NANOCARRIERS

Centre for Excellence in Nanobio Translational REsearch(CENTRE)

DST supported -National Facility for Drug Development

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CONTENTS

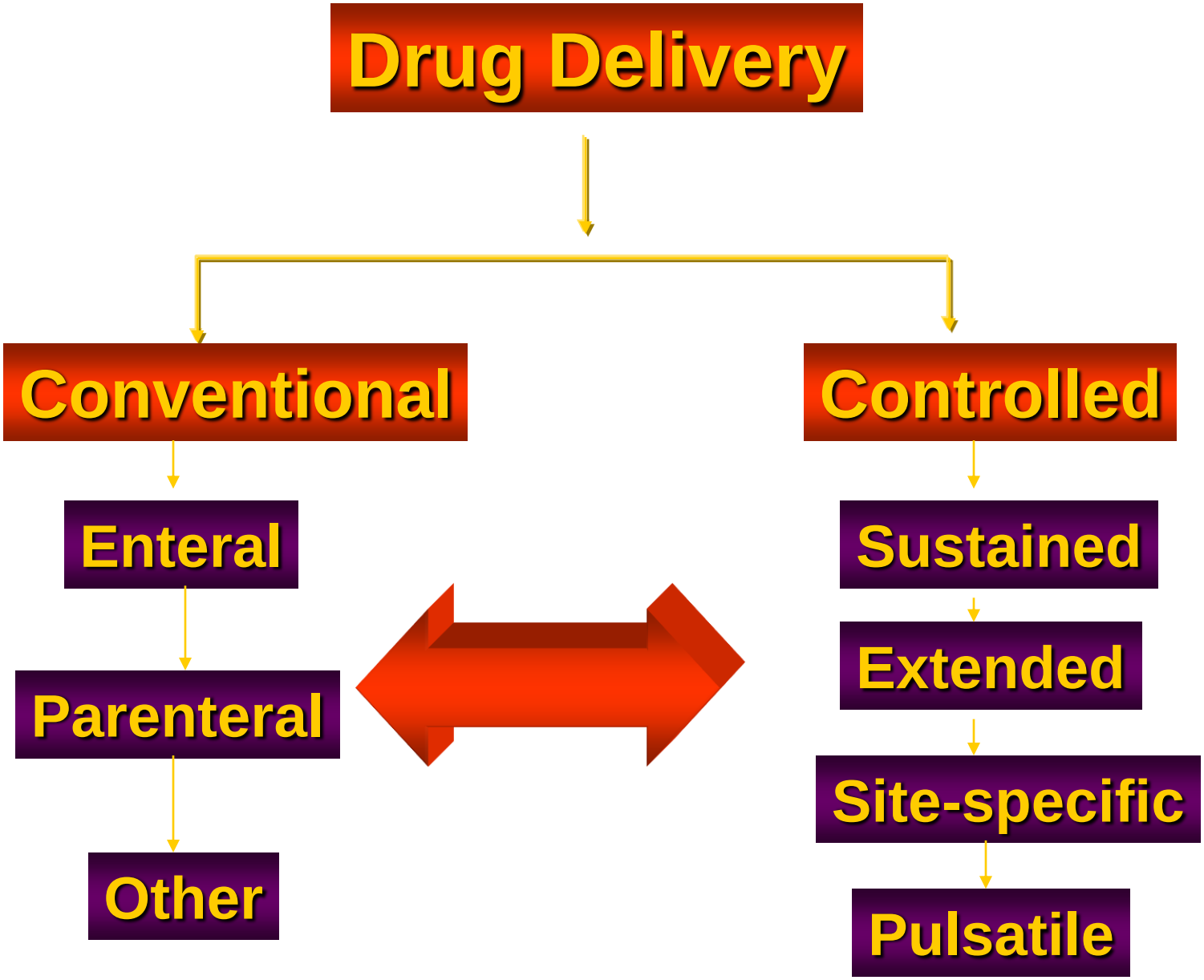
- Introduction to drug delivery
- Need of novel delivery systems
- Role of Nano carriers
- Characteristics of nano carriers
- Types of delivery systems
    - Solid Lipid Nanoparticles
    - Micro and Nano emulsion
    - SEDDS & SMEDDS

