Formulation of biologics

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 101007939. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA companies.

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What to achieve with formulation

- Safety and efficacy
  - Correct dose
  - Safety and stability of the pharmaceutical
  - Correct pharmacokinetics
- Patient convenience and compliance
  - Pain
  - Intrusion in daily life
- Convenience for the healthcare system
  - Safe handling at hospitals
  - Shelf-life
  - Self-medication

To live a full life - not only to survive

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Key things to know when formulating a biological drug

- Desired pharmacokinetic profile
- Stability and compatibility of the active substance
- Known risks to patients

Decisions to make:

- Route of delivery
- Type of formulation
- Choice of excipients
- Choice of primary packing or device

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Excipients

- All ingredients except the active substance
- There to give the pharmaceutical product it's desired properties
  - Physical characteristics
  - Pharmacokinetics
    - Enhance uptake
    - Controlled release
  - Stability

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Excipients

- Only use if necessary
- Be safe or proven safe
- Use excipients for injection

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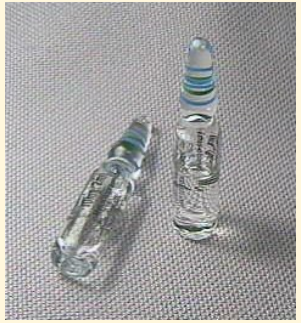
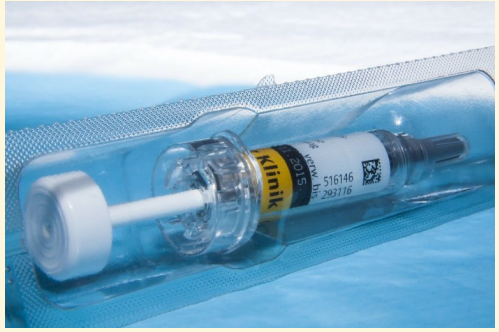
Primary packing material





- The packing material in contact with the pharmaceutical formulation
- Typical packing materials for injections
  - Vials
  - Ampoules
  - Prefilled syringes
  - Auto-injectors
  - IV-bags
  - Pumps
- Be aware of extractable
  - Plasticisers and monomers from plastics
  - Alkali from glass

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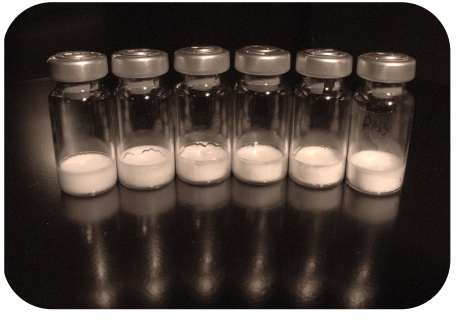
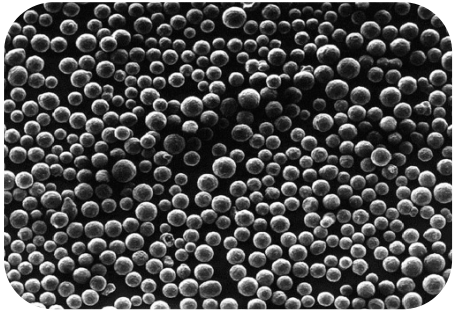
Type of formulation

Solutions



Lyophilized powder



Controlled release
and targeted delivery

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Solutions

Why

- Easy to produce and handle
- Rapid onset

Why not

- Stability issues
- Patient compliance

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Solutions

Excipients

- solvent
- Tonicity agents
- Buffers for pH control
- Stabilising agents
- Surfactants
- Preservatives
- Rheology modifiers

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Common solvents in formulations

Water

- Water for injection (Distilled)
  - Pyrogen-free and endotoxin-free
  - Have low conductivity
  - Have low amounts of organic molecules

Cosolvents

- They increase the solubility of other substances by lowering the dielectric constant of water

Other solvents

- Polar liquids
  - ethanol,
  - glycerin
  - propylene glycol
  - n–lactamide.
  - Low molecular PEG
- Non-polar liquids
  - Oils - corn oil, cottonseed oil, peanut oil, and sesame oil

