NANOPARTICLES

AS DRUG DELIVERY SYSTEM

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OVER VIEW

- Definition
- Type of Nanoparticles
- Method of Manufacturing
- Requirement of material
- Purification
- Physico-chemical Evaluation
- Summary

DEFINITION:

- Nanoparticles - small colloidal particle
- Made up of biodegradable or non-biodegradable polymer
- Size rage :1—1000nm.

- Type of nanoparticles :

  Commonly classified in to two type

  Nanospheres (matrix type structure)

  Nanocapsules (vesicular system)

ADVANTAGES OF NANOPARTICLES

- The emphasizes of nanoparticles over come to microparticles and liposomes.
- Higher intercellular uptake compared with microparticles.
- Target drug delivery especially to cancer treatment.

METHODS OF MANUFACTURING

- Emulsion Polymerization
- Interfacial Polymerization
- Interfacial Polycondensation
- Solvent Evaporation
- Solvent Displacement
- Interfacial Deposition
- Salting-Out
- Emulsification or Solvent Diffusion

REQUIREMENT OF MATERIAL

- Solvent
- Monomer
- Polymer
- Stabilizing agent
- Surfactant/Emulsifier
- Initiator

SOLVENT

- Organic Solvent are Classified according to International Conference on Harmonization (ICH) and placed into one of three class as follows,
- **CLASS-1(solvent to be avoid)**

  Eg: propylene carbonate
- **CLASS-2 (solvent to be limited)**

  Eg: Chlorofom,Cyclohexane,toluene
- **CLASS-3 (solvent to be low toxic)**

  Eg: n-pentene, ethylacetate

MONOMERS:

Eg: Isobutyl cyanoacrylate,

Isohexyl cyanoacrylate,

n butyl cyanoacrylate.

POLYMERS:

Eg: Polylactic acid, polylactic-glycolic acid co polymer.

STABILIZERS:

To enhance the stability of the polymer particle by adding stabilizer.

Eg: Dextran 70, Pluronic F68.

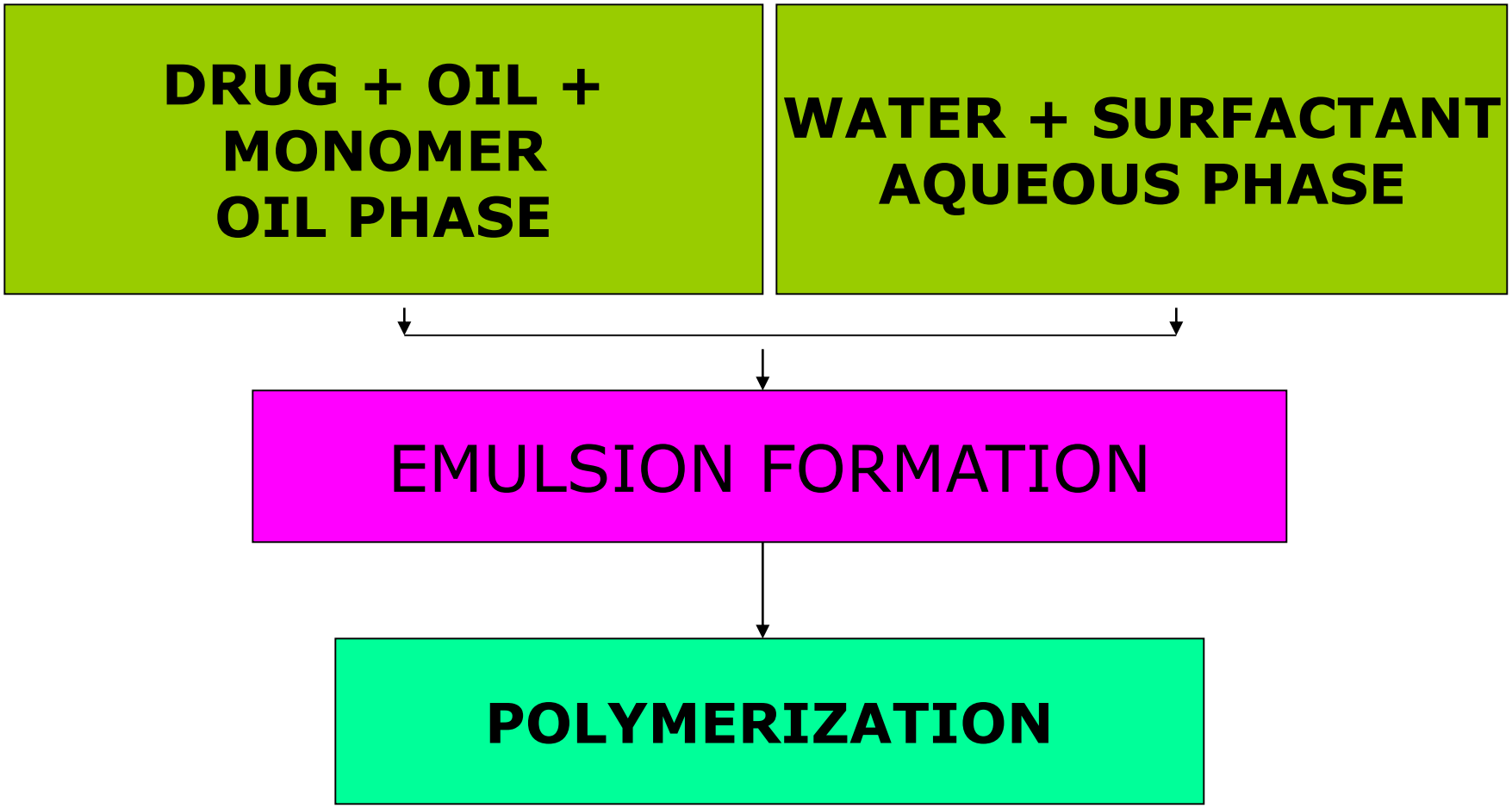
SURFACTANTS:

Eg: Tween 80, Span 80.

INTIATOR:

Eg: Ions or pre radicle and gamma radiation

EMULSION POLYMERIZATION METHOD:



EMULSION POLYMERIZATION METHOD

- Polymerization continues monomer molecule diffuse to growth of continuous phase.
- Stabilizing agents such as Dextran 70 and Pluronic F68 are used.
- When it reaches certain molecular weight, the polymer are insoluble due to this separation occurs which leads to nucleation of polymer particle.
- Example Ampicillin and Doxirubicin.