Summary

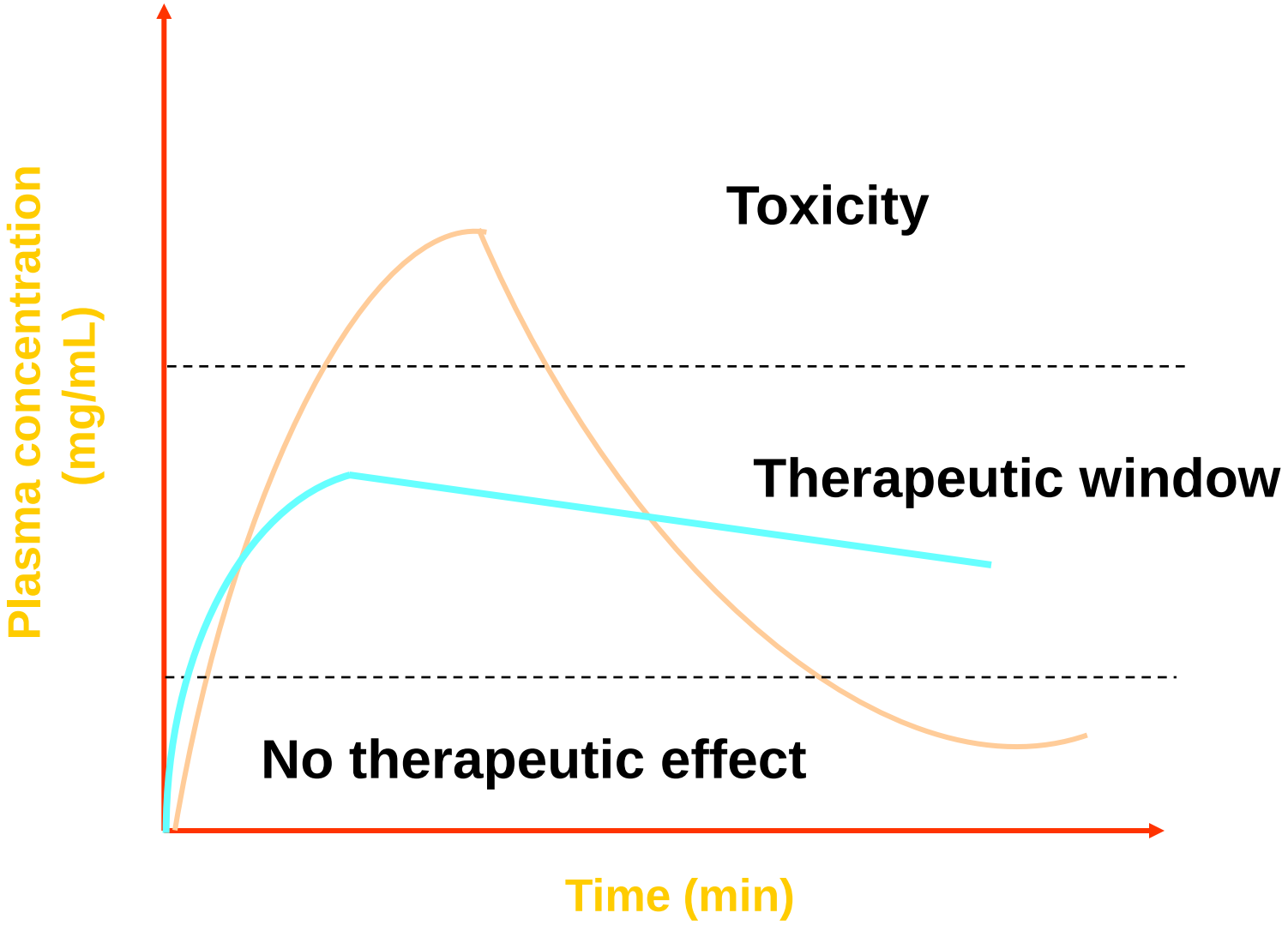
Drug Delivery

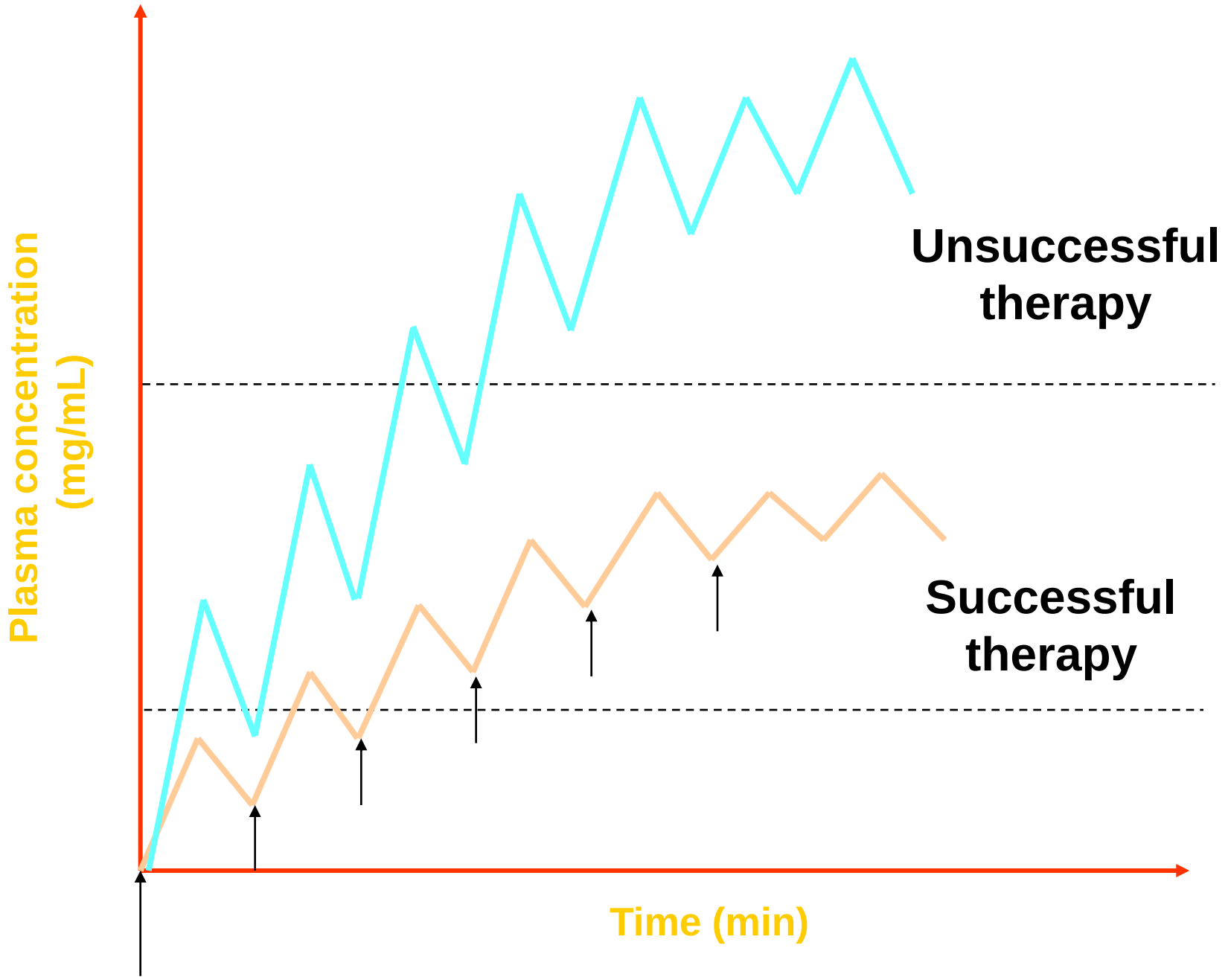
- **Definition**
  - **The appropriate administration of drugs through various routes in the body for the purpose of improving health**
  - **It is highly interdisciplinary**
  - **It is not a young field**
  - **It has recently evolved to take into consideration**
    - **Drug physico-chemical properties**
    - **Body effects and interactions**
    - **Improvement of drug effect**
    - **Patient comfort and well being**

Controlled Drug Delivery


Drug Delivery
Conventional
Controlled
Enteral
Parenteral
Other
Sustained
Extended
Site-specific
Pulsatile

Plasma Concentration




Plasma concentration
(mg/mL)
Unsuccessful
therapy
Successful
therapy
Time (min)

Drug Solubilisation – A Problem?

Issue

Active Ingredients in development are *poorly soluble*

Poor solubility, **major challenge in drug delivery**

90% of the active ingredients have low aqueous solubility

Drug solubilisation techniques could potentially impact up to 90% of R&D

Effect on R&D

***Time and cost* involved with screening for salts**

Hydrophobic nature of the New Chemical Entity (NCE) prompts for screening of its various salts - To improve safety, efficacy and a better solubility/bioavailability

Salt selection - Time consuming process - Delays the drug development

Increases the development cost of a drug

Effect on Pipeline

***Failure* of drugs to move from preclinical to phase I**

Nearly 75% of preclinical stage drugs do NOT move to phase I

Around 39% of these failures - Poor drug-like properties of the drugs (implying low solubility)

Impact in market

Increase in number of poorly soluble drugs *on the market*

About 40% of drugs currently on the market - Poor solubility leading to poor dissolution kinetics and suboptimal bioavailability

Low product efficacy and reduced commercial success

At the Nano scale in Pharmaceuticals ….