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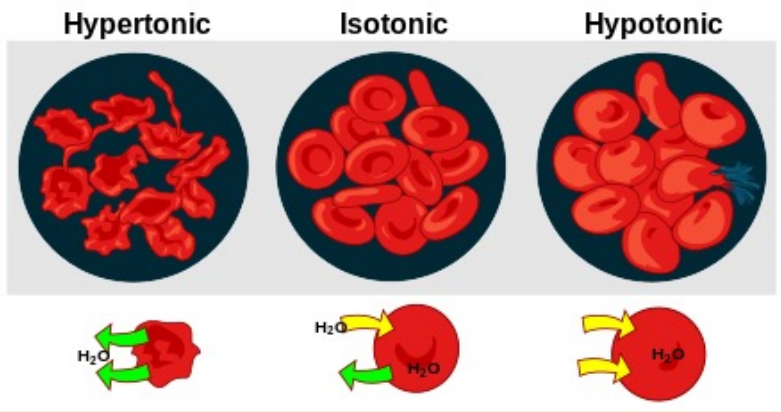
Tonicity agents



A colligative property of solutions similar to osmolality

- Hypertonic
- Isotonic
- Hypotonicity

Tonicity provided by:

- Sodium chloride
- Glucose
- Mannitol

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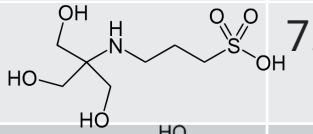
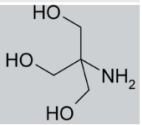
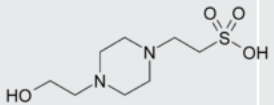
Buffers

Buffer	Structure	pH
Citric acid		2.1-7.4
Acetic acid		3.8-5.8
Phosphate		5.7-8.2
Borate		8.2-10.2
TAPS		7.7–9.1
TRIS		7.5-9.0
HEPES		2.5 -3.5 6.8 -8.2

- pH important for
  - Chemical stability
  - Physical stability
- Things to consider
  - Buffer capacity
  - Specific ion effects
  - Patient compliance
  - Transparency
  - Interaction between the ions of the buffer and the formulation

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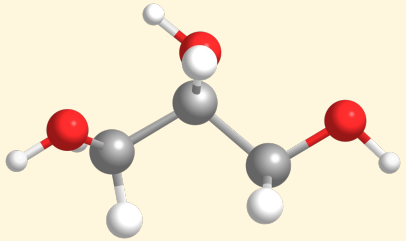
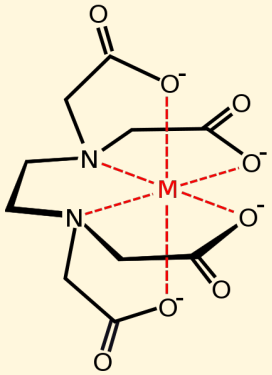
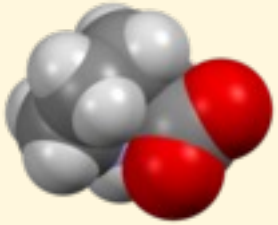
Stabilising agents



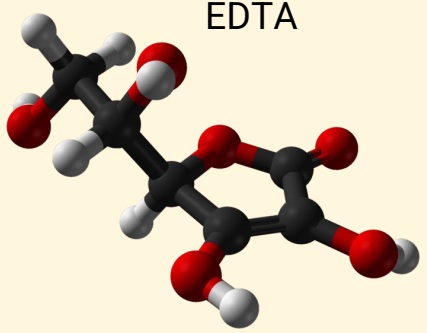
Glycerol



EDTA



Proline



ascorbic acid

- Chemical degradation
  - Polyols/disaccharides/polysaccharides
  - Amino acids
  - Antioxidants
  - Chelating agents
- Aggregation
  - Polyols/disaccharides/polysaccharides
  - Amino acids
  - Surfactants