INTERFACIAL POLYMERIZATION

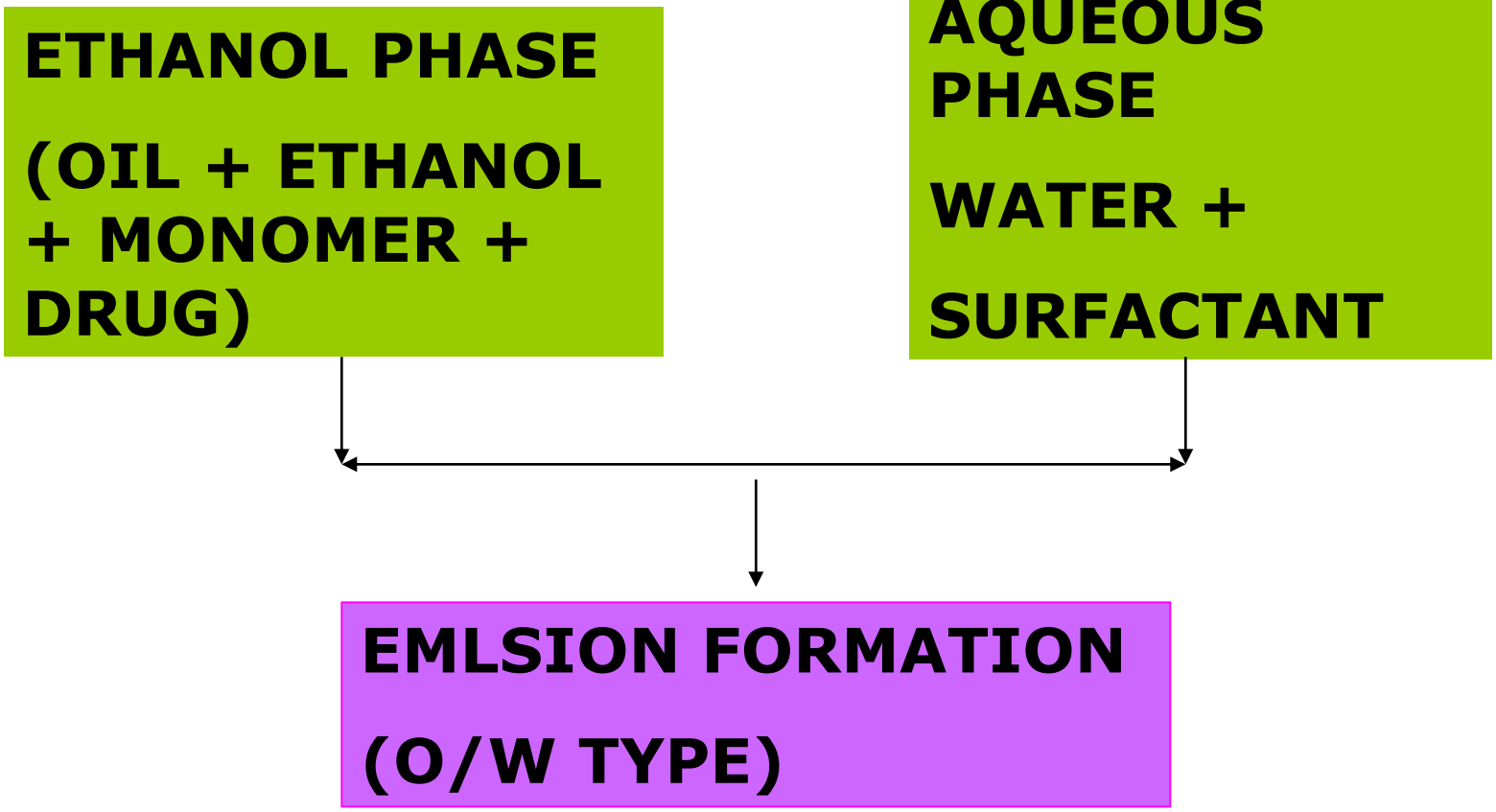
- This method is used for preparation of Nanocapsule particle, the monomer undergoes very fast polymerization

- Two types :