Size reduction – Fundamental unit operation – Having important applications in Pharmacy

- Improves Solubility
- Improves Bioavailability
- Reduces Toxicity
- Enhances Release
- Provides better formulation opportunities for drugs

Advantages with drugs in the nm size range (Nano sizing)

- Increased surface area
- Resistant to settling
- Enhanced Solubility
- Increased Rate of Dissolution
- Increased Oral Bioavailability
- Enhanced adhesion to biological surfaces
- More rapid onset of Therapeutic action
- Less amount of dose required
- Reduced side effects
- Low systemic exposure
- Decreased fed/fasted variability
- Decreased patient-to-patient variability
- More convenient dosage forms
- Excellent compliance in human beings

Significant achievements of Nano devices

Cancer Nanotechnology	- One-dose-a-day formulation using NT
Taxol delivery (for targeting the tumors)	- Using Nanoparticles
Improved ophthalmic delivery formulation	- Using smart hydrogels nanoparticles
Oral insulin formulation	- Using Nano particle carriers
Amphotericin B formulation	- Using Liposome

OPPORTUNITIES AND CHALLENGES

- The main goals are to improve stability of API in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers.
- Controllable release profiles, especially for sensitive drugs;
- Materials for nanoparticles that are biocompatible and biodegradable;
- Functions (active drug targeting, on-command delivery, intelligent drug release devices/ bioresponsive triggered systems, self-regulated delivery systems, systems interacting with the body, smart delivery);
- Virus-like systems for intracellular delivery;
- Nanoparticles to improve devices such as implantable devices/nanochips for nanoparticle release, or multi reservoir drug delivery-chips;

- **Aim of Nanocarriers-based drug delivery:**

∗ To minimize drug degradation and inactivation upon administration

∗ prevent undesirable side effect

∗ Increase drug bioavailability

∗ fraction of drug delivery in pathological area

PROPERTIES OF NANO CARRIERS

1. **Prolong circulation in the blood**
2. **Ability to specifically recognize and bind target tissues**
3. **Ability to respond to local stimuli characteristic of the pathological site**
4. **Ability to penetrate inside cells bypassing lysosomal degradation for efficient targeting of intracellular drug targets**

Advantages of Pharmaceutical drug carriers:

- **Biodegradable**
- **Easy and reasonably cheap**
- **To have a small particle size**
- **To posses a high loading capacity**
- **To demonstrate prolonged circulation**
- **To specifically and nonspecifically accumulate in required sites in the body.**

- **Some of the carriers can be engineered and that can be activated by:**

  - Change in environmental pH

  - Chemical stimuli

  - Application of rapidly oscillating magnetic field

  - Application of an external heat source

Solid Lipid Nanoparticles as Drug Carriers

Problems can be overcome by Nano sized carriers:

- Low and highly variable drug concentrations after peroral administration due to poor absorption, rapid metabolism and elimination
- Poor drug solubility which excludes i.v. injection of an aqueous drug solution
- Drug distribution to other tissues combined with high toxicity (e.g.cancer drugs).

Advantage

- Increase drug solubilization
- Protect drug from degradation
- Decrease of toxic side effects
- Produce a prolonged release of the drug
- Improve the bioavailability of the drug
- Modify the pharmacokinetics and tissue distribution of the drug
- Provide a targeted delivery of the drug (cellular/tissue)
- High physical stability due to solid state of particle matrix
- Physical stability easy to prove (DSC)
- Chemical stabilization of actives due to solid character

Examples of commercially available loaded NLC

- Coenzyme Q10
- Vitamin E
- Tocotrienol
- Retinol
- Black current oil (BCO)
- KuKui oil
- Makui oil
- use of special lipids: e.g. Carnauba wax

Solid Lipid Nanoparticles (SLN) Ingredients

General ingredients

- **Solid lipid(s)**

  - (triglycerides, partial glycerides, pegylated lipids, fatty acids, steroids, waxes)
- **Emulsifier(s)**

  - (poloxamer, polysorbates, lecithin and bile acids)
- **Water.**

Solid Lipid Nanoparticles (SLN) Ingredients

Lipids
Triglycerides
Tricaprin
Trilaurin
Trimyristin
Tripalmitin
Tristearin
Hydrogenated coco-glycerides (Softisan® 142)
Hard fat types
Witepsol® W 35
Witepsol® H 35
Witepsol® H 42
Witepsol® E 85
Glyceryl monostearate (Imwitor®900)
Glyceryl behenate (Compritol® 888 ATO)
Glyceryl palmitostearate (Precirol® ATO 5)
Cetyl palmitate
Stearic acid
Palmitic acid
Decanoic acid
Behenic acid
Acidan N12

Emulsifiers/Coemulsifiers
Soybean lecithin (Lipoid® S 75, Lipoid® S 100)
Egg lecithin (Lipoid® E 80)
Phosphatidylcholine (Epikuron® 170, Epikuron 200)
Poloxamer 188
Poloxamer 182
Poloxamer 407
Poloxamine 908
Tyloxapol
Polysorbate 20
Polysorbate 60
Polysorbate 80
Sodium cholate
Sodium glycocholate
Taurocholic acid sodium salt
Taurodeoxycholic acid sodium salt
Butanol
Butyric acid
Dioctyl sodium sulfosuccinate
Monooctylphosphoric acid sodium