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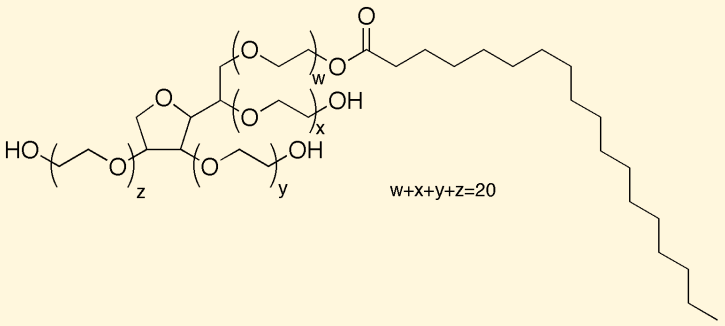
Surfactants



Surfactants in injectabilia
Polysorbate 20 and 80
Poloxamer

Hinders aggregation

- Hinders adsorption to interfaces
- Adsorb to hydrophobic patches

Improve solubility

Reduce surface tension

Enhancing permeability of biologics

Used in controlled release formulations

- Stabilises dispersions
- Part of lipid formulations

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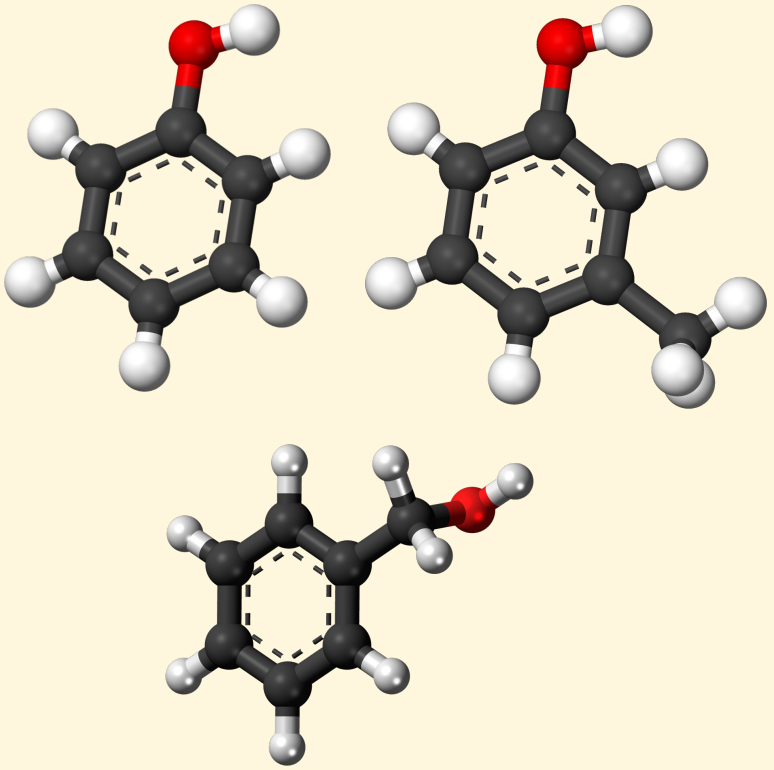
Preservatives



- Needed for multidose preparations
- Need different preservatives for different microorganisms
- Toxic limited amounts allowed
- Might interact with surfactants - decrease cloud point of polysorbates
- pH sensitive
- Can be absorbed by plastic packing

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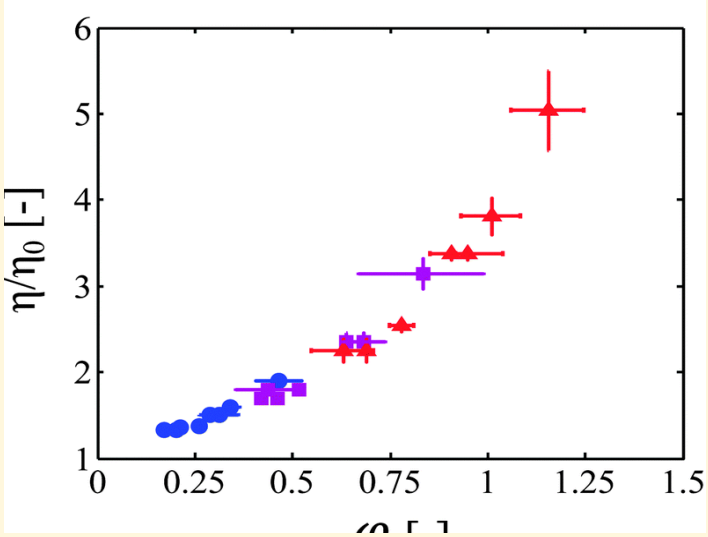
Rheology modifiers