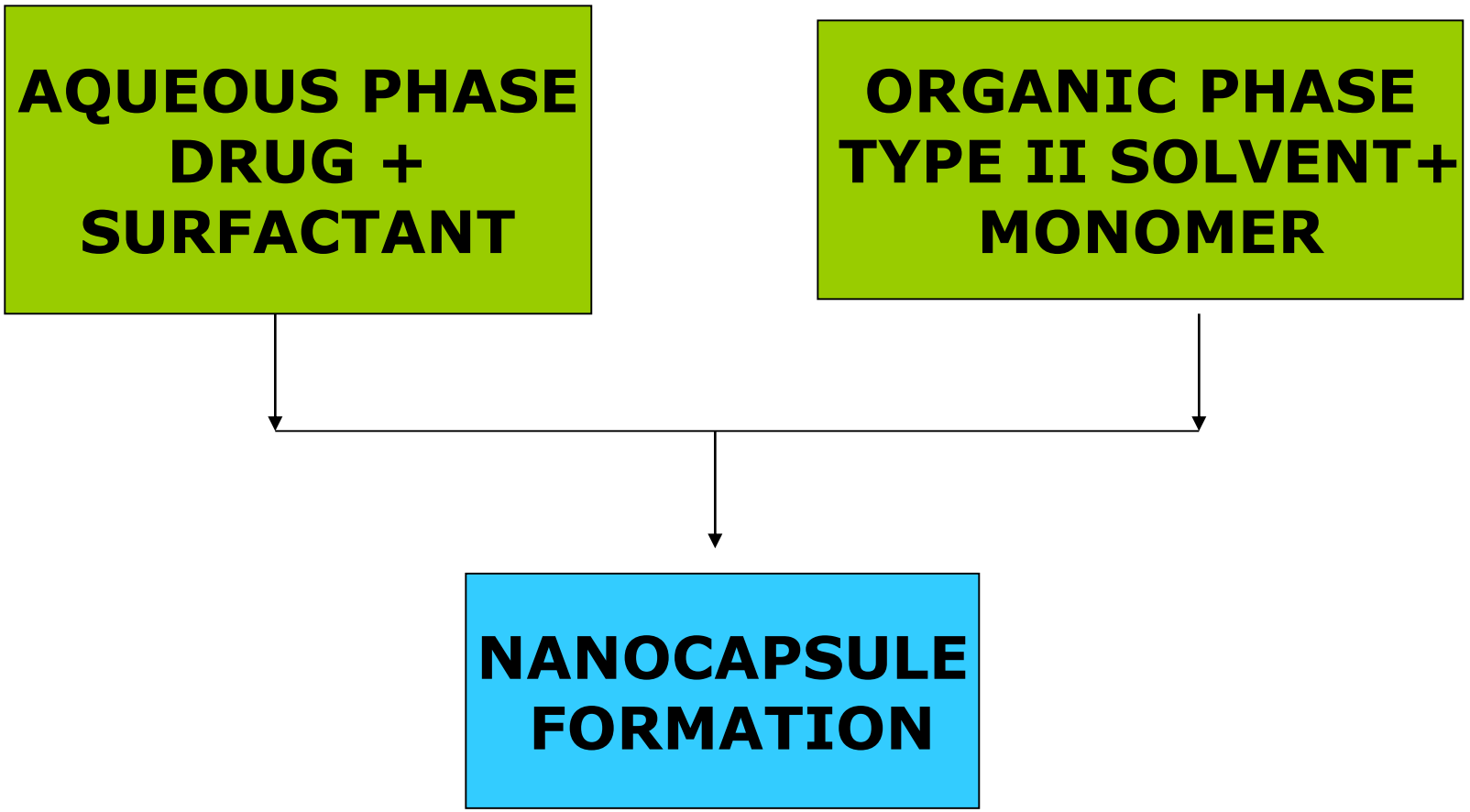
  Oil containing Nanocapsules

  Water containing Nanocapsules.

OIL NANOCAPSULES



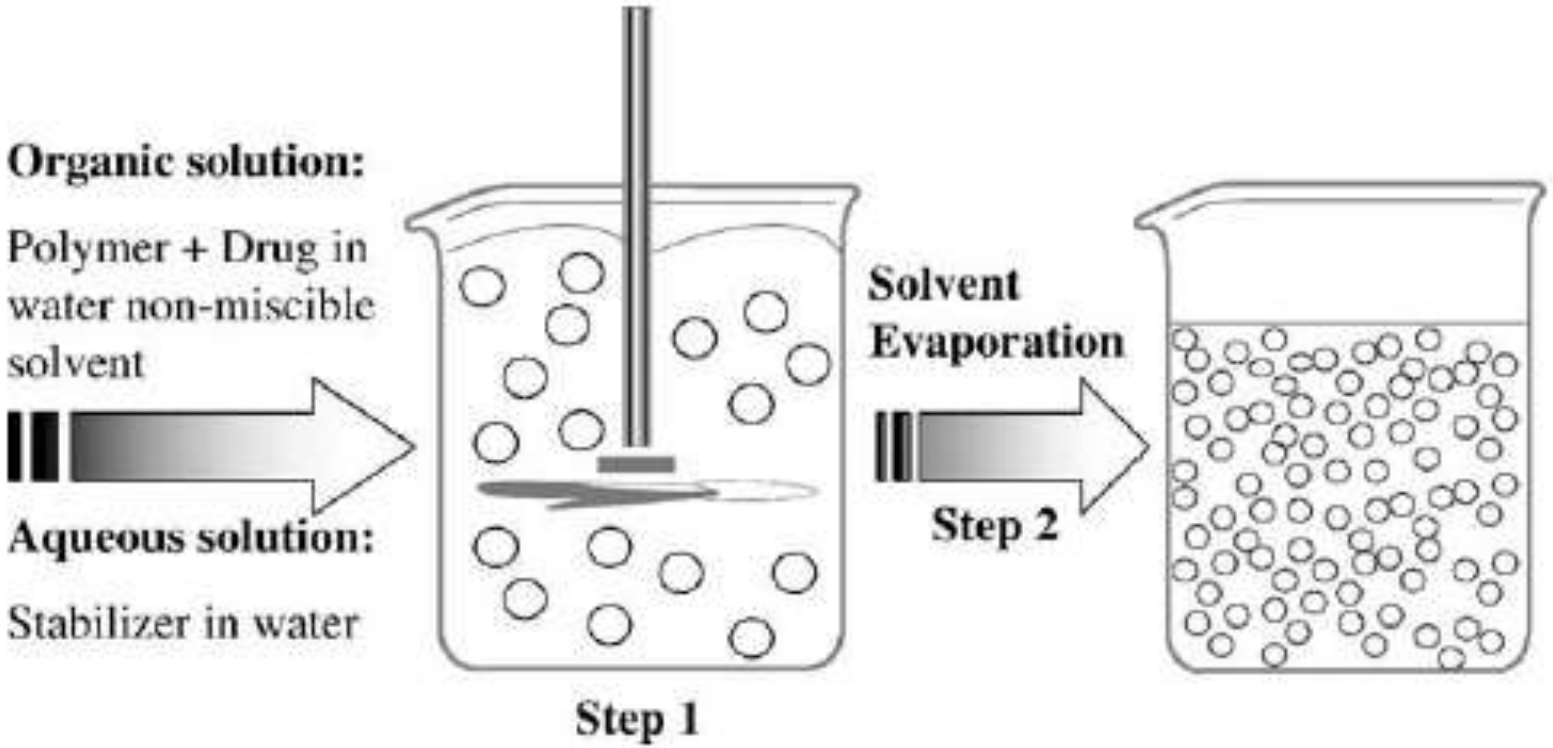
WATER NANOCAPSULES



INTERFACIAL POLYCONDENSATION

- Polymeric nanoparticle can be prepared by interfacial condensation of lipophilic monomer and hydrophilic monomer.
- Lipophilic monomer such as phtaloyl dichloride.
- Hydrophilic monomer such as diethylene triamine.
- It is a modified Interfacial condensation method.
- Polyurethane and polyether urethane nanoparticles were synthesized by this method.

EMULSIFICATION OR SOLVENT EVAPORATION



EMULSIFICATION OR SOLVENT EVAPORATION

Size of the particle controlled by:

- Adjusting Stirrer Rate
- Conc. of the dispersing agent
- Viscosity of the organic and aqueous solution
- Temperature.

Limitations

- only applicable for lipid soluble drugs.