SLN Preparation

- High pressure homogenization (HPH)
- Hot homogenization
- Cold Homogenization
- SLN prepared by solvent emulsification/evaporation
- SLN preparation by solvent injection
- SLN preparation by dilution of microemulsions or liquid crystalline phases
  - **Further processing**
  - Sterilization
  - Drying by lyophilization, nitrogen purging and spray drying

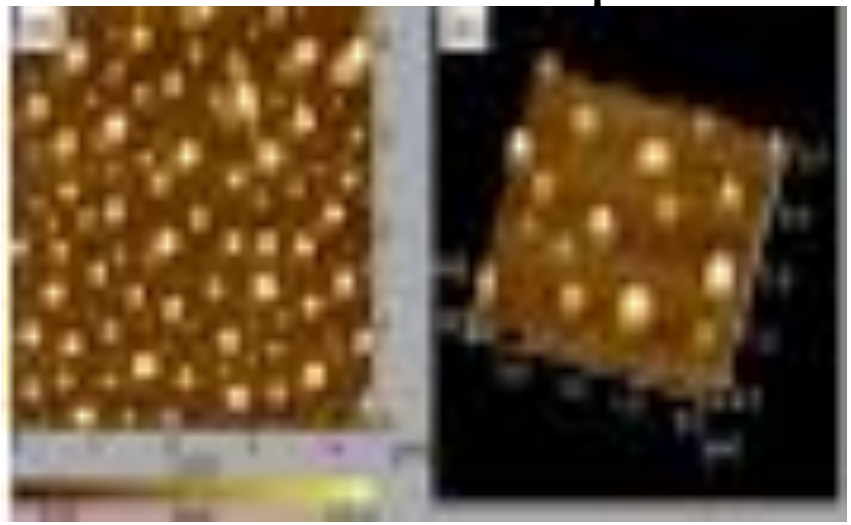
SLN Structure and Characterization

Characterization of Solid Lipid Nanoparticles

Microscopy:

- Scanning Electron Microscopy (SEM) not ideal shrinkage of particles in the electron beam
- Cryo-TEM feasible, but time consuming
- AFM offers the best tool to investigate AFM 3-D structure and even surface morphology

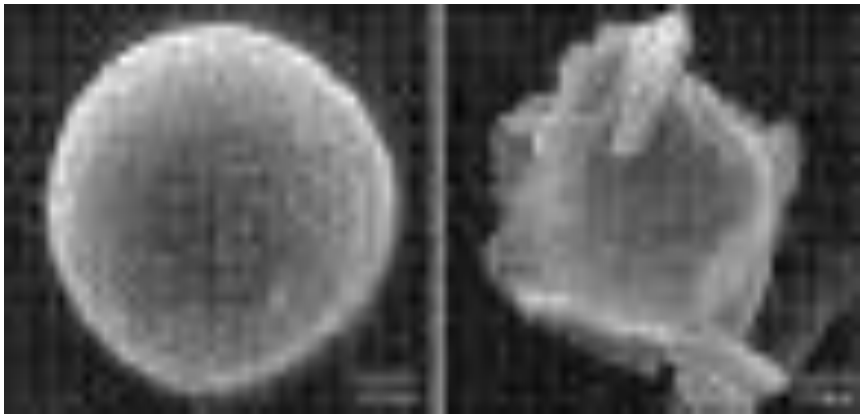
AFM of SLN Preparation



Spectroscopy:

- ❖ Photon Correlation (PSD)
- ❖ TEM of SLN Preparation
- ❖ X-Ray Diffraction
- ❖ Fourier Transform Infrared
- ❖ Other Analysis:
- ❖ Differential Scanning Calorimetry
- ❖ Zetapotential

TEM of SLN Preparation after 1 year storage



Dubes et al, B Euorpean Journal, of Pharmaceutics and Biopharmaceutics, 2003, Vol 55, 279-282.

Possible problems in SLN preparation and SLN performance

High pressure-induced drug degradation

- decrease the molecular weight of polymers
- HPH might be not suitable for the processing of shear sensitive compounds (DNA, albumin, erythropoietin)

Lipid crystallization and drug incorporation

- Lipid crystallization is an important for performance of the SLN carriers

key aspects – should be considered for drug incorporation into SLN

- The existence of supercooled melts
- The presence of several lipid modifications
- The shape of lipid nanodispersions
- Gelation phenomena

Coexistence of several colloidal species.