It is affected by using formulation strategies that

- Change the degree of aggregation/oligomerisation
- Gives compacter structure
- Reduce electrostatic interaction

- Typical excipients
  - Salt (preferably chaotropes)
  - hydrophobic salts
  - Amino acids for example ArgHCl, HisHCl, LysHCl,

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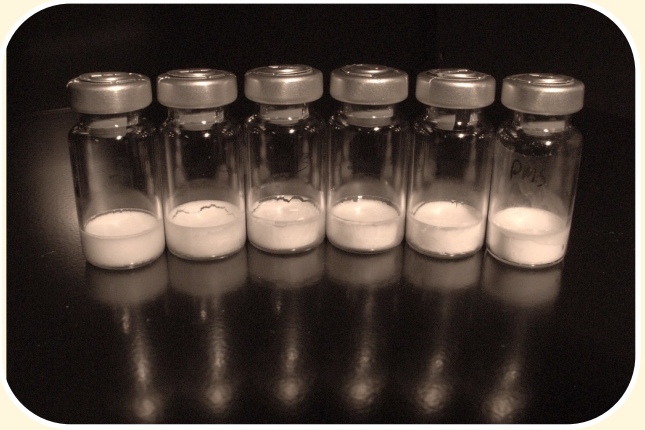
Lyophilized product



Why Lyophilization?

- Stability
- Mild drying technology
- Easy to reconstitute

Why not?

- Needs more handling and more expensive production
- Patient compliance

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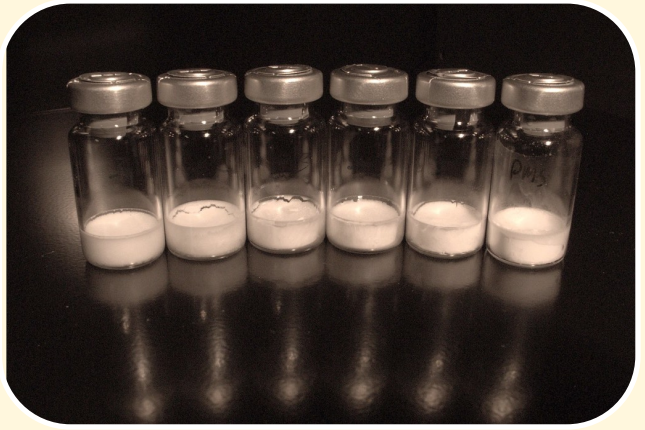
Lyophilized product



Excipients

- Similar for solutions
  - Buffers
  - stabilizers
- Cryoprotectants and Lyoprotectants
- Bulking agent
- Diluent
  - Isotonicity
  - Stabilizers

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Cryoprotectants and Lyoprotectants

- Cryoprotectants are added to minimize damage caused by ice crystal formation
- Cryoprotectants include glycerol, dimethyl sulfoxide (DMSO), ethylene glycol, and trehalose
- Lyoprotectants are used to protect biologics during freeze-drying processes,
- Some of them hinder long-term changes by minimizing the uptake of water
- Typical lyoprotectants; sugars (sucrose and trehalose), polyols (e.g., mannitol, sorbitol), and certain amino acids (glycine)