SOLVENT DISPLACEMENT METHOD

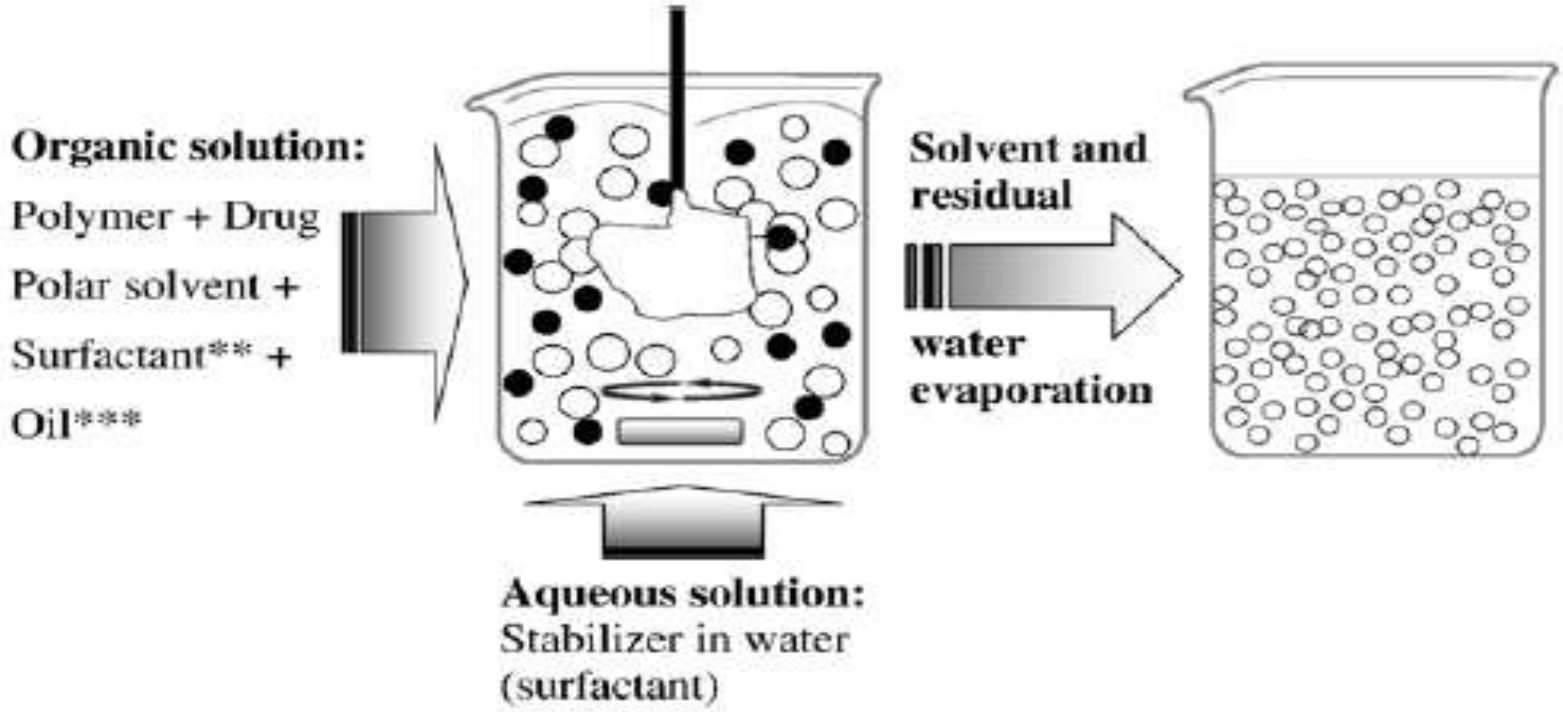
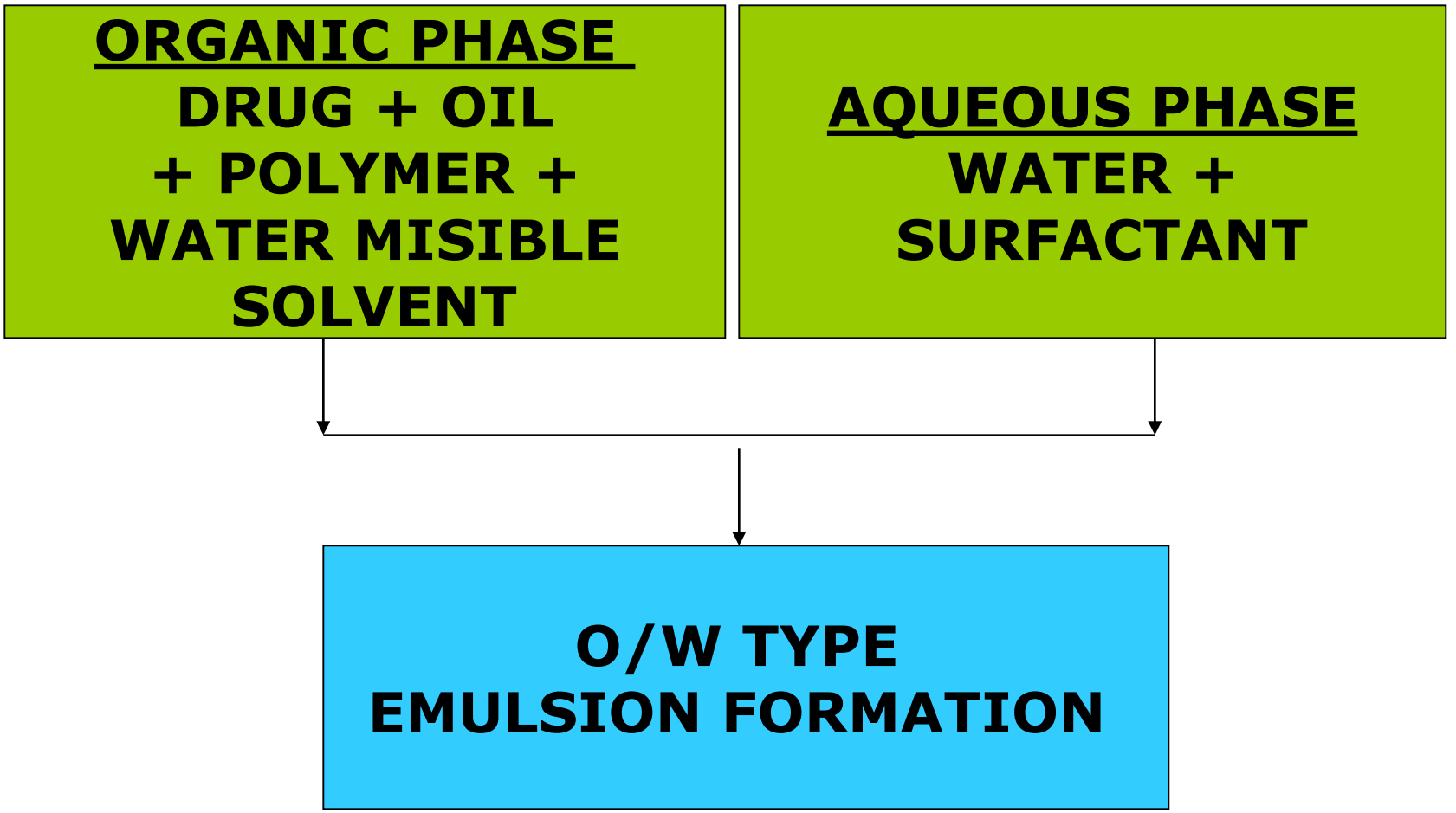


Fig 2. Schematic representation of the solvent displacement technique. **Surfactant is optional. ***In interfacial deposition method, a fifth compound was introduced only on preparation of nanocapsules.