Administration routes and in vivo fate

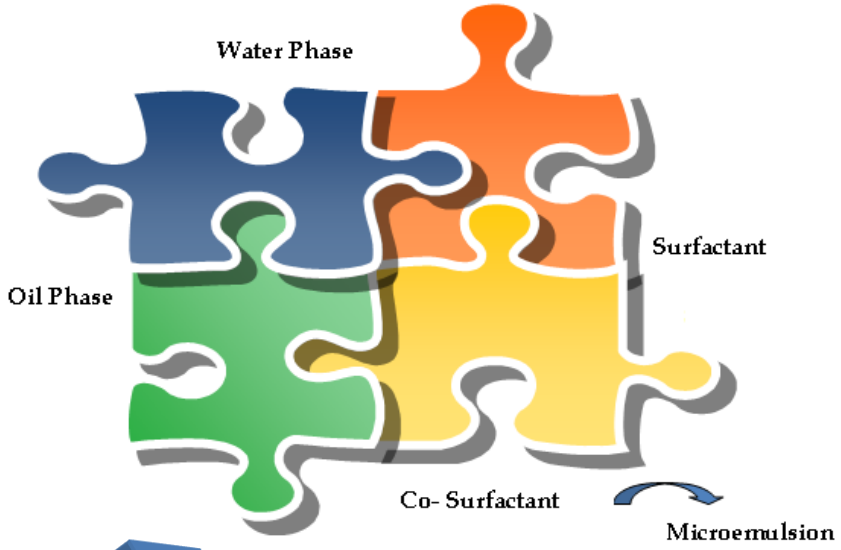
- ***Peroral administration***
- Includes aqueous dispersions or SLN loaded traditional dosage forms, e.g. tablets, pellets or capsules.
- After peroral administration of **cyclosporine** containing lipid nanodispersions to animals - Increased bioavailability and prolonged plasma levels.
- ***Parenteral administration***
- Pharmacokinetic studies of **doxorubicin** incorporated into SLN showed higher blood levels in comparison to a commercial drug solution after i.v. injection in rats.
- ***Transdermal application***

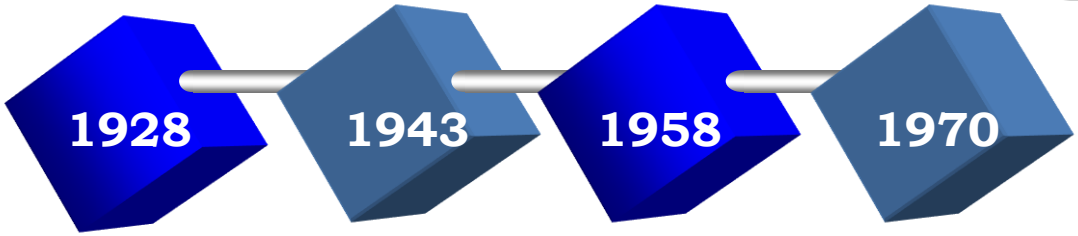
  Incorporation of the SLN dispersion in an ointment or gel is necessary

Microemulsion

Isotropic and **thermodynamically stable** dispersed micro heterogeneous systems composed of water, oil and amphiphile

Stability and unique solubilization properties





The first Commerci -al Micro - emulsion by Radawald.

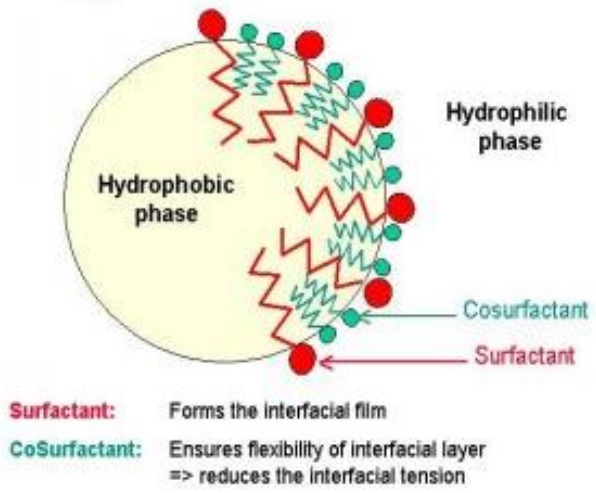
Special kind of colloidal dispersion before the work of Schulman.

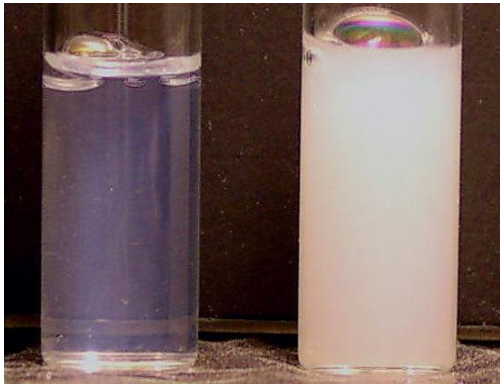
Be named micro - emulsions in 1959.

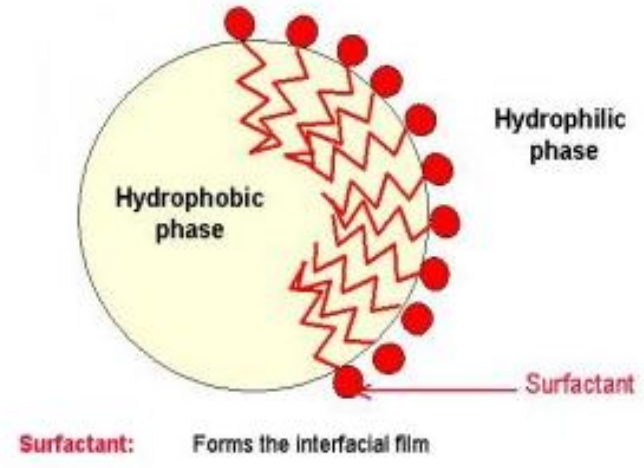
1970, research in microemu- lsion reached a large scale.

Microemulsion Vs. Emulsions

Microemulsion	Emulsion
Thermodynamically stable	Thermodynamically unstable
Highly dynamic system	Relatively static system
Interface may be highly curved	Small curvature
Interfacial tension 4-10 mN/m	Interfacial tension 20-50 mN/m
High surface area: 200 m^2/g	Low surface area: 15 m^2/g
Forms at CPP = 1	Forms at CPP > or < 1
Droplet size 10 - 100 nm (transparent)	1-10 μm (opaque)





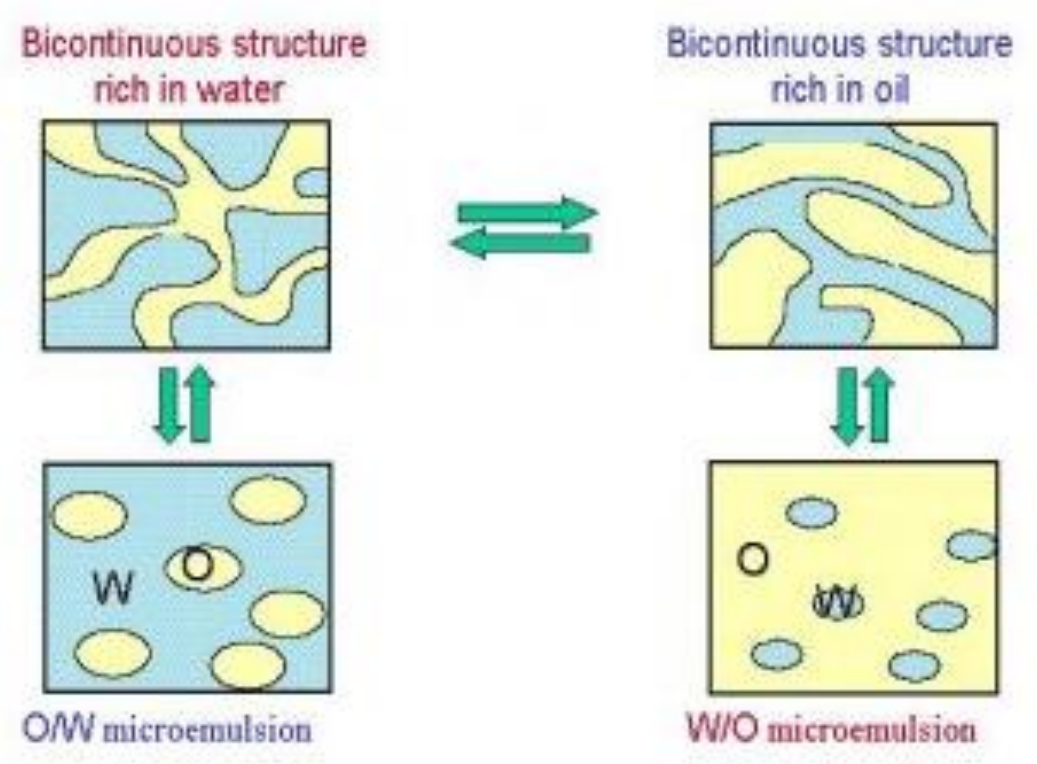


Microemulsions vs Nanoemulsions

- Nanoemulsions are positioned between microemulsions and traditional emulsions.
- Typical particle radii range between 30 and 300 nm which causes their typical blue-shining experience.
- Brownian motion prevents creaming - so nanoemulsions often have a **long-term good stability**.
- Nanoemulsions are **kinetically stable -** Like classical emulsions,
- Typically not easy-to-produce as they require either high-pressure homogenizers
- Requires a lower surfactant concentration for its formation.
- Ostwald ripening is the primary instability process
- Can be reduced by the addition of a second less soluble oil phase and/or addition of a strongly adsorbed and water insoluble polymeric surfactant.

Jürgen Meyer – Evonik, Nanoemulsions for PEG-free cosmetics, July 2008

Microemulsion : Structure



Why microemulsions?

- Ability to protect labile drugs (thermo and enzymatic)
- Controlled release
- Increase the solubility and bioavailability
- Reduce patient variability
- Possible to prepare different formulations suitable for different routes of administration
- Ease of preparation
- Clarity
- Low viscosity (no pain on injection)

(Lawrence and Ress, Adv. Drug Deliv. Rev. 2000, 45, 89-121)

Drawbacks

- Use of a large concentration of surfactant and co-surfactant necessary for stabilizing the nanodroplets.
- Limited solubilizing capacity for high-melting substances.
- Surfactant must be nontoxic for using pharmaceutical applications .
- Microemulsion stability is influenced by environmental parameters such as temperature and pH.

Characterization of microemulsions and related systems

- To Elucidate the microstructure and monitor phase behavior changes
- To Determine the droplet size of the disperse phase by
- Polarized light microscopy
- Transmission electron microscopy
- Electrical Conductivity Measurements
- Viscosity Measurements
- Other Characterization Techniques

  Optical Technique

  - static and dynamic light scattering

  Nonoptical Technique

  - small angle X - ray scattering and
  - small - angle neutron scattering
  - pulsed field gradient NMR
  - and dielectric measurements

Commercial lipid based formulations exhibiting enhanced bioavailability

Product	Excipients	Enhancement of bioavailability
Neoral (Cyclosporin)	Mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil, DL-∝-tocopherol and propylene glycol	20-50% compared to sandimmune
Norvir (Ritonavir)	Caprylic/capric triglycerides, polyoxyl 35 castor oil, citric acid, ehanol, polyglycolyzed glycerides, tween 80 and propylene glycol	Similar to an oral solution
Fortovase (Saquinavir)	Medium chain mono and diglycerides, povidone and DL-∝-tocopherol	3.3 fold increase of AUC compared to Invirase
Agenerase (Amprenavir)	Tocopheryl polyethylene glycol 1000 succinate, polyethylene glycol 400 and propylene glycol	Conventional Oral formulation gave no detectable blood levels

(Subramanian et al., IJEB, 2004)

SEDDS & SMEDDS

- Mixture of drug, oil, surfactant(s) and/or co- solvents which form fine oil in water and/ or water in oil emulsion/ microemulsions upon dilution with aqueous medium or in vivo after oral administration
- SEDDS formulations are either anhydrous or low in water content which allows encapsulation of a unit dose (soft or hard gelatin).
- Materials are suitable for oral ingestion (i.e. vegetable oil derivatives, nonionic surfactants etc.)
- Self-emulsification - Emulsification which occurs with little or no input of energy.
- Spontaneous or may require low levels of shear – Contrast with conventional emulsification which requires high shear.

Pouton, EJPS, 2006

SEDDS & SMEDDS

- Solubilization in the excipient matrix or interface and dispersion in the GIT
- These formulations avoid the dissolution step for the lipophilic drug.
- Very high surface area to volume ratio
- Faster drug release from microemulsion in a reproducible manner
- Release characteristics independent of the GI physiology and the fed/fasted state of the patient

Pouton, EJPS, 2006

Key Formulation Issues

Ability of formulation to maintain solubilization and prevent precipitation on dispersion and digestion…

- **Nature of lipid (chain length)**
- **Importance of self-emulsification/particle size**
- **Relative proportions of lipid vs surfactant**
- **Impact of digestion of lipids and surfactants on solubilisation properties**

Porter et al., Nature Review Drug Discovery, 2007

Microemulsions and Nanoemulsions as drug delivery systems

- Oral Drug Delivery
- Topical Drug Delivery
- Parenteral Drug Delivery
- Ocular Drug Delivery
- Pulmonary Drug Delivery

Desired Characteristics for a Parenteral Formulation of a Marketed Drug or NCE

- High drug solubility/loading
- Low toxicity
- Efficacy at least equal to the marketed drug
- Good stability (shelf-life ≥ 2 years)
- Ease of processing and manufacturing
- Fast track development status to address “unmet medical needs”

Vehicles for IV Administration of Poorly Soluble Drugs

- Surfactant : alcohol solutions (Cremophor : Ethanol) diluted with saline or PBS prior to administration
- Good solvent for poorly soluble drugs
- Require special infusion systems at extra expense and time
  - Ability of this solution to extract toxic plasticizers from various manufacturing and i.v. infusion tubing
- Have to be diluted first and then administered by slow infusion to avoid:
  - Venous irritation
  - Anaphylactic reactions (respiratory distress)

SUMMARY

- Exploiting the nano carriers in delivery systems is need of hour.
- Measures should be taken to ascertain the safety of the formulations.