DISSOLUTION RATE ENHANCING TECHNIQUES

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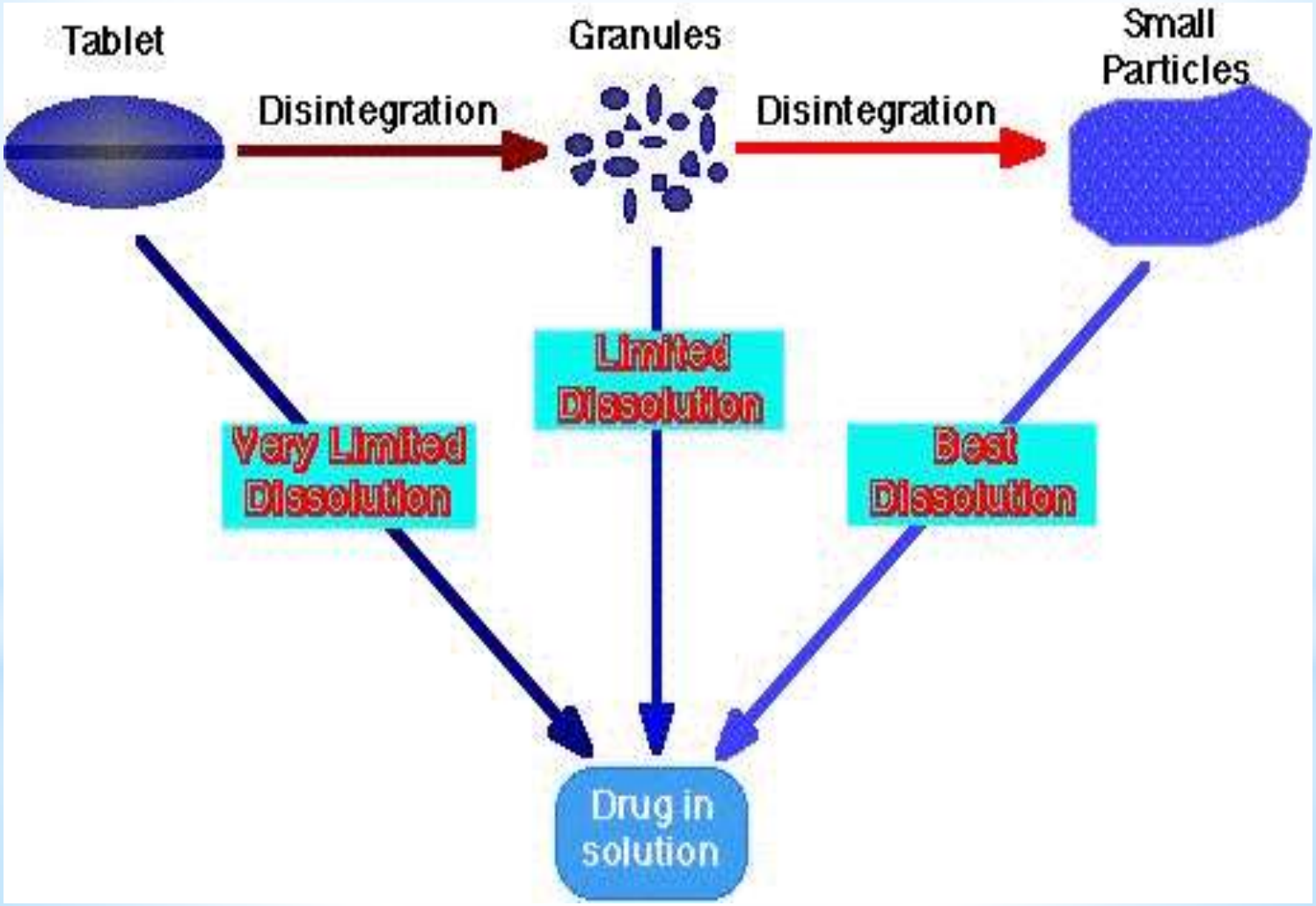
DISSOLUTION: Dissolution is a mass transfer process from solid phase to liquid phase

- It is rate limiting step in absorption of drugs



- Absorption of a drug and its bioavailability mainly depends on solubility and dissolution rate

DISSOLUTION RATE : Dissolution rate is the amount of solute enter into dissolution medium pre unit time under standard conditions of temperature, pH, Composition of dissolution medium, effective surface area

Dissolution rate can be calculated using equation

Noyes And Whitney Equation: dc/dt=K(Cs-Cb)

Modified Noyes and whitney equation:

$$\frac{dc}{dt} = \frac{DAKw/o(Cs-Cb)}{Vh}$$

DISSOLUTION RATE ENHANCING TECHNIQUES

I. PHYSISICAL MODIFICATION

(A). PARTICLE SIZE REDUCTION

(B). SOLID DISPERSION

(C). COMPLEXATION

II . CHEMICAL MODIFICATION

(A). pH ADJUSTMENT

(B). DRUG DERIVITISATION

(C). SALT FORMATION

III. MISCELLANEOUS

(A). SOLVENT DEPOSITION

(B). HYDROTROPHY

I. PHYSICAL MODIFICATION

(A) PARTICLE SIZE REDUCTION

(1) Micronization:

- Micronization increases the dissolution rate of the drugs by increasing the surface area
- This process involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of attrition methods (fluid energy or jet mill).

Ex; sulpha drugs,steroids, griseofulvin

Colloid mill

*dc/dt ∝ A

- This is practically true in nonhydrophyllic drugs like griseofulvin, Chloramphenicol, Steroids, Sulpha drugs.

- This is practically false in hydrophobic drugs like Asprin, Phenacitin, Phenobarbital.

Reasons:

1) Absorb air on hydrophobic surface
2) Due to their high surface free energy
3) Impart surface charges to the particles

(2) Nanonization:

Micropaticles → Sub micronised particles (Nano particles)

- An average particle size ranging between 200 and 600 nm.
- This technology is applied for poorly soluble drugs that are insoluble in both water and oils.
- Size reduction results ↑ surface area ↑ dissolution rate and ↑ bio availability.

Ex: Amphotericin-B

Patented engineering process based on the principles of ; .

(a) Pearl milling

(b) High pressure homogenization

(c) Co-micronization

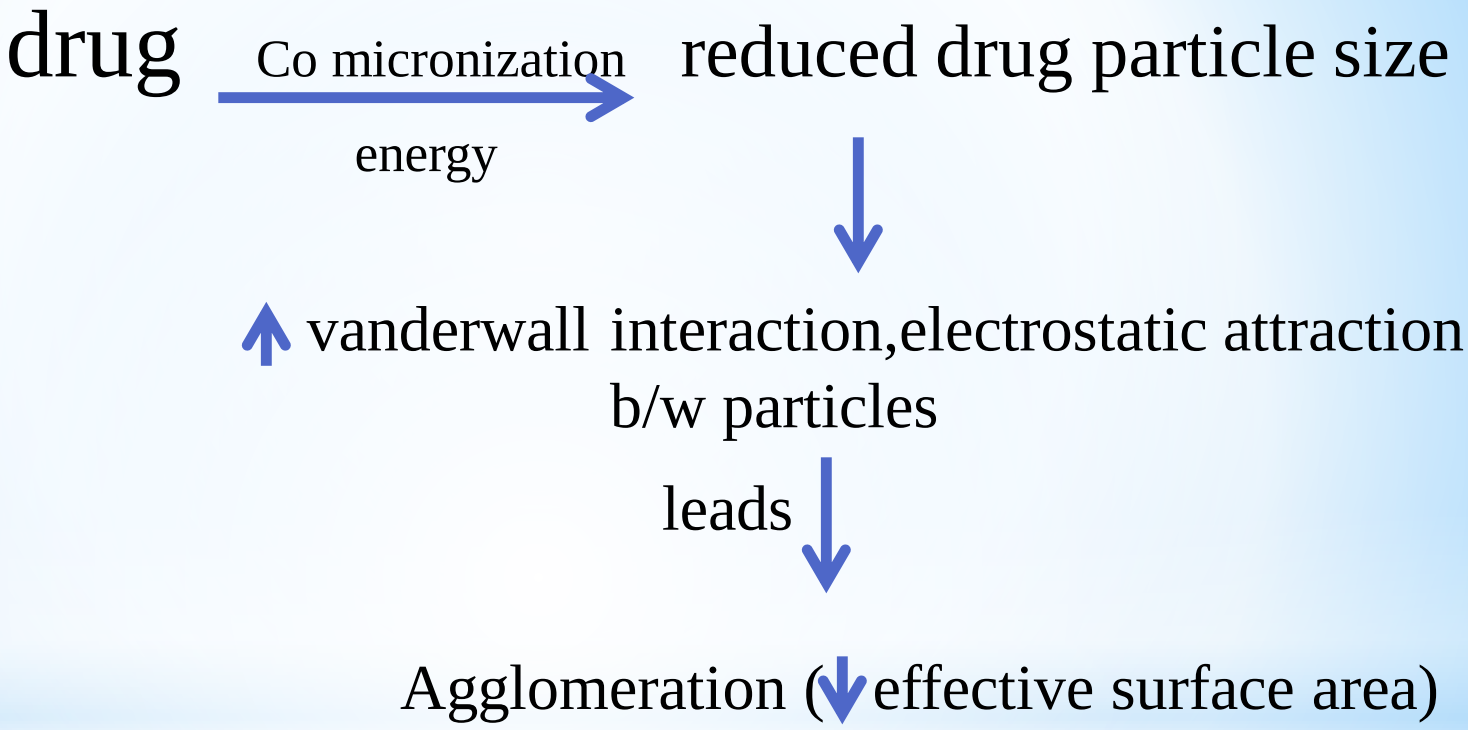
(d) Supercritical fluid process

(e) Spray freezing into liquid

(f) Rapid expansion from super critical to aqueous solution

Patented engineering techniques under nanonization:

(a) Co-micronization :

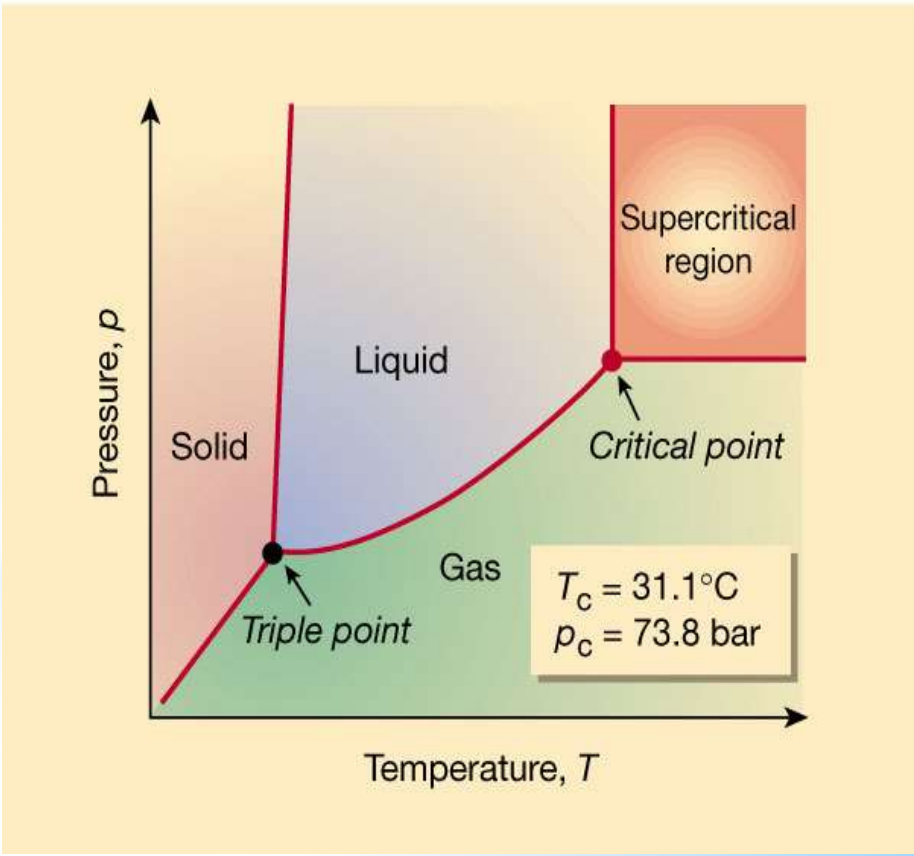


- Microcrystalline cellulose can be used to reduce vanderwall interaction,electrostatic attraction b/w particles

(b)Supercritical fluid process:

- This is the novel nano-sizing and solubilization technology and it's application has increased in recent years is particle size reduction via supercritical fluid (SCF)processes

- Commonly used supercritical solvents include Co_2, nitrous oxide, ethylene, propylene,propane, n-pentane,C_2H_5OH,NH_3, and H_20.



(B). DRUG DISPERSION IN CARRIERS:

(1).Solid dispersions:

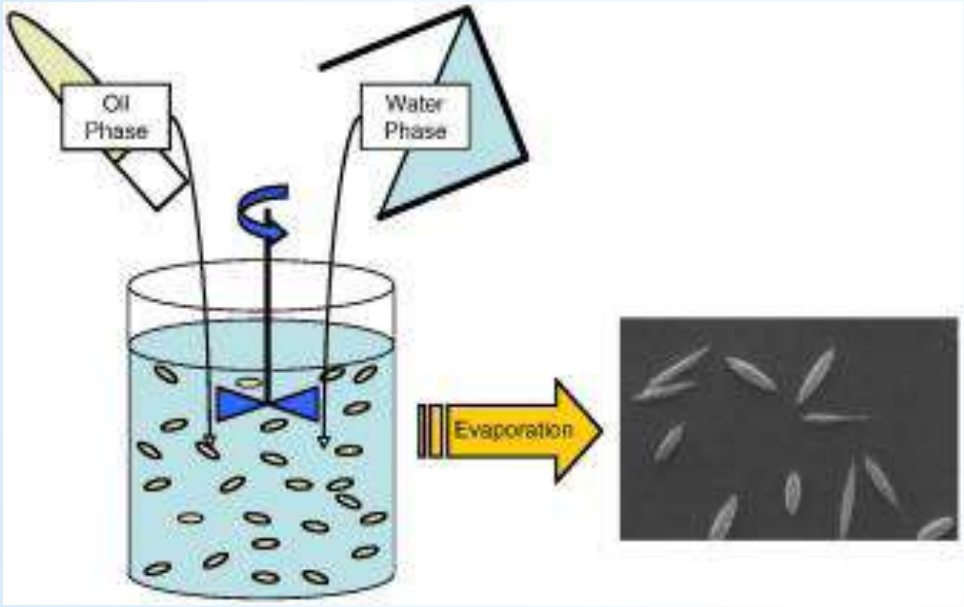
- In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, by that enhances the dissolution of the drug.

- Solid dispersion techniques yields eutectic or solid solution products.

- Eg: A solid dispersion of carbamazepine in polyethylene glycol 4000 (PEG-4000) increased the rate and extent of dissolution of carbamazepine.

DRUG DISPERSIONS are mainly prepared by 3 methods

(a) SOLVENT EVAPORATION METHOD:



Ex; ß-Carotene, Meloxicam, Naproxen, Nimesulide

(b) HOT MELT METHOD :

Drug +carrier —melting→ Solution —Cooling→ Super saturation —milled→ Particle size is reduced

Ex; Sulphathiazole drug,urea as carrier

(c) HOT MELT EXTRUSION METHOD**:**

- Hot melt extrusion method is most preferable for the preparation of Solid solutions. Eg: The solubility of the drug itraconazole has increased by this technique by using HPMC as carrier.

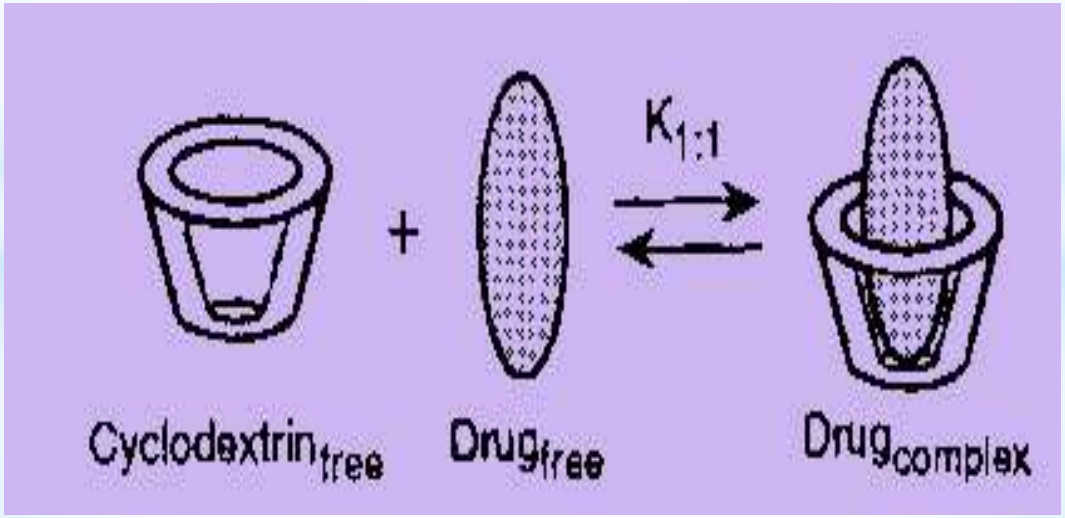
(2) EUTECTIC MIXTURES:

- Eutectic mixtures are prepared by rapid solidification of the fused liquid of two components
- Which show complete liquid miscibility.
- When eutectic mixtures composed of poorly soluble drugs is exposed to water (or) GI Fluid
- The carrier (urea) gets released into the aqueous media leaving the drug in fine crystalline form

Eg: Paracetamol-urea, Griseofulvin-urea.

(C). COMPLEXATION:

- Inclusion complexes are formed by the insertion of the nonpolar molecule of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host).
- Eg: Rofecoxib54, Piroxicam55 and Carvedilol56 can be improved by using cyclodextrins



- Different types of complexing agents are used for different types of complexation techniques,

S.No	Type	Example
1.	Coordination	Hexamine(III)cobalt chloride
2.	Chelates	EDTA,EGTA
3.	Metal-olefin	Ferrocene
4.	Molecular complexes	Polymers

(D). MODIFICATION OF THE CRYSTAL HABIT:

- Changing the crystal habit means changing one form to another form (i.e; crystalline form to amorphous)

- Amorphous form shows more solubility than meta stable polymorphs, anhydrates are more soluble than hydrates and solvates are more soluble than non-solvates.

Order for dissolution of different forms of drug is

Amorphous > Metastable polymorphs > Stable polymorphs