SOLVENT DISPLACEMENT METHOD



INTERFACIAL DEPOSITION METHOD

ORGANIC PHASE

DRUG + OIL + POLYMER + SOLVENT MIXTURE

AQUEOUS PHASE

WATER + SURFACTANT

O/W TYPE EMULSION

EMULSION SOLVENT DIFFUSION METHOD

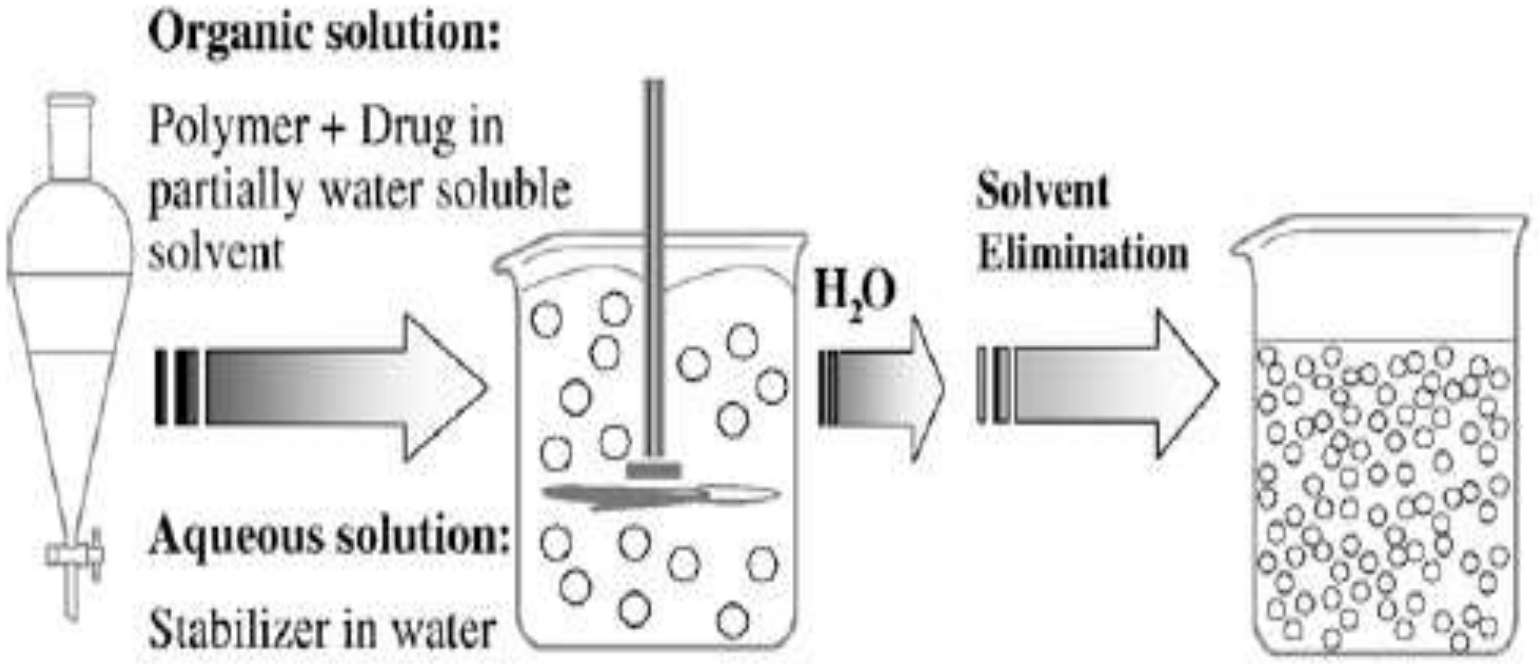


Fig 3. Schematic illustration of the ESD technique.

EMULSION SOLVENT DIFFUSION METHOD

This technique present several advantages such as,

- High encapsulation efficiency > 70%.
- No need for homogenizer.
- Reproducibility and easy scale up.
- Simplicity.

Limitation:

- Applicable for only lipophilic drug.