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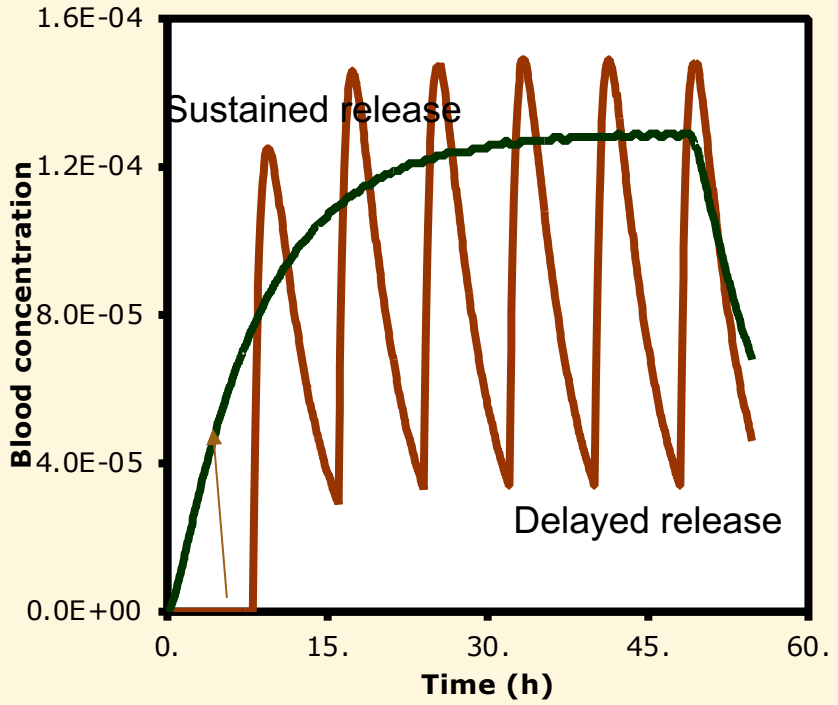
Controlled release formulations



- The material used must be biocompatible and not trigger immune or blood clotting responses.
- Dose dumping is of particular concern
- There is often a risk for burst effects.
- The active substance needs to be stable throughout the duration of the release.

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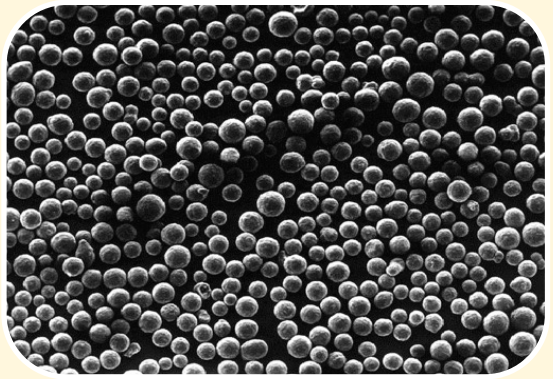
Implants and Biodegradable particles



- Implants
  - Can be removed
  - Often composed of non degradable polymer such as polyethylene vinyl acetate
- Biodegradable particles
  - Most common PLGA (poly lactic glyco acid) particles
  - New generations on the way, for example pure protein particles

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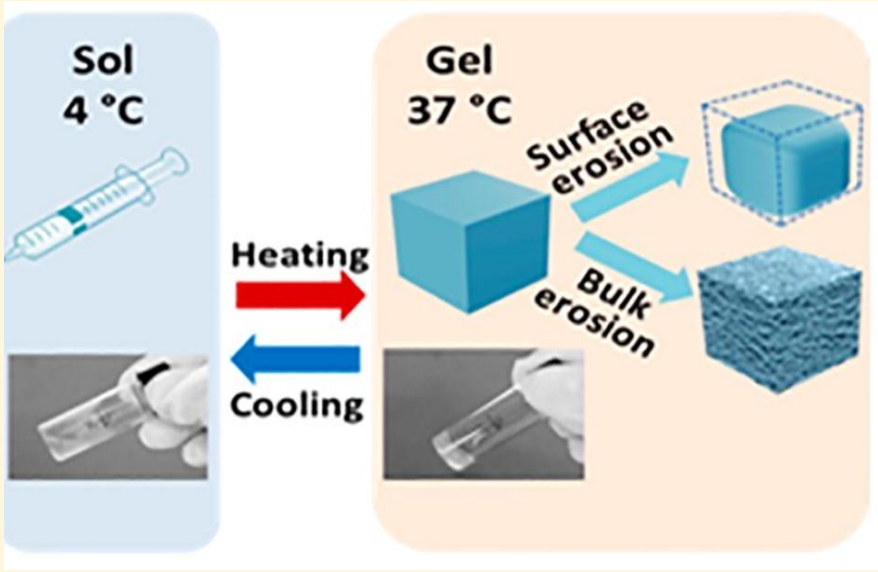
In situ gelling systems



