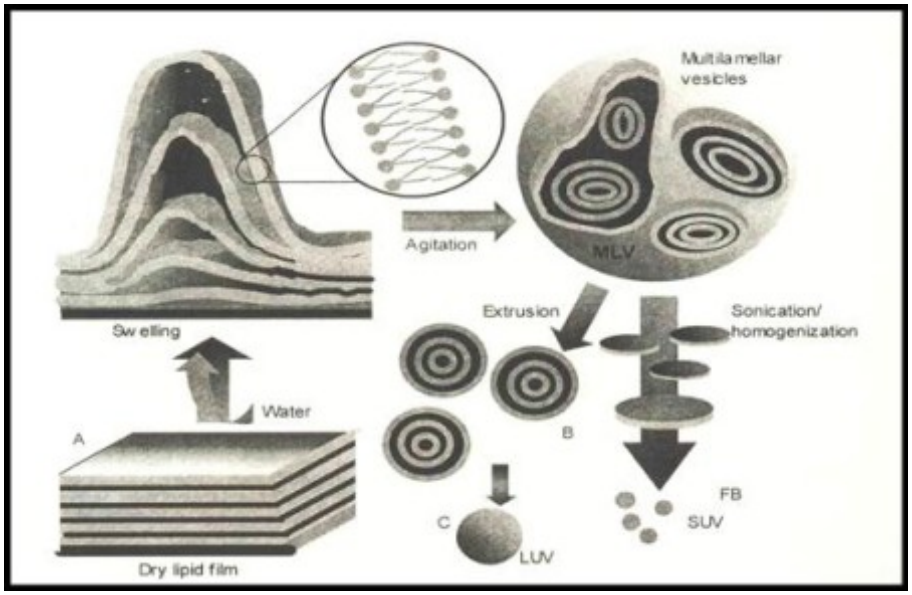

0.5 nm
0.75 nm
1.5 nm
4.0 nm
1.5 nm
Headgroup pressure
Interfacial pressure
Chain pressure

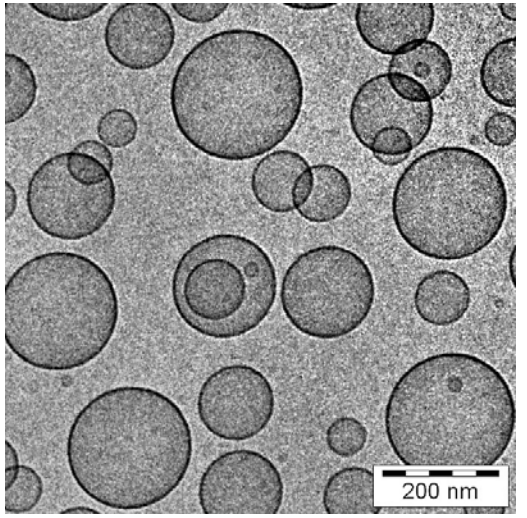
Vescicole e doppi strati

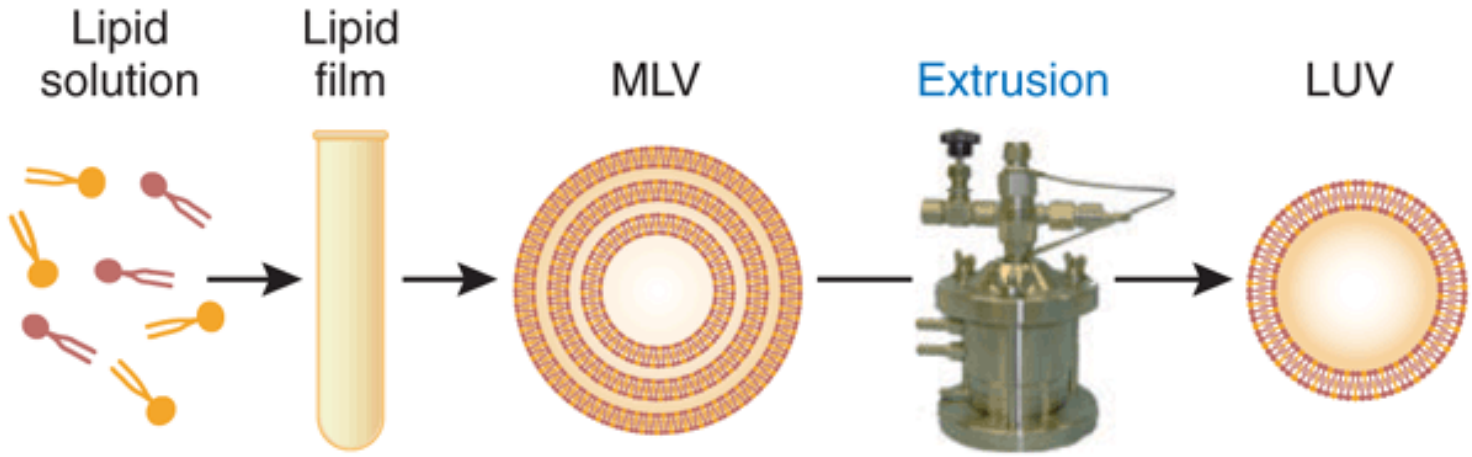


Liposomes: synthesis

Classical methods: sonication and extrusion



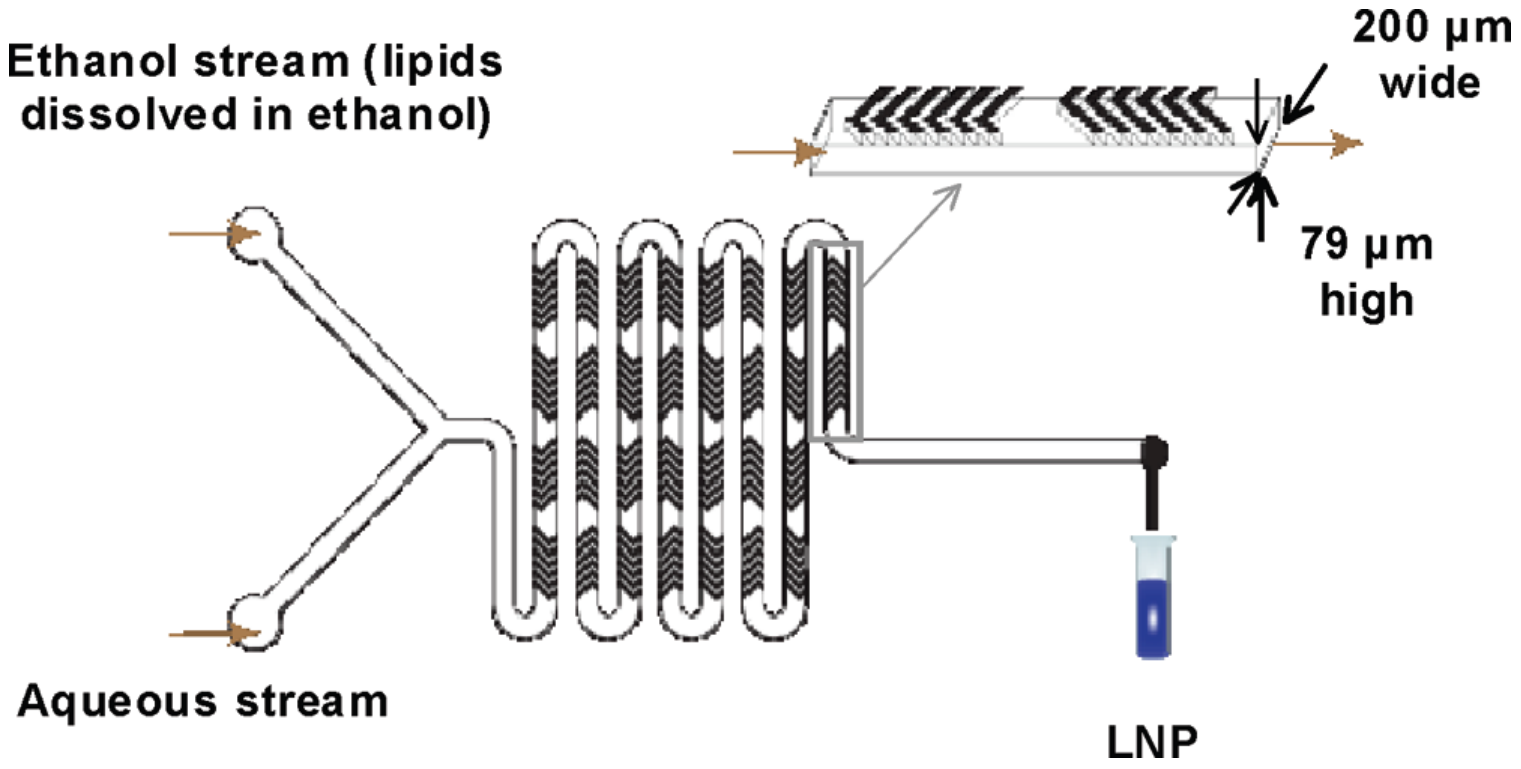




Liposomes: synthesis

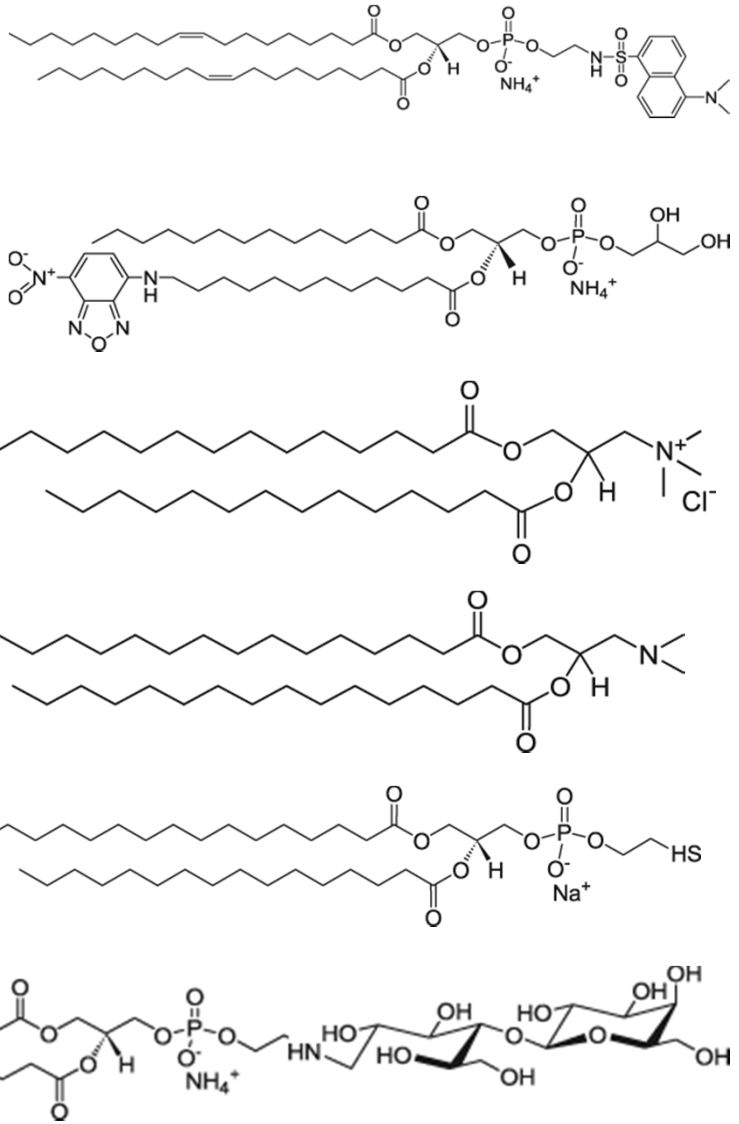
Classical methods: microfluidics

- Extrusion: large liposomes (down to 80-50 nm)
- Sonication: small liposomes (down to 20 nm). Contamination, degradation, scaling-up.
- Microfluidics: fast mixing prevents formation large aggregates.