SALTING OUT

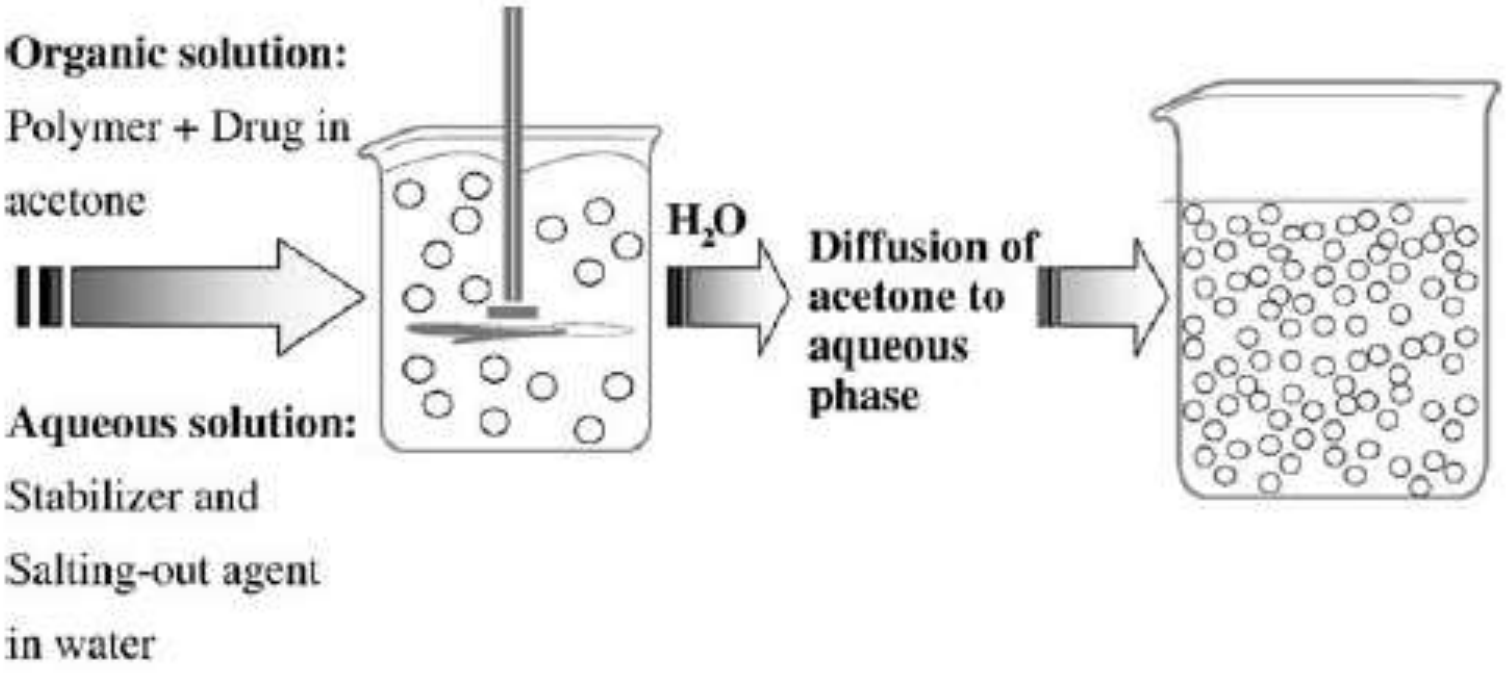
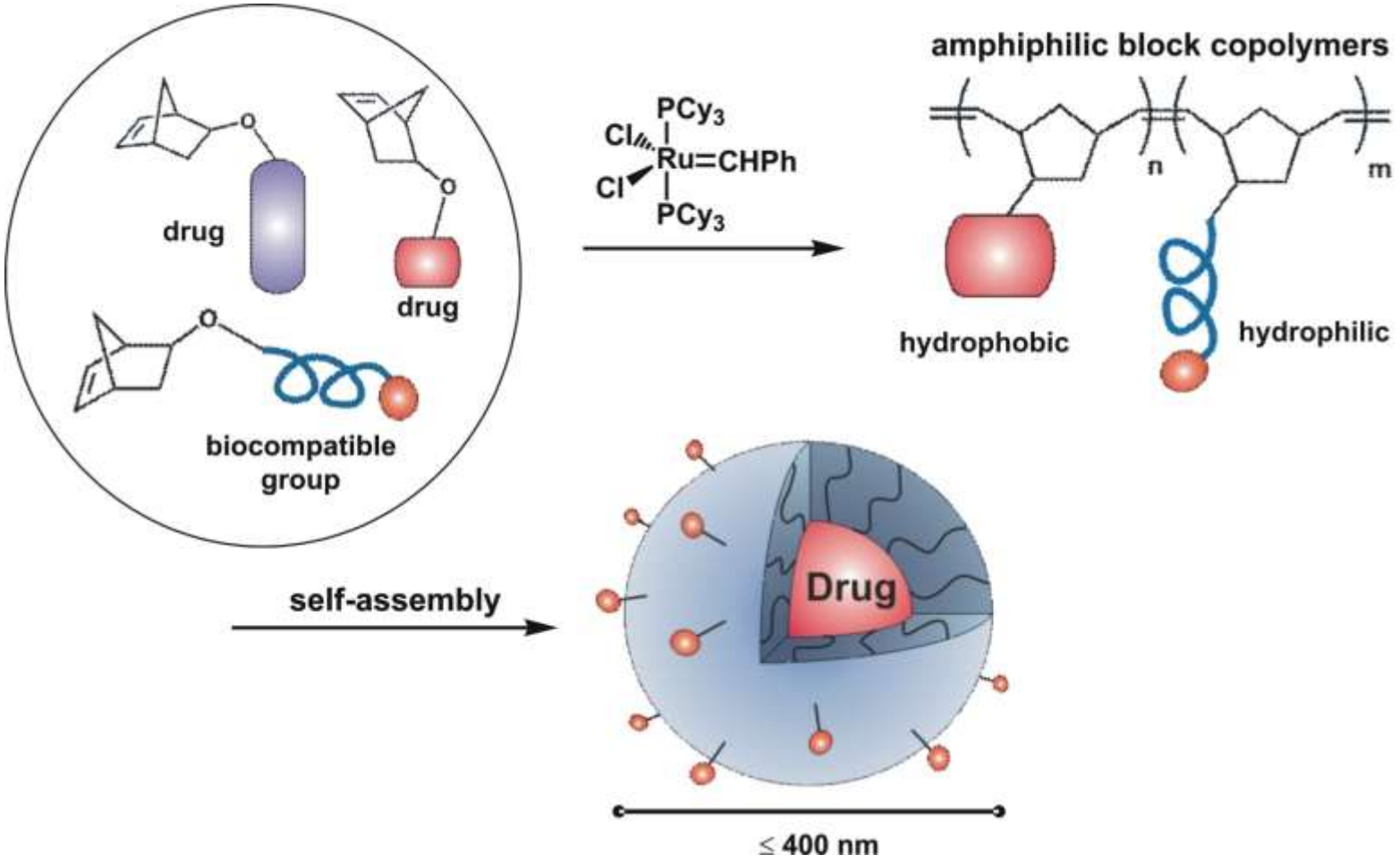


Fig 4. Schematic of the salting-out technique.

SALTING OUT

- Based on separation of water miscible solvent from aqueous solution via salting out effect.
- Salting out agents such as $MgCl_2, CaCl_2$.
- Salting out agent eliminate by cross flow filtration.
- In this method no need for high temperature so sensitive substance prepared by this method.

NP with biocompatibility



SUMMARY

Method	Simplicity	EE (%)	Safety of compounds
EP	High	High	Medium
IP	Low	High	Low
SE	High	Medium	Medium
SD	High	High	Medium
SO	High	High	Low

SUMMARY

Table 2
Polymeric nanoparticles: general advantages and drawbacks of the preparation methods

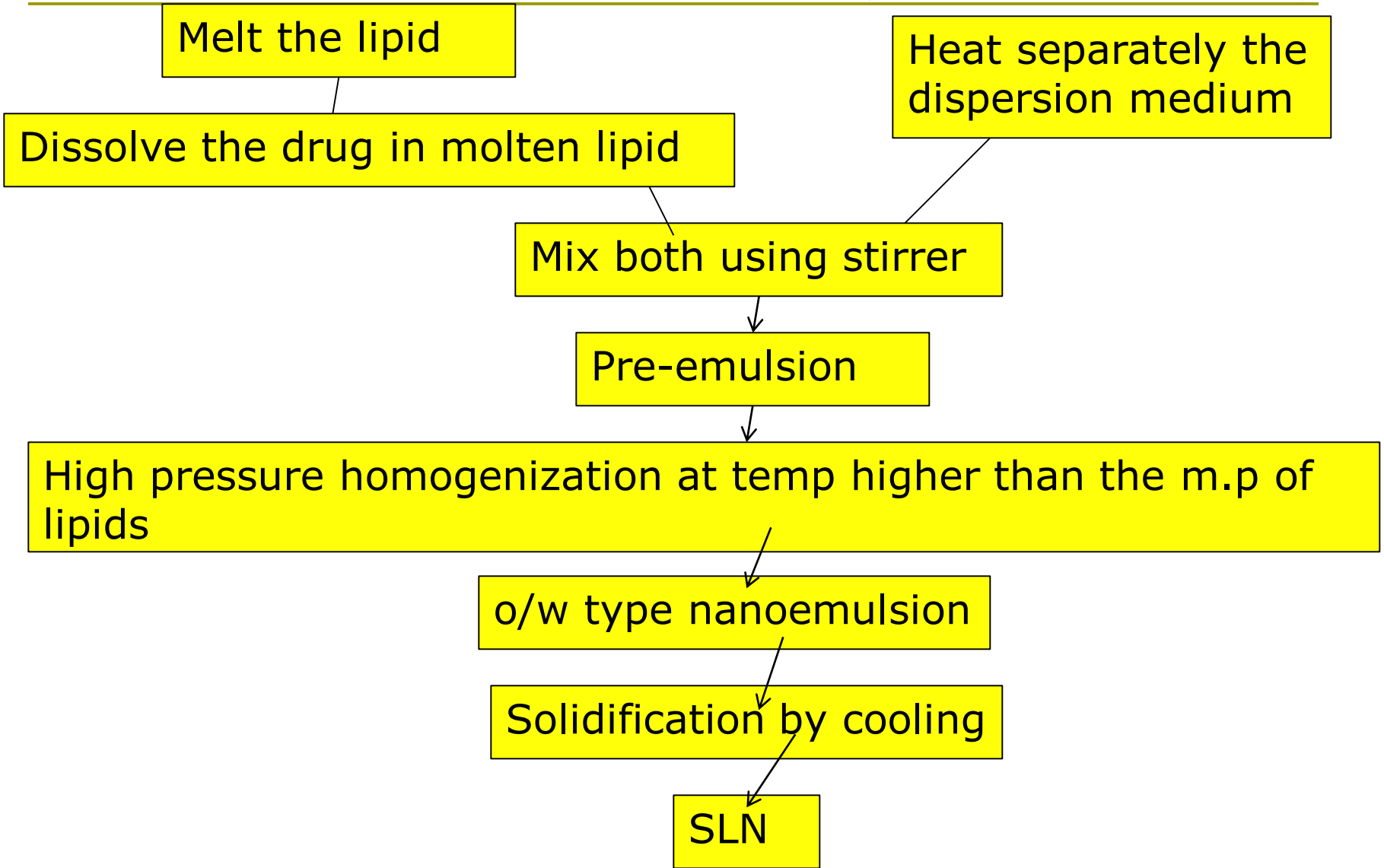
Method	Simplicity of procedure	Need for purification	Facility scaling-up	EE (%)	Safety of compounds
Polymerization of monomers					
Emulsion polymerization					
Organic	Low	High	NR	Low	Low
Aqueous	High	High	High	High	Medium
Interfacial polymerization	Low	High	Medium	High	Low
Preformed polymers					
Synthetic					
Emulsification/solvent evaporation	High	Low	Low	Medium	Medium
Solvent displacement and interfacial deposition	High	NR	NR	High	Medium
Salting out	High	High	High	High	Low
Emulsion/solvent diffusion	Medium	Medium	High	High	Medium
Natural					
Albumin	NR	High	NR	Medium	Low
Gelatin	NR	High	NR	Medium	Low
Polysaccharides					
Alginate	High	Medium	High	High	High
Chitosan	High	Medium	High	High	High
Agarose	Medium	High	NR	NR	High
Desolvation	NR	High	NR	Low	Low

EE, encapsulation efficiency; NR, no reference available.

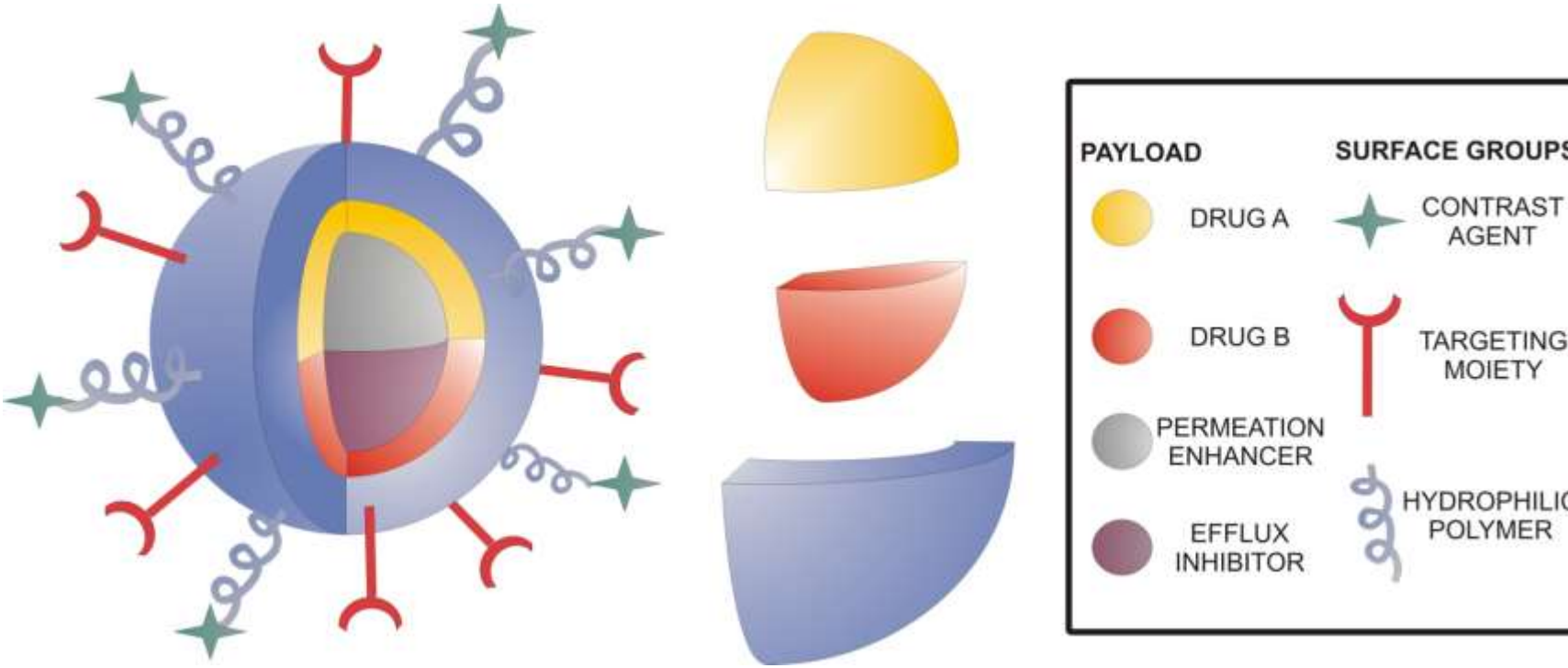
Solid Lipid Nanoparticles

- Submicron colloidal carriers composed of physiological lipid, dispersed in water or in an aqueous surfactant solution
- Size range: 50-1000nm
- Advantages:
- Highlight: combined advantages of both liposomes & nanoparticles
- Controlled release of drug fpr long period of time
- Protection of the drug incorporated from degradation
- Sterilization possible by autoclaving & gamma irradiation
- Can be lyophillized or spray dried
- Metabolites –non toxic
- Scope for scaling up.

Preparation of SLN



Magic Bullet



PURIFICATION

- Gel Filtration
  - Do not remove high mol.wt substances
- Dialysis
  - Do not remove high mol.wt substances
  - Time consuming
  - Difficult for large quantities
- Ultracentrifugation
  - Aggregation of particles
  - Time consuming
  - Difficult for large quantities

Freeze Drying

- Freezing of NP suspension & subsequent evaporation of water content(sublimation)
- Advantages
  - Prevention of degradation
  - Prevention of solubilization of the polymers
  - Prevention of drug leakage/desorption
  - Easy to handle & transport
  - Ideal for long term preservation
  - Readily re-dispersed in water
  - No physicochemical changes occurs

Sterilization

- NP for parentral and ophthalmic preparations- strictly sterile
- Sterile-free from microorganism & pyrogens
- Methods:
  - Membrane filtration
  - Autoclaving
  - Gamma irradiation
  - Aseptic manufacturing

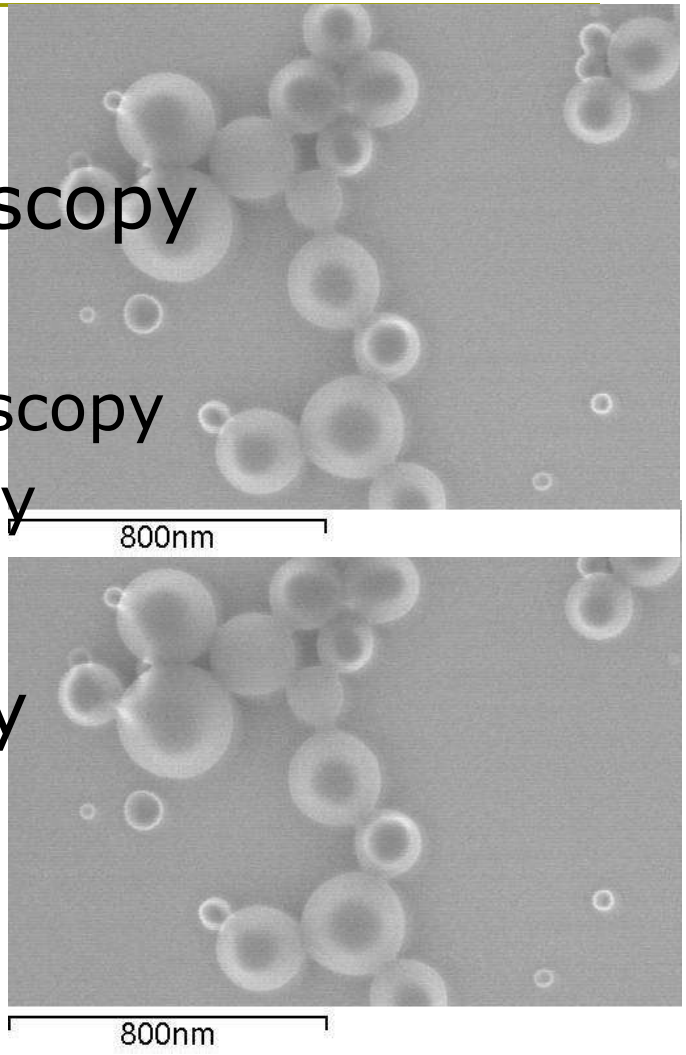
Characterization

Size and Morphology

- Photon correlation spectroscopy
- Electron Microscopy
  - Transmission Electron Microscopy
  - Scanning Electron Microscopy

Charge Determination

- Laser Doppler Anemometry
- Zeta potentiometry



Characterization

Surface Hydrophobicity

- Water contact angle measurement
- Rose Bengal(dye) binding
- Hydrophobic interaction chromatography
- X-ray photoelectron spectroscopy

Carrier-drug interaction

- Differential scanning calorimetry

Characterization

Density

- Helium/cryo/air pycnometer

Molecular weight determination

- Gel permeation chromatography aided with refractive index detector

Nanoparticle recovery

$$= \frac{\text{Conc. Of drug in nanaoparticles x 100}}{\text{conc. Of nanoparticles recoverd}}$$

Characterization

Drug content(%w/w)

=Conc. Of drug used x 100

conc. Of drug loaded in nanoparticles

In vitro release studies

- Diffusion studies across semipermeable membrane

Donar compartment-Known conc of drug in NP

Receptor compartment-PBS/PB pH 7.4

Entrapment Efficiency

- Entrapment efficiency gives you an idea about the %drug that is successfully entrapped/adsorbed into nanoparticles. It is calculated as follows:
- %EE = [(Drug added - Free "unentrapped drug")/Drug added] *100
- Example: If the %EE is 30%, it means that 30% of your drug is entrapped into the nanoparticles.

Loading Capacity

- Loading capacity helps you to deal with nanoparticles after their separation from the medium and to know their drug content. It is calculated using the following equation:
- %LC = [Entrapped Drug/nanoparticles weight] * 100
- Example: If the loading capacity is 30%, it means that 30% of the nanoparticles weight is composed of the drug! i.e. Each 1 mg nanoparticles contains 0.3 mg drug.

Problem

- A drug coded as e2nk is loaded in PLGA nanoparticles. 500mg of e2nk is dissolved in 0.2% Pluronic f20 solution(5ml) and mixed with 5ml of PLGA(500mg) dissolved in acetone for 20 minutes at 600 rpm. The emulsion is sonicated for 25 min and nanoparticles were collected by fractional centrifugation at 16000g. The total amount of nanoparticles obtained was 720mg. The prepared nanoparticles were lyophilized and stored at -10^{o}C for further studies. Amount of free drug=188mg
- Find out the entrapment efficiency and Loading Capacity

Applications

- Brain Delivery of Drugs
- Ocular Delivery
- Gene delivery
- Treatment of Cancer
- Lung Targeting
- GI Epithelial cell targeting
- Delivery of Proteins and Peptides.

REFERENCE

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- www.nanomedijournal.com
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Thank You