Fluid when injected but forms a gel or solid-like structure after injection

Triggers

- Heat
- Ions
- pH

Systems

- Polymers - Chitosan, PEG-based
- Lipids- Laminar to Cubic
- Peptides

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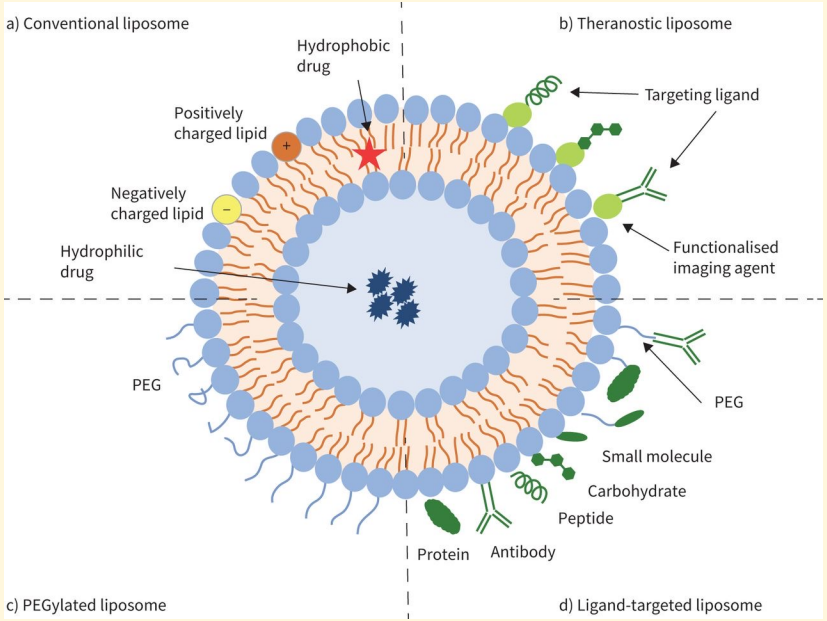
Targeting and enhanced uptake



To obtain

- Higher specificity
- Oral uptake
- Uptake to target cells

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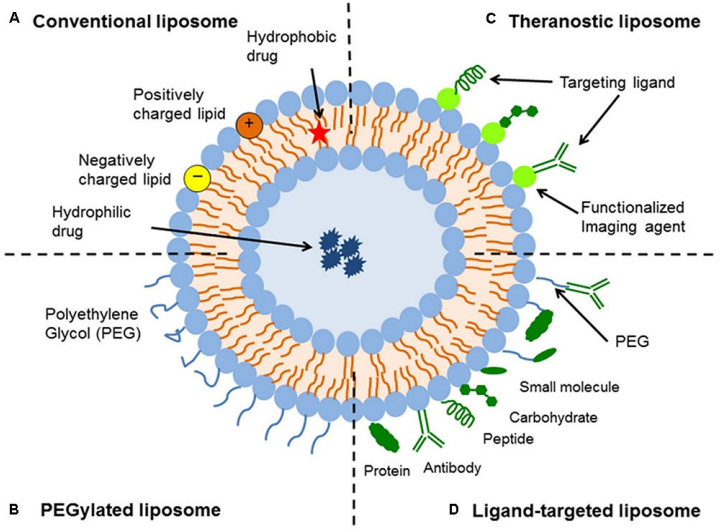
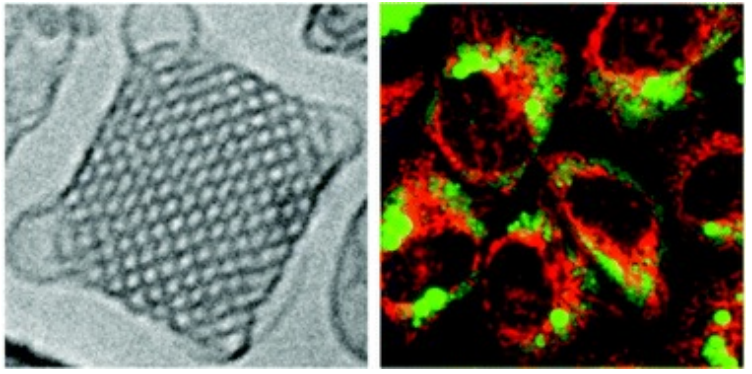
Lipid nano-formulations for drug delivery