Self-assembled system

Large library of building blocks



Evolution of liposomes for drug delivery

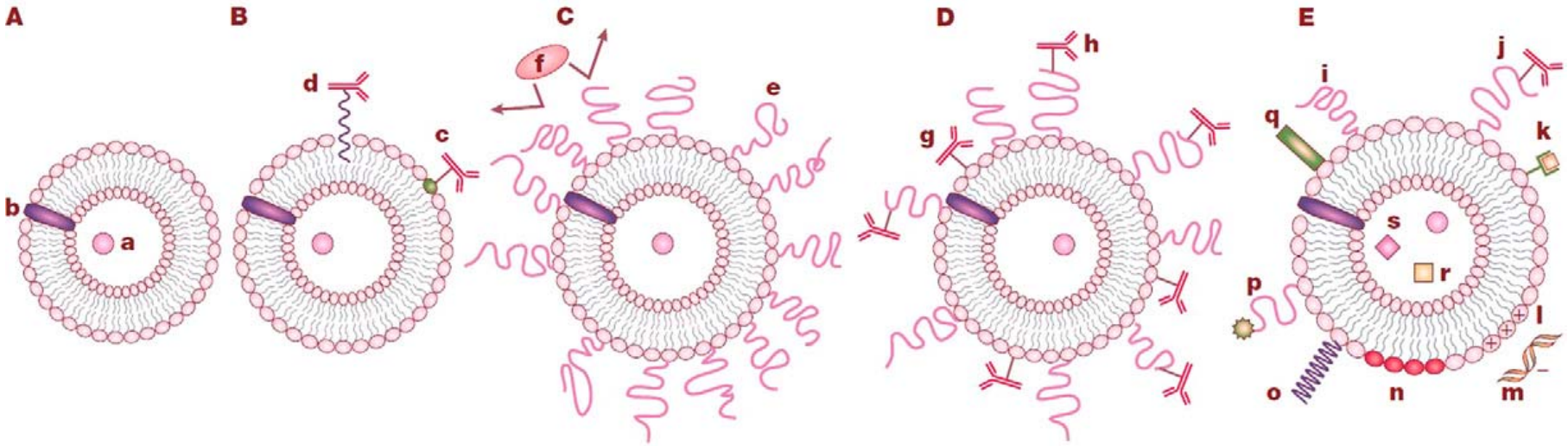
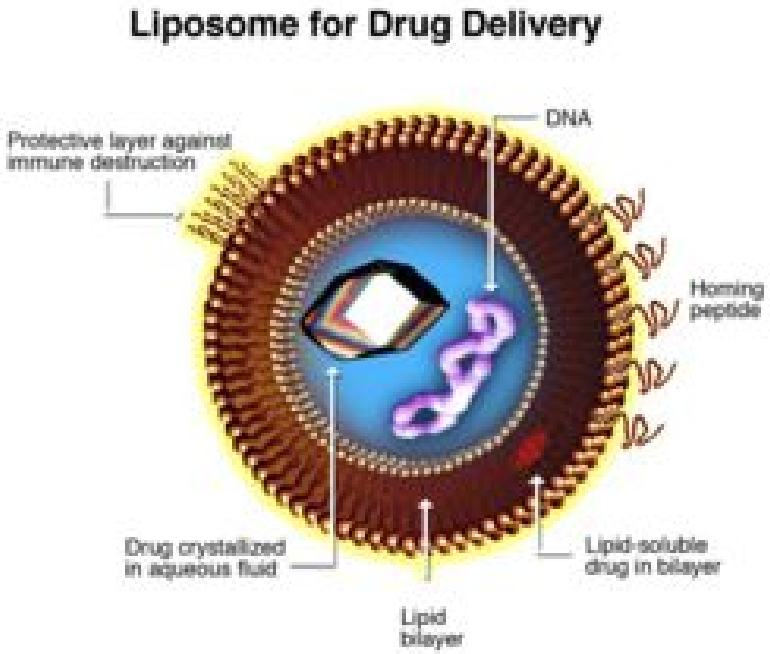
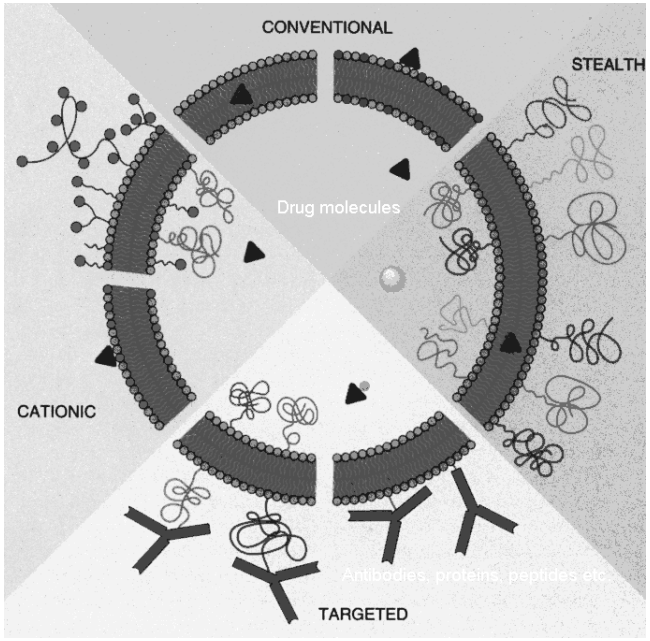


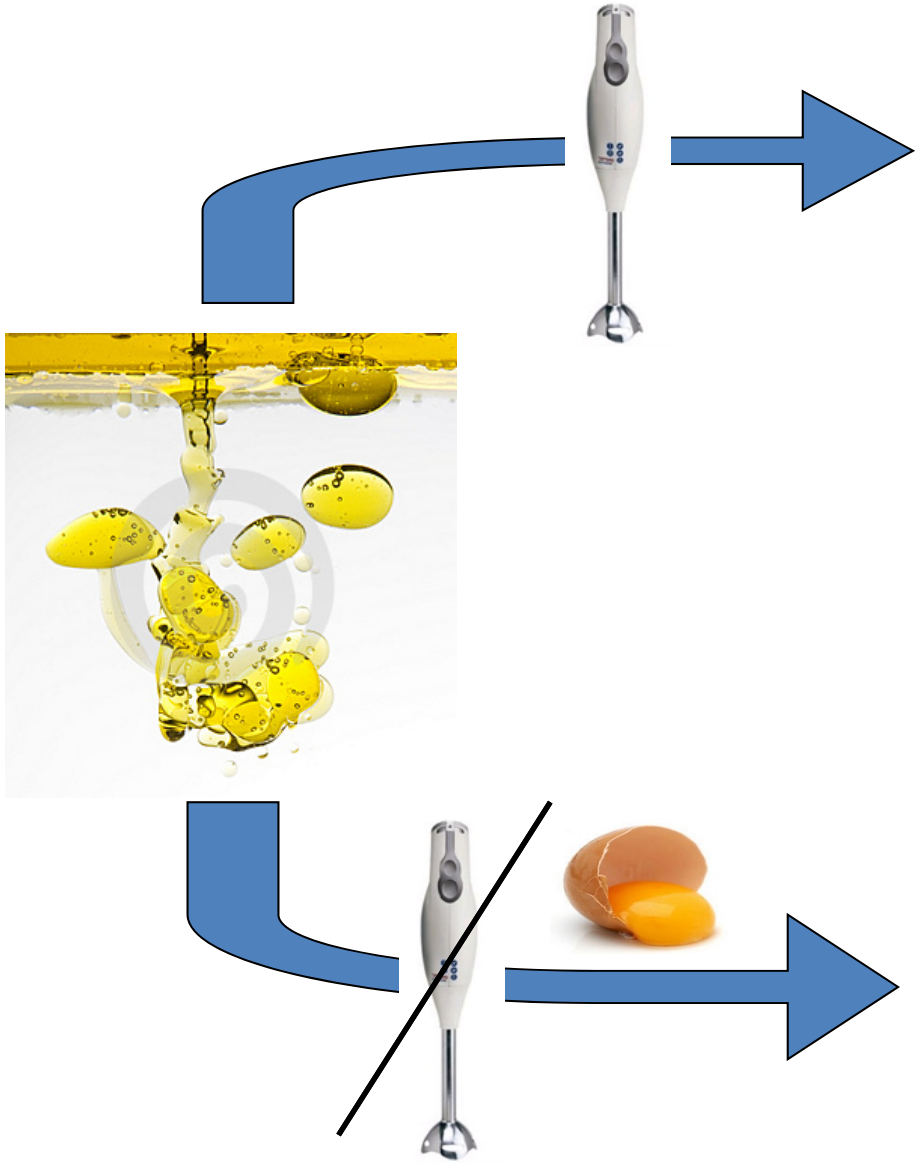
Fig. 2. Evolution of liposomes. (A) Early traditional liposomes with water soluble drug (a) entrapped into the aqueous liposome interior, and lipophilic drug (b) incorporated into the liposomal membrane. (B) Antibody-targeted immunoliposome with antibody covalently coupled (c) to the reactive phospholipids in the membrane, or hydrophobically anchored (d) into the liposomal membrane after preliminary modification with a hydrophobic moiety. (C) Long-circulating liposome grafted with a protective polymer (e) such as PEG, which shields the liposome surface from the interaction with opsonizing proteins (f). (D) Long-circulating immunoliposome simultaneously bearing both protective polymer and antibody, which can be attached to the liposome surface (g) or, preferably, to the distal end of the grafted polymeric chain (h). (E) New-generation liposome, the surface of which can be modified (separately or simultaneously) by different ways. Among these modifications are: the attachment of protective polymer (i) or protective polymer and targeting ligand, such as antibody (j); the attachment/incorporation of a diagnostic label (k); the incorporation of positively charged lipids (l) allowing for the complexation with DNA yielding lipoplex structures (m); the incorporation of stimuli-sensitive lipids (n); the attachment of a stimuli-sensitive polymer (o); the attachment of a cell-penetrating peptide (p); the incorporation of viral components (q). In addition to a drug, liposomes can be loaded with magnetic particles (r) for magnetic targeting and/or with colloidal gold, silver particles or fluorescent molecules (s) for microscopic analysis. Reproduced from 20: Torchilin VP. Nat Rev Drug Discov. 2005;4(2):145–160.

Liposomi: nanooggetti multifunzionali



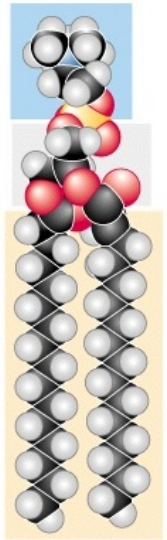


Microemulsioni: stabilizzare la superficie

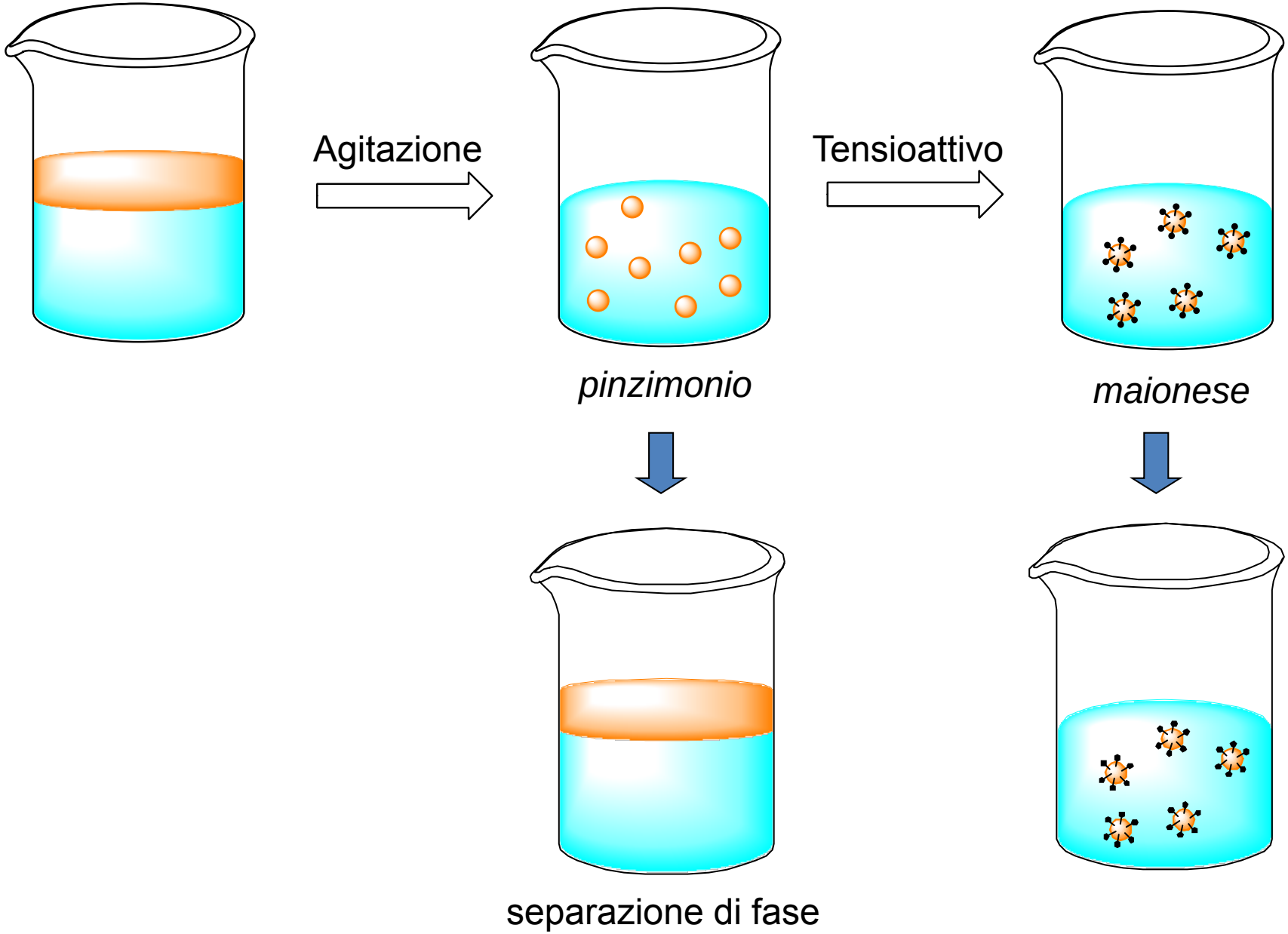


pinzimonio

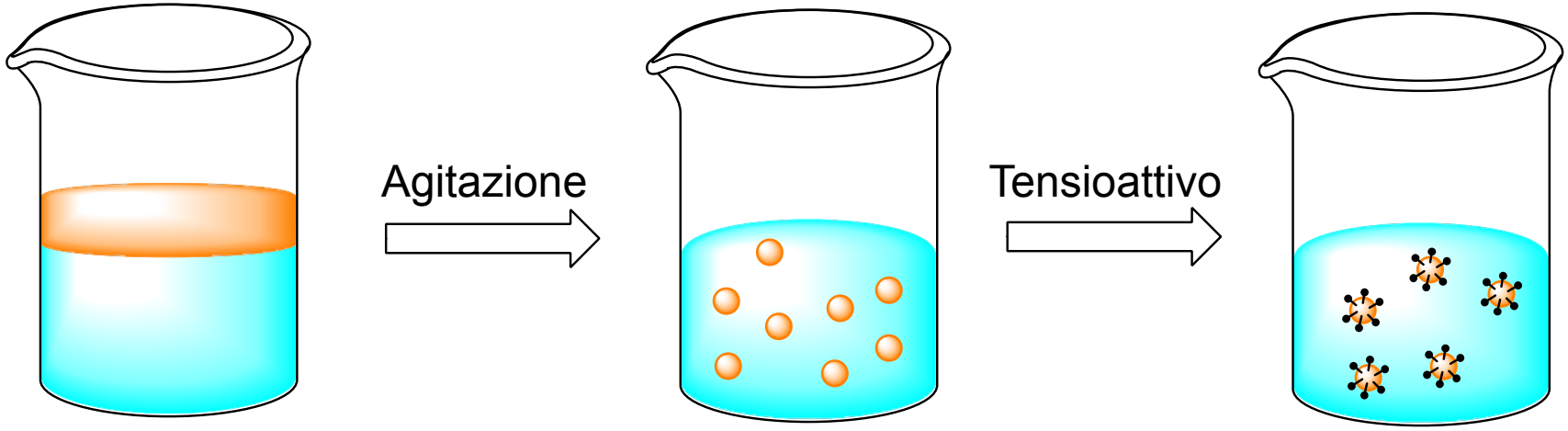
maionese



Microemulsioni: stabilizzare la superficie



Microemulsioni: stabilizzare la superficie



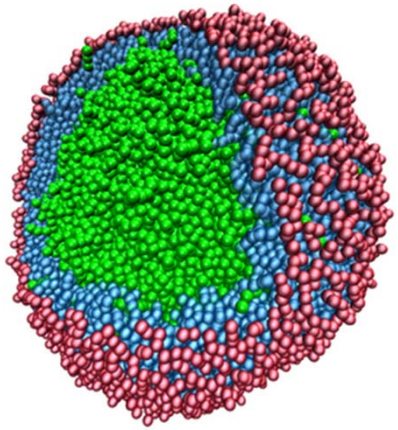
Un intervento meccanico (agitazione, sonicazione) può separare la fase immiscibile in goccioline anche piccolissime (fino a 50 nm).

La superficie totale della fase idrofobica diventa molto elevata, inoltre la zona superficiale è instabile a causa della repulsione acqua-olio (= tensione superficiale).

Ricombinandosi, le gocce diminuiscono l'area totale della fase immiscibile.

Il tensioattivo stabilizza l'emulsione impedendo la ricombinazione delle gocce: effetto **sterico** ed **elettrostatico**. Solitamente non è richiesta energia per formare la microemulsione, mentre è necessaria per formare un'emulsione.

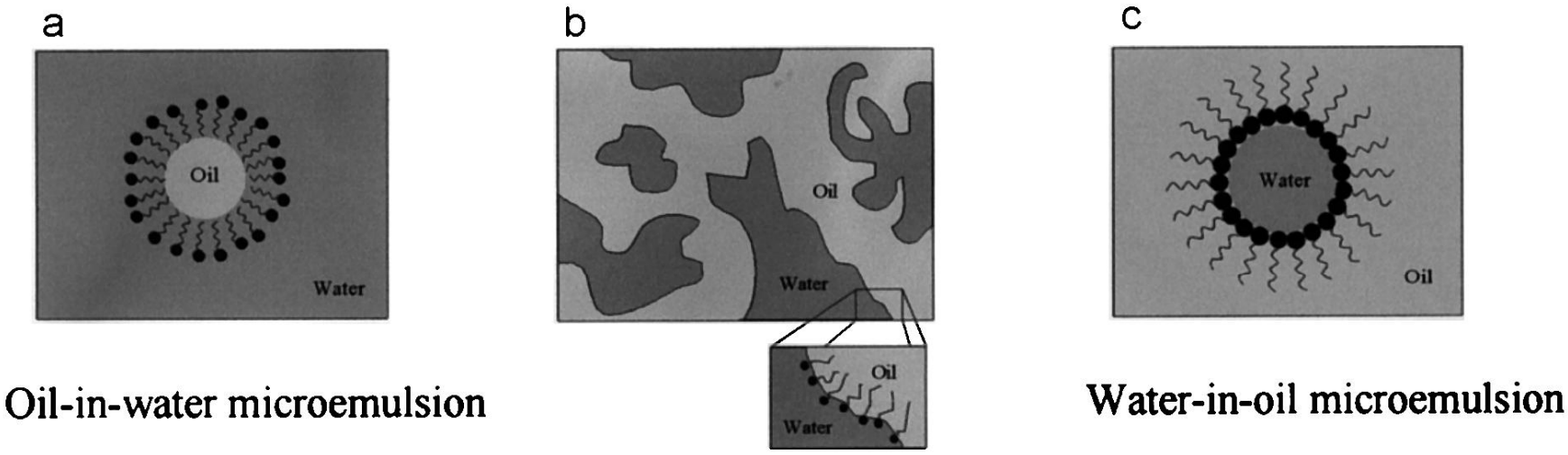
Microemulsioni: stabilizzare la superficie



Microemulsions are thus defined as ‘a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution.’

Danielsson and Lindman, 1981

“the system **contains** some and definite microstructure, in other words there is a definite boundary between the oil and water phases at which the surfactant is located”.

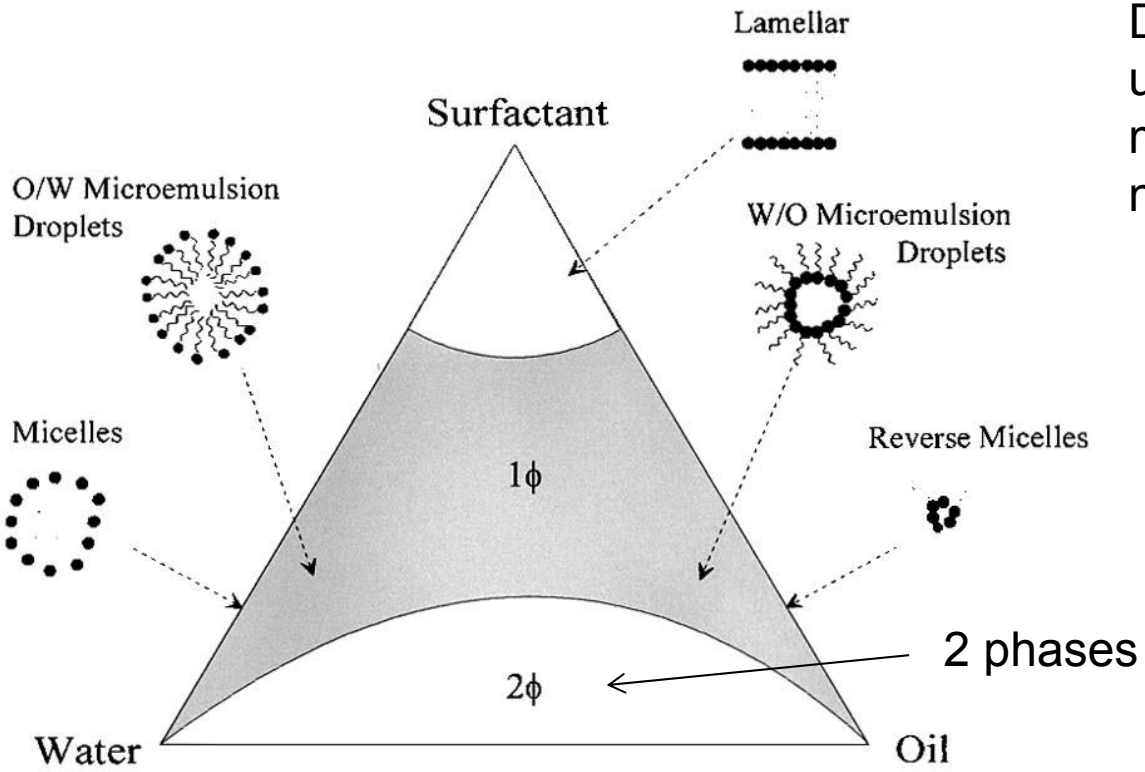


Oil-in-water microemulsion

Water-in-oil microemulsion

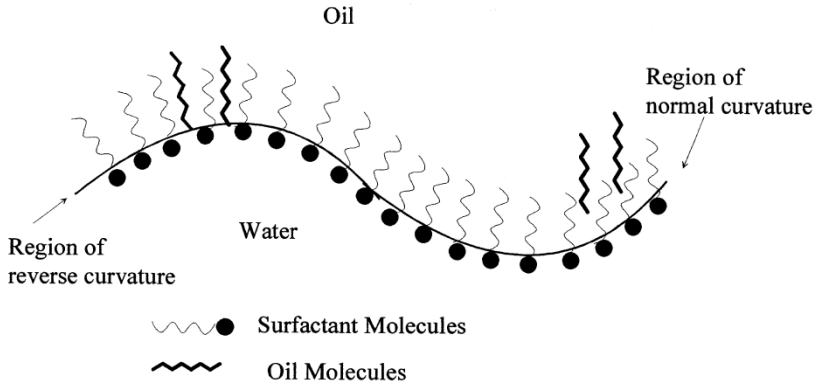
Bicontinuous microemulsion

Microemulsioni: stabilizzare la superficie

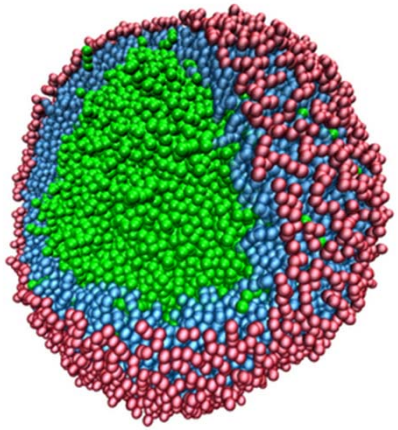


Depending on the components used, microemulsion existance may be confined to a very narrow composition range.

Water exposure of the oil phase is greater in regions of reverse curvature.

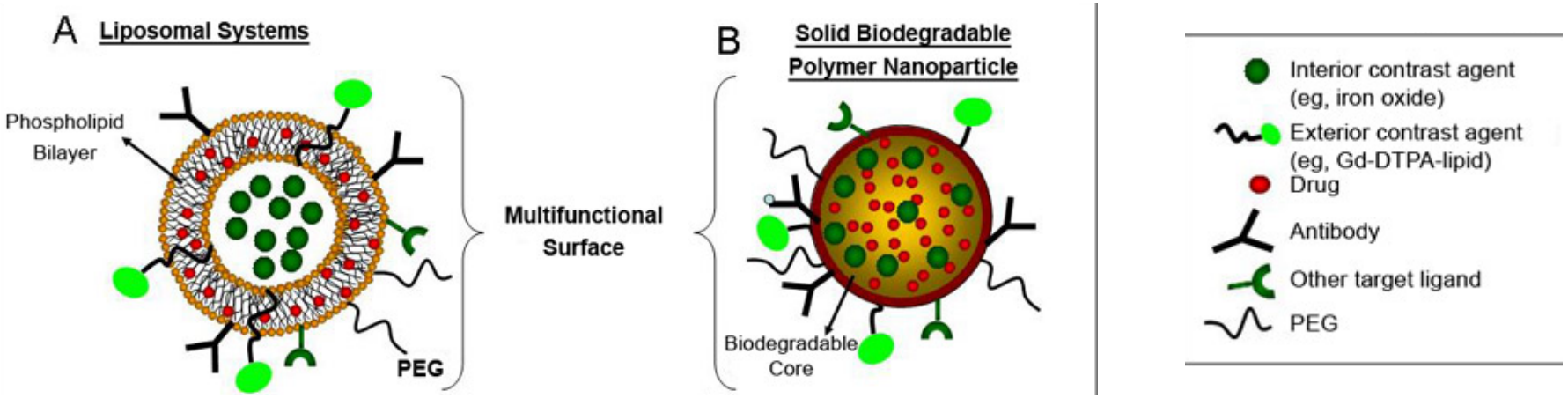


Microemulsioni: stabilizzare la superficie



Il tensioattivo può agire anche da funzionalizzante, impartendo capacità stealth, di targeting attivo, ecc.

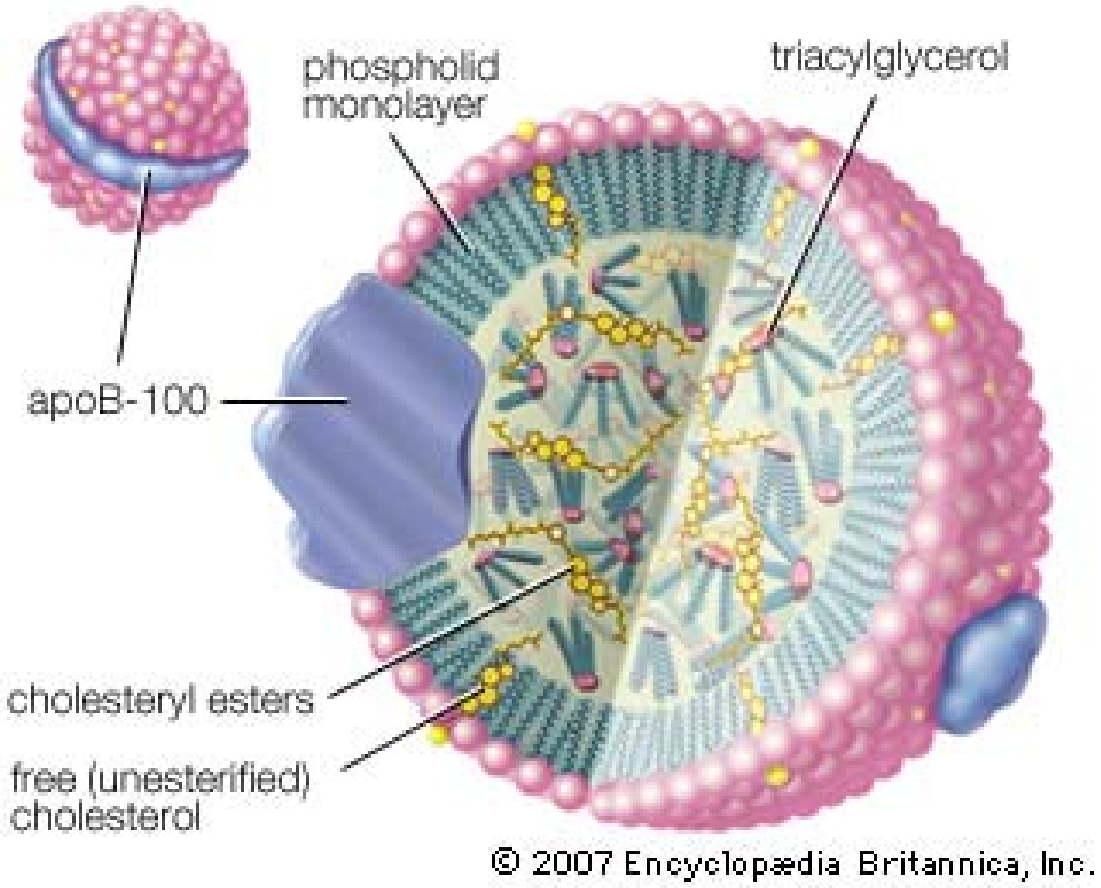
Molecole di farmaco possono essere caricate nella fase idrofobica.



Vantaggi

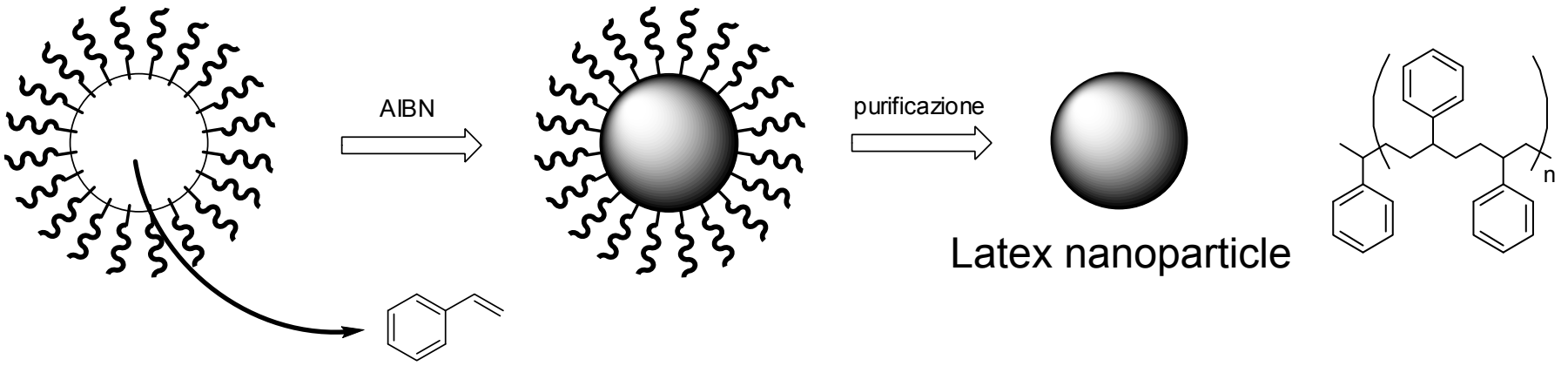
- Nanoparticelle più grandi delle micelle
- Maggior capacità di carico di molecole idrofobiche rispetto a micelle e liposomi

Microemulsioni in natura: lipoproteine



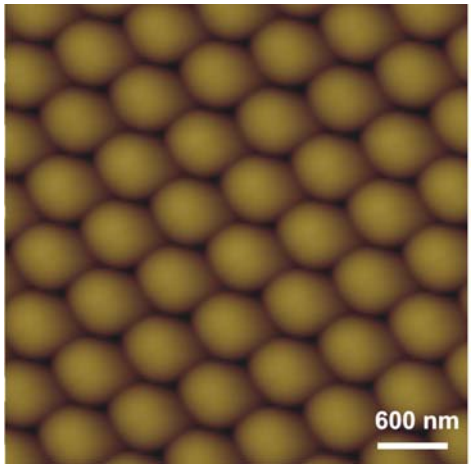
Microemulsioni: nanoreattori

All'interno di microemulsioni (anche a fase inversa) possono essere sintetizzati altri tipi di nanosistemi



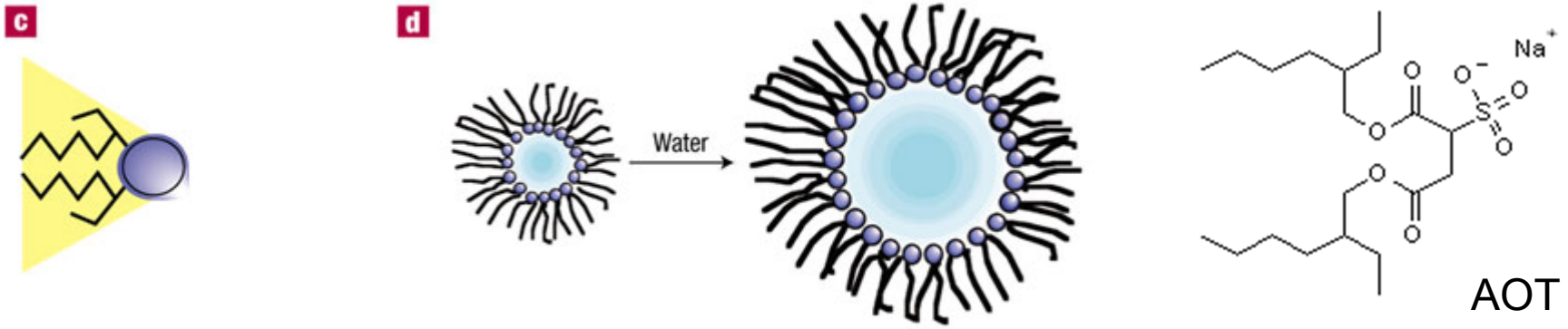
Latex nanoparticle

Se le molecole che compongono/sono contenute nella fase idrofobica vengono indotte a polimerizzare si possono ottenere nanoparticelle polimeriche.



Microemulsioni: nanoreattori

Emulsioni a fase inversa (water in oil, w/o), sono piccole goccioline d'acqua in un solvente organico stabilizzate da un tensioattivo.

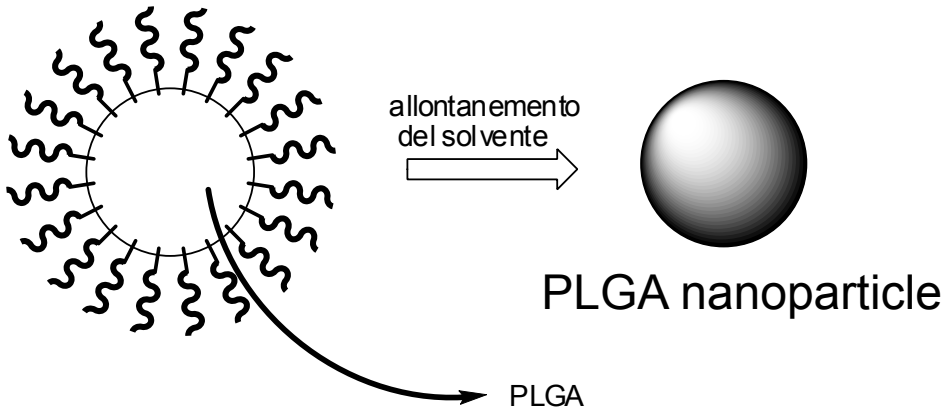


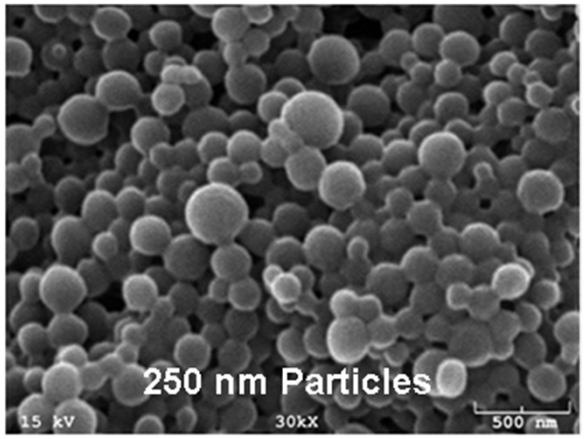
Le dimensioni dipendono essenzialmente dalla quantità di acqua e di tensioattivo aggiunta.

Non sono utili in campo biomedico, ma possono essere un utile nanoambiente in cui crescere diversi tipologie di nananosistemi.

Microemulsioni: nanoreattori

All'interno di microemulsioni (anche a fase inversa) possono essere sintetizzati altri tipi di nanosistemi





Se la fase idrofobica è costituita da una **soluzione**, in genere di un *polimero* o un *farmaco*, in un solvente organico, l'allontanamento del solvente lascia come residuo nanoparticelle organiche.

Microemulsioni: nanoreattori

L'allontanamento del solvente organico può avvenire in diversi modi:

- evaporazione
- diffusione in acqua

Evaporazione

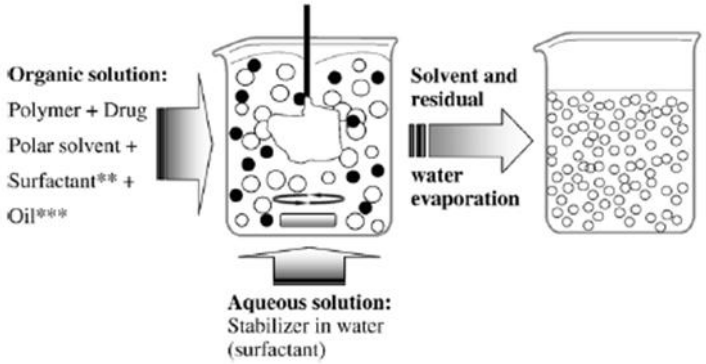


Fig 2. Schematic representation of the solvent displacement technique. **Surfactant is optional. ***In interfacial deposition method, a fifth compound was introduced only on preparation of nanocapsules.

Diffusione

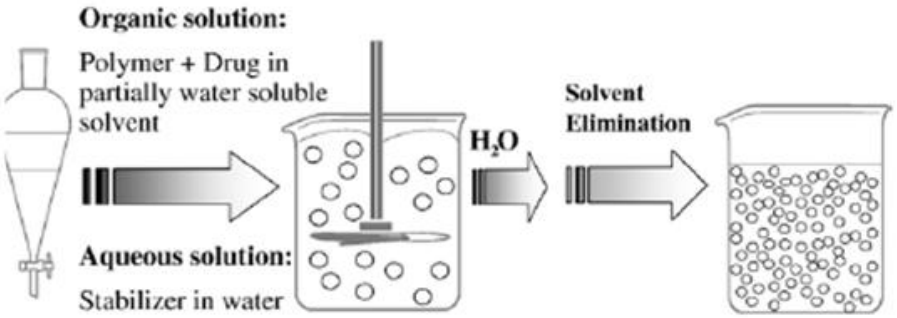


Fig 3. Schematic illustration of the ESD technique.

Diffusione

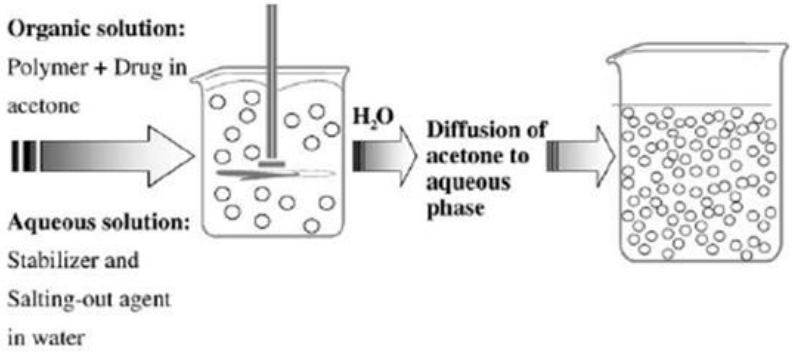
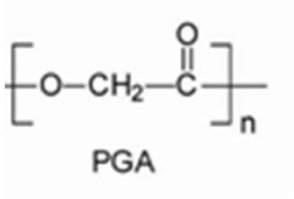
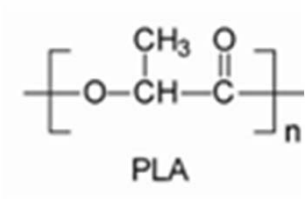


Fig 4. Schematic of the salting-out technique.

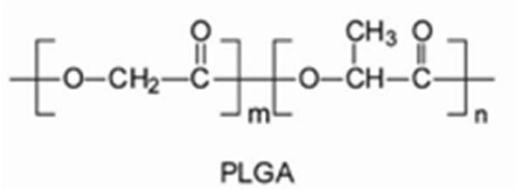
Nanoparticelle di PLGA



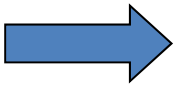
acido poliglicolico
idrofilico

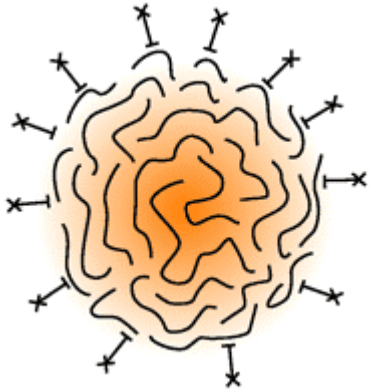


acido polilattico
idrofobico

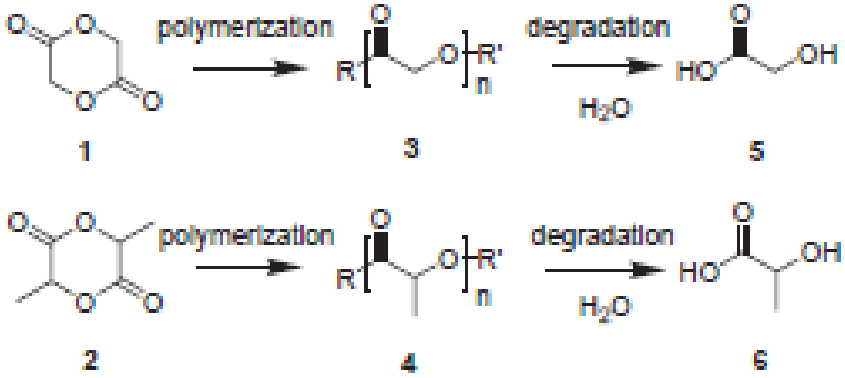


copolimero polilattico-co-glicolico





PGA e PLA sono due **polimeri biodegradabili**: in presenza di acqua i gruppi esterei vengono idrolizzati ed il contenuto della particelle rilasciato.



Nanoparticelle di PLGA

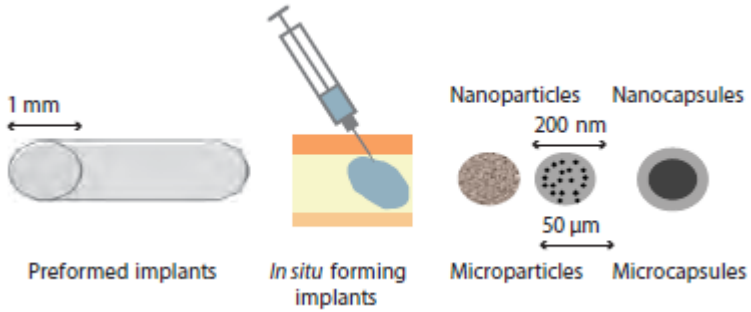


Table 1. Key parameters and corresponding effects on RESOMER® properties.

Parameter	Influence
Molecular Weight	High M_w increases the degradation time
Ratio Lactide/Glycolide	Polymers with one monomer degrade more slowly. Degradation times: PLA > PGA > PLGA 50:50
Stereochemistry	L-PLA: semicrystalline D,L-PLA: amorphous
Blockage of Acidic Endgroups	Polymers with free -COOH groups are more hydrophilic (e.g., R503H compared to R503)
PEGylation	Increase in hydrophilicity, change of degradation and release behavior

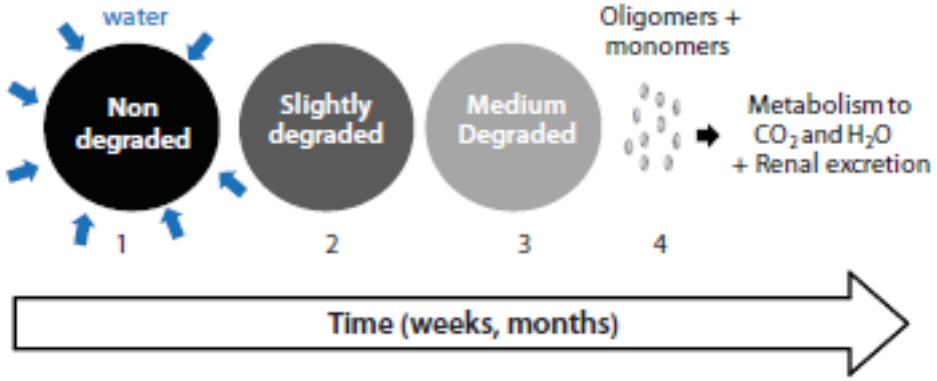
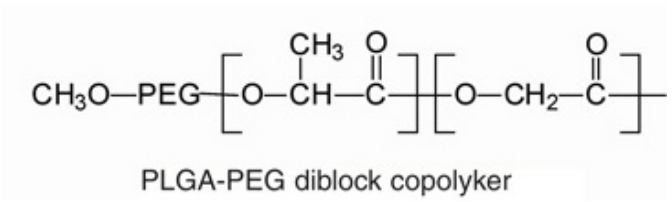


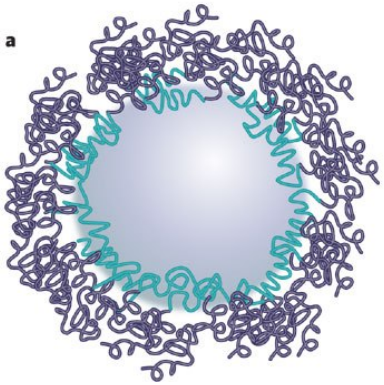
Figure 2. The biofate of RESOMER® polymers includes several steps: (1) Wetting and water diffusion, (2) Decrease of the molecular weight = Polymer degradation (3) Mass loss = Polymer erosion and (4) Renal excretion or metabolism to carbon dioxide and water.

La velocità di degradazione viene controllata variando il **rapporto PLA/PGA**: maggiore il numero di unità idrofiliche (PGA), più veloce l'idrolisi.

Enzimi esterasi presenti nei tessuti biologici accelerano la degradazione.

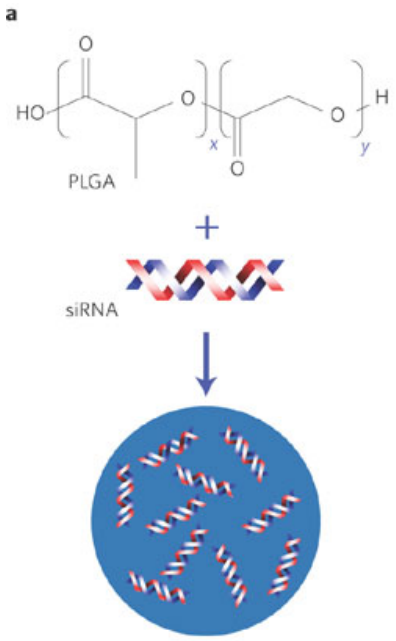
Nanoparticelle di PLGA

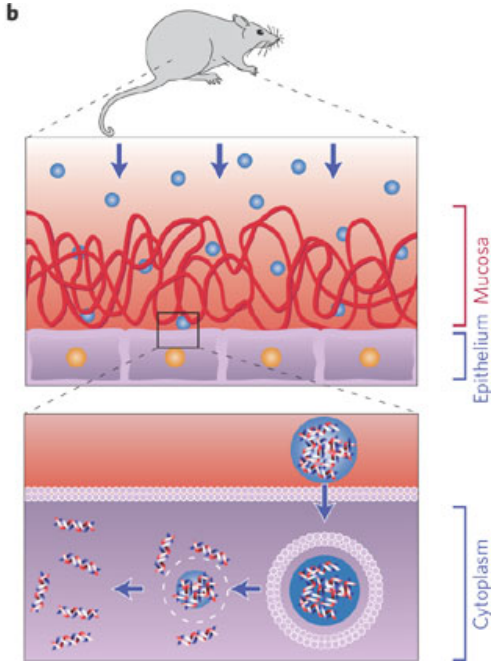




Il copolimenro PLGA-PEG si comporta come un tensioattivo: il PEG rimane sulla superficie, stabilizza la nanoparticella e la rende stealth.

La velocità di degradazione è minore.





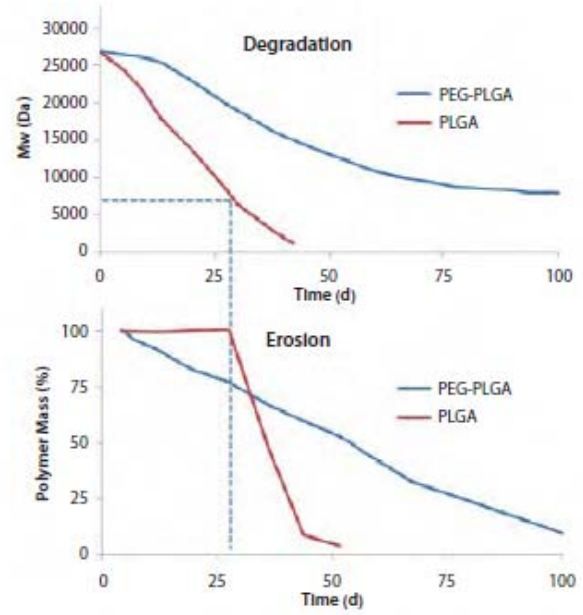
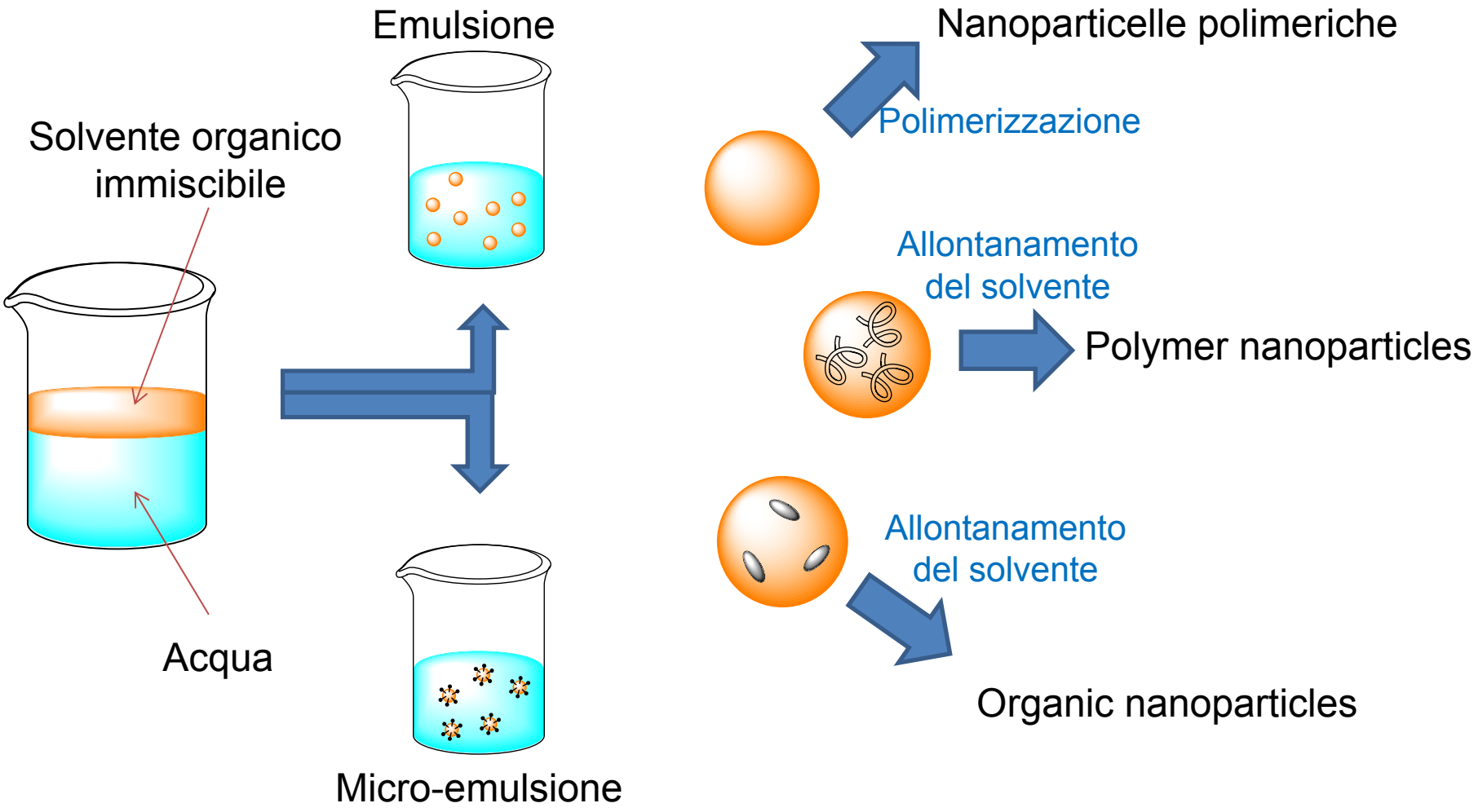


Figure 4. Typical time course of polymer degradation (top) and erosion (bottom) for PLGA and PEG-PLGA polymers.[10-12]

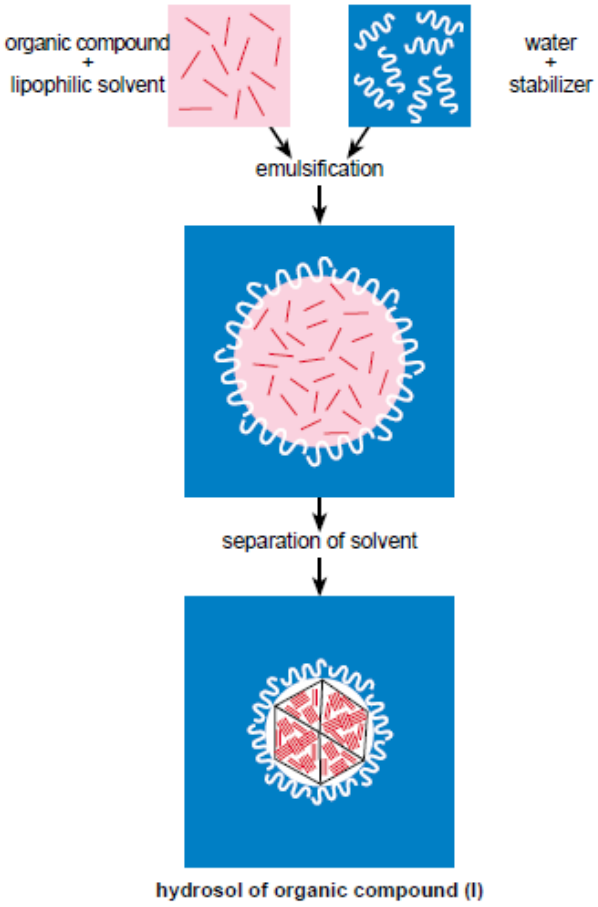
Nature, 2009, 447

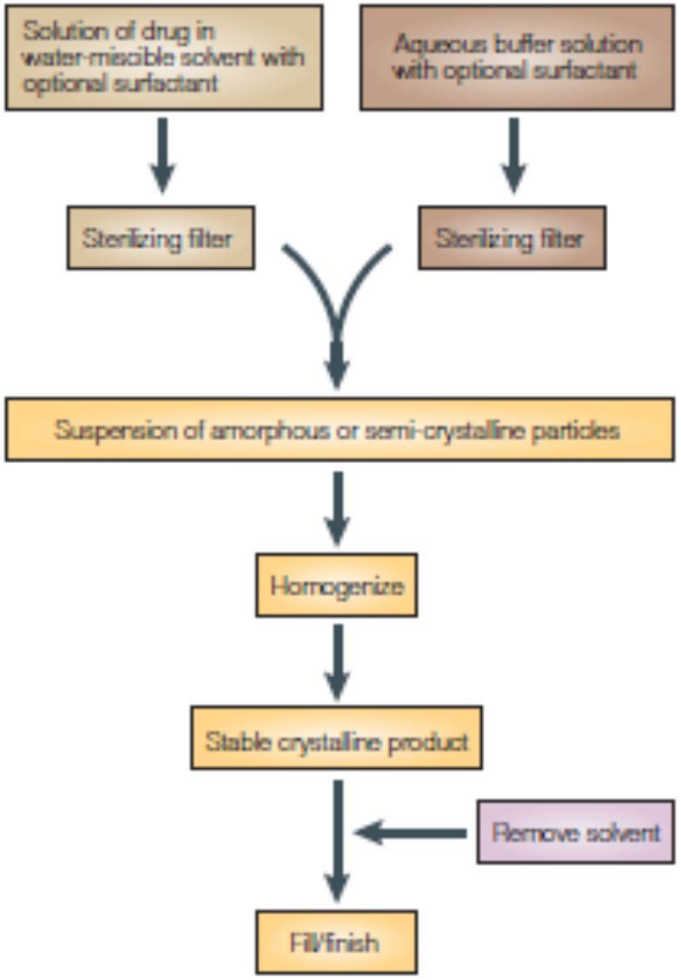
Nanoparticelle organiche da emulsioni



Nanoparticelle di molecole organiche

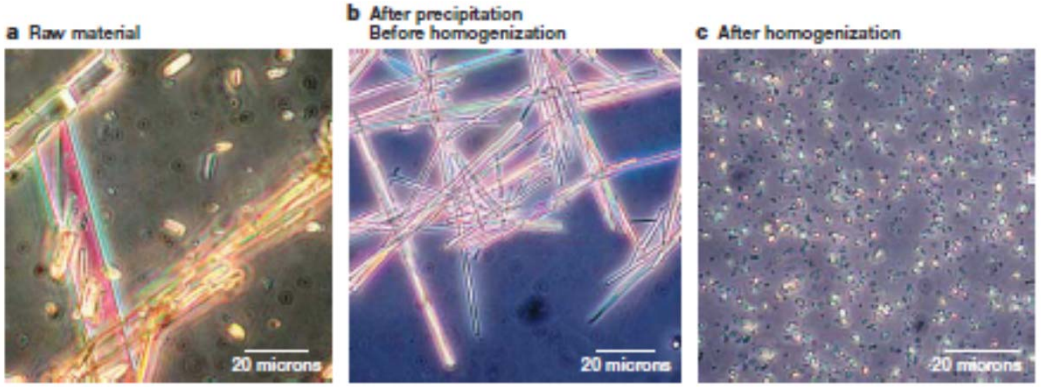
Usando le tecniche di microemulsione e omogeneizzazione, le nanoparticelle possono essere preparate anche con piccole molecole organiche, ad esempio farmaci

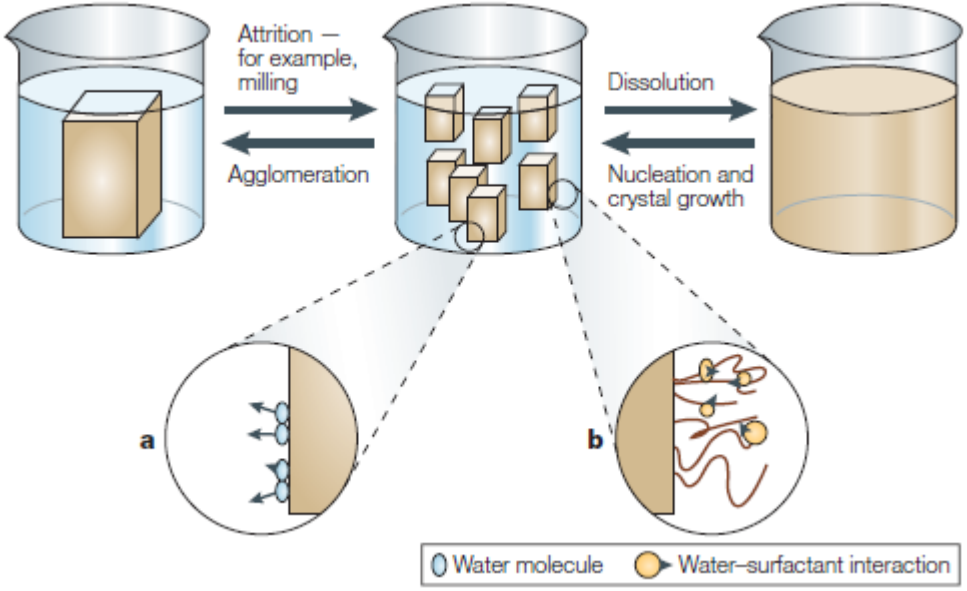


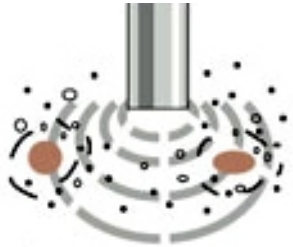


Nature Reviews, 2004, 785

Nanoparticelle di molecole organiche

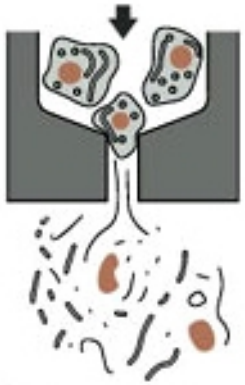




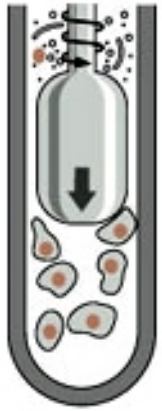


1 break cells with high frequency sound

2 use a mild detergent to make holes in the plasma membrane



3 force cells through a small hole using high pressure



4 shear cells between a close-fitting rotating plunger and the thick walls of a glass vessel

Nature Reviews, 2004, 785

Nanoparticelle di molecole organiche

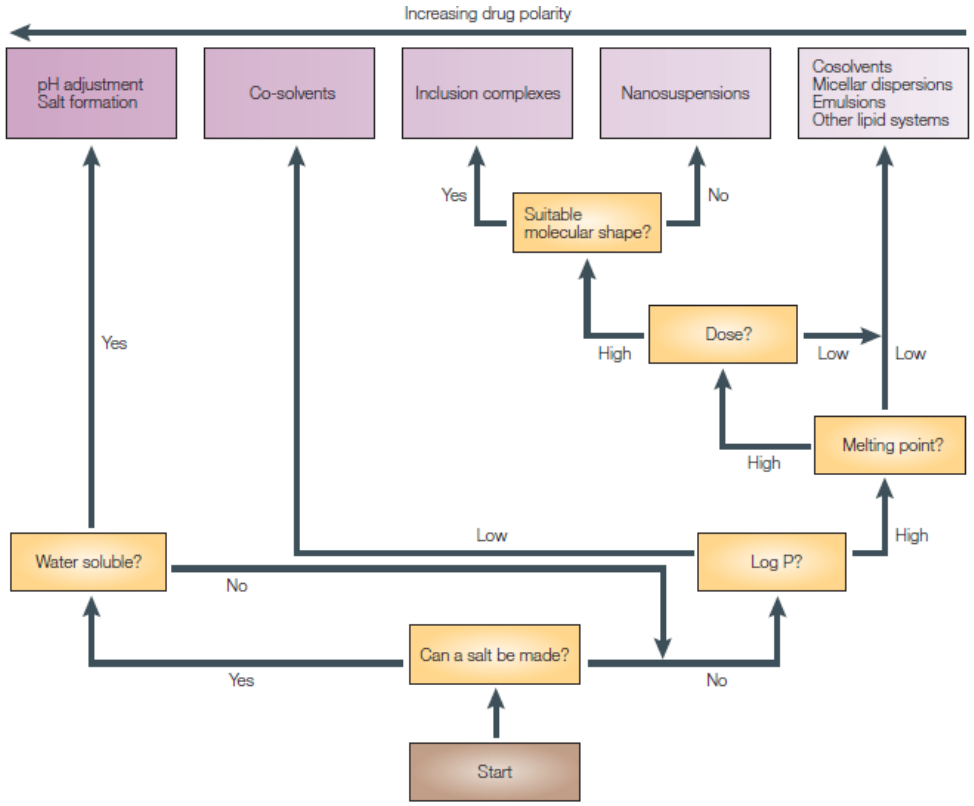


Table 1 | **Benefits of nanosuspensions**

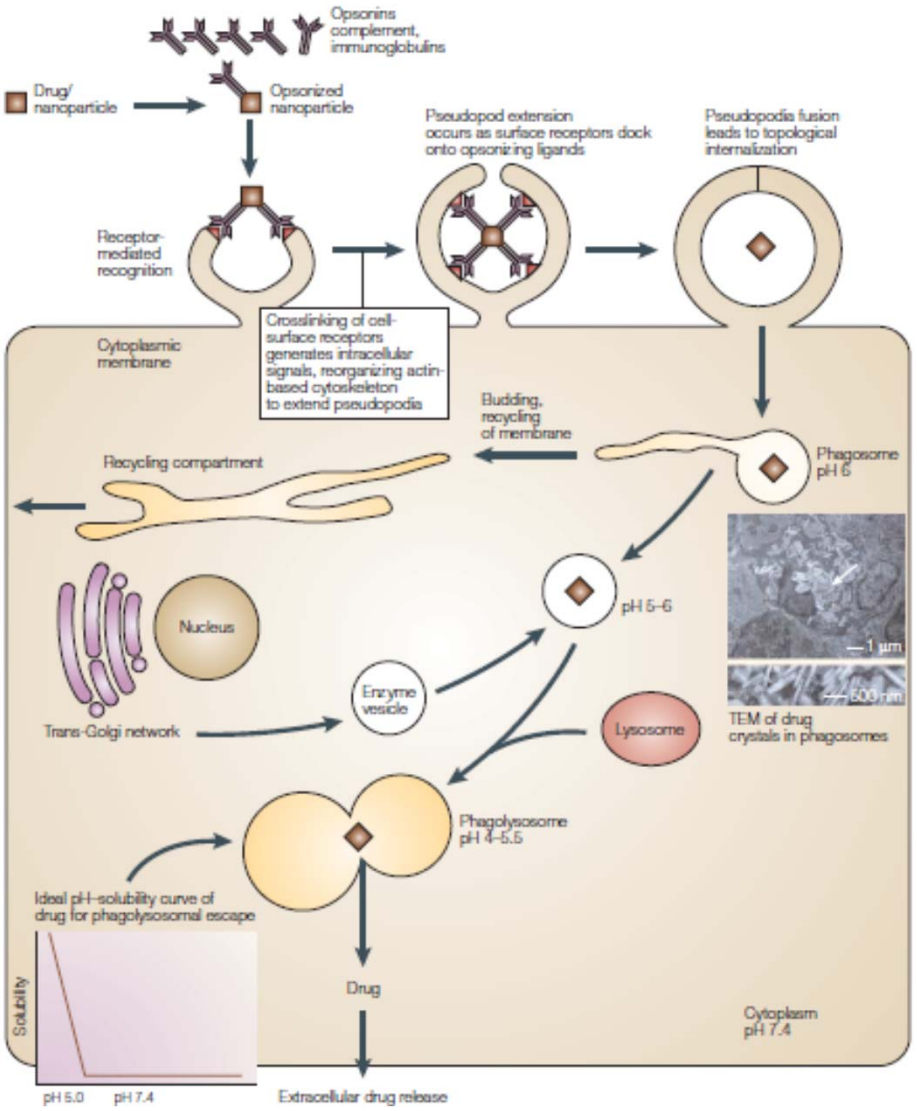
Physicochemical characteristic	Potential benefits
Increased drug amount in dosage form without harsh vehicles (extreme pH, co-solvents)	Intravenous: reduced toxicity, increased efficacy
Reduced particle size: increased drug dissolution rate	Oral: increased rate and extent of absorption, increased bioavailability of drug: area under plasma versus time curve, onset time, peak drug level, reduced variability, reduced fed/fasted effects. Pulmonary: increased delivery to deep lung
Solid state: increased drug loading	Reduced administration volumes; essential for intramuscular, subcutaneous, ophthalmic use
Solid state: increased stability	Increased resistance to hydrolysis and oxidation, increased physical stability to settling
Particulate dosage form	Intravenous: potential for intravenous sustained release via monocyte phagocytic system targeting, reduced toxicity, increased efficacy. Oral: potential for reduced first-pass hepatic metabolism

Table 2 | **Solid-particulate-nanosuspension-based formulations in development and in the market**

Drug	Indication	Drug delivery company	Pharma company	Route	Status
Paclitaxel	Anticancer	American BioScience	American Pharmaceutical Partners	Intravenous	Phase III
Undisclosed multiple	Anti-infective	Baxter NANOEDGE	Undisclosed	Oral/ intravenous	Preclinical to Phase II
Undisclosed	Anticancer	Baxter NANOEDGE	Undisclosed	Intravenous/ oral	Preclinical to Phase I
Rapamune	Immuno-suppressant	Elan Nanosystems	Wyeth	Oral	Marketed
Emend	Anti-emetic	Elan Nanosystems	Merck	Oral	Marketed
Cytokine inhibitor	Crohn's disease	Elan Nanosystems	Cytokine PharmaSciences	Oral	Phase II
Diagnostic Agent	Imaging agent	Elan Nanosystems	Photogen	Intravenous	Phase I/II
Thymectacin	Anticancer	Elan Nanosystems	NewBiotics./Ilex Oncology	Intravenous	Phase I/II
Fenofibrate	Lipid lowering	SkyePharma	Undisclosed	Oral	Phase I
Busulfan	Anticancer	SkyePharma	Supergen	Intrathecal	Phase I
Budesonide	Asthma	Elan Nanosystems	Sheffield Pharmaceuticals	Pulmonary	Phase I
Silver	Eczema, atopic dermatitis	NUCRYST	Self-developed	Topical	Phase I
Calcium phosphate	Mucosal vaccine adjuvant for herpes	BioSante	Self-developed	Oral	Phase I
Insulin	Diabetes	BioSante	Self-developed	Oral	Phase I

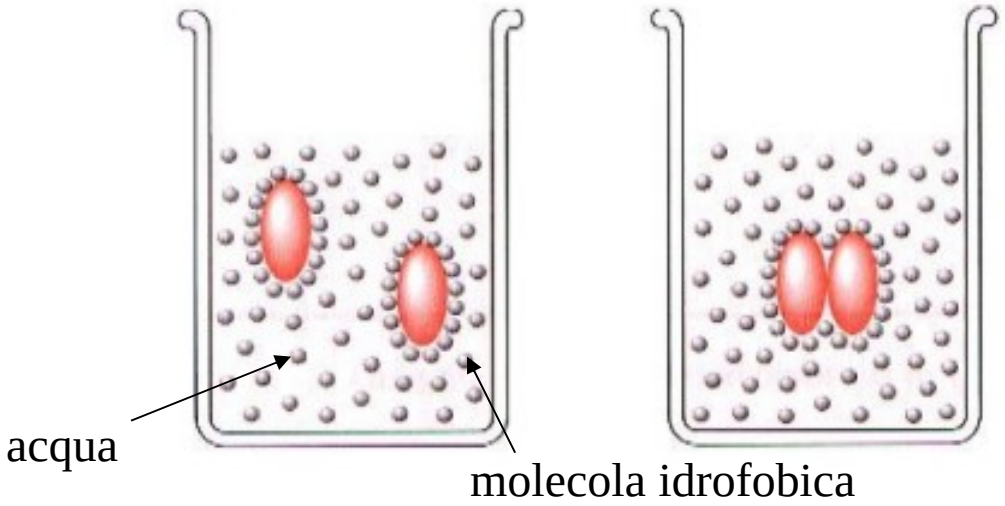
Nature Reviews, 2004, 785

Nanoparticelle di molecole organiche



Nature Reviews, 2004, 785

Effetto idrofobico

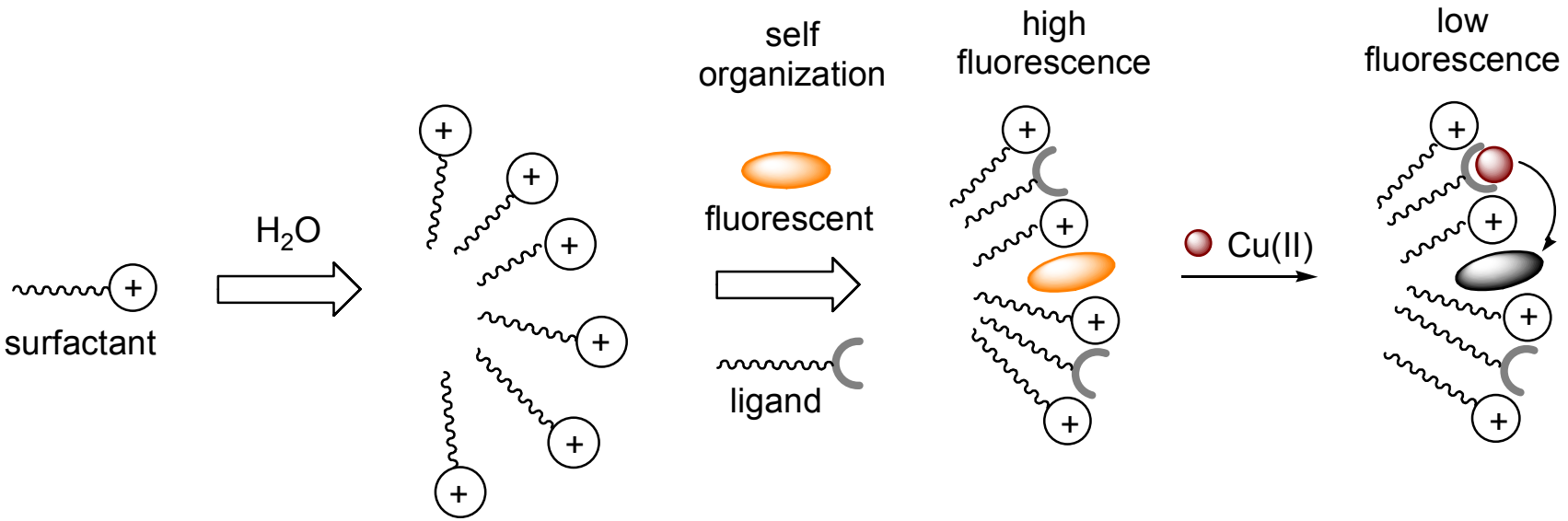


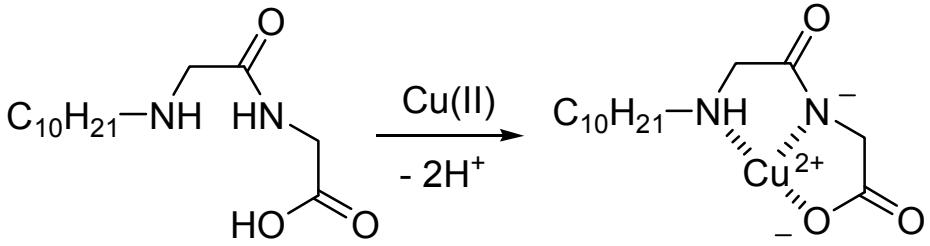
Molecole non polari, se disperse in acqua, tendono a formare dimeri ed aggregati non covalenti. L'interazione che tiene insieme tali entità si chiama **effetto idrofobico.**

La natura dell'effetto idrofobico è essenzialmente **entropica**. Infatti l'interazione tra due molecole poco polari (es. idrocarburi) è basata solo sulle deboli interazioni di Van der Waals. Al contrario, l'interazione tra acqua e una molecola poco polare è basata su interazioni dipolo-dipolo indotto, generalmente più forti.

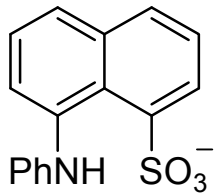
Dal punto di vista energetico, l'interazione tra le molecole d'acqua ed un soluto non polare dovrebbe quindi essere positiva.

Sistemi autoorganizzati: un esempio





ligand = C_{10}GlyGLy



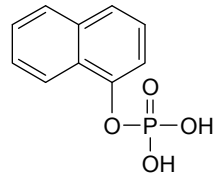
fluorescent dye = ANS

Angew. Chem. Int. Ed. **1999**, *38*, 3061-3064

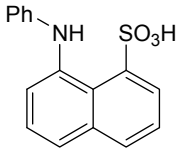
Langmuir **2001**, *17*, 7521-7528.

Sistemi autoorganizzati: un esempio

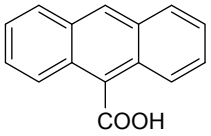
Fluorophores



1-NAFOSF



ANS



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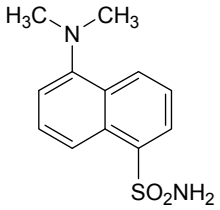
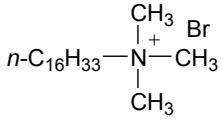
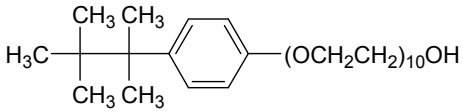


DANSA

Surfactants



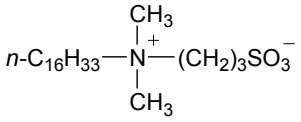
CTABr



Triton X-100

n-C12H25(OCH2CH2)23OH

Brij 35



DMMAPS