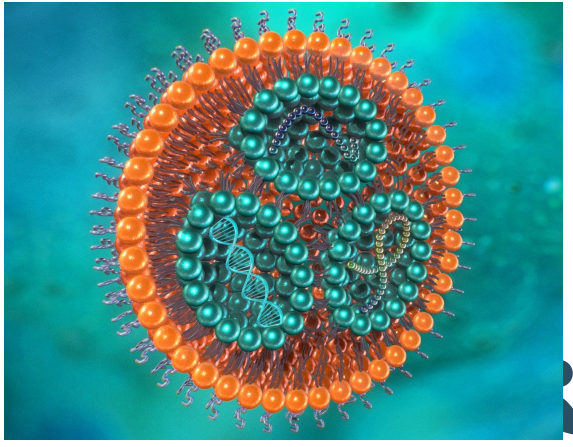
Liposomes



Cubusomes



Solid Lipid Nanoparticles



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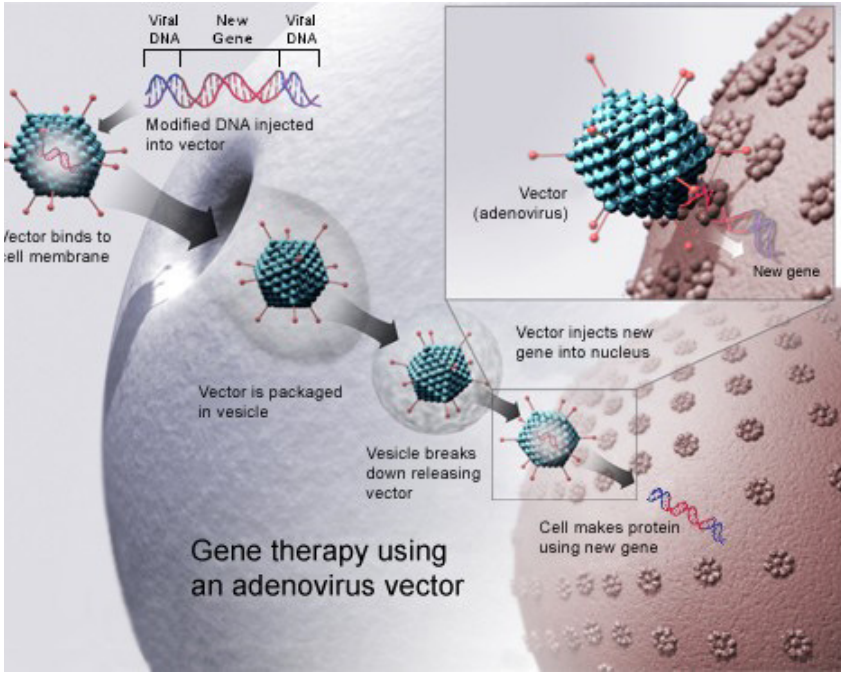
Viral vectors

- Several viruses are employed
  - Adenovirus -50% -Trigger immune response
  - AAV- Adeno associated viruses
  - Retrovirus -25%
- 2021 - 3 products on the market. 1140 Clinical trials
- There have been reports of sever effects when viral vectors been used
  - Cancer
  - Immunological responses
- Only limited amounts of DNA can be used



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Improve uptake

- Modification of the protein
- Use excipients or drug formulations that
  - Inhibits or protects from enzymes
  - Enhance transport over the epithelial barrier
  - Prolong the residence time in the intestinal

Type of formulations and excipients

- Nanoparticles
- Microparticles and polymers that open tight junctions- Chitosan
- Receptor-mediated uptake -Transferrin, Cholix
- Penetration enhancers -Sodium caprate
- Bioadhesive polymers

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Real World Handling of Protein Drugs – Exploration, Evaluation & Education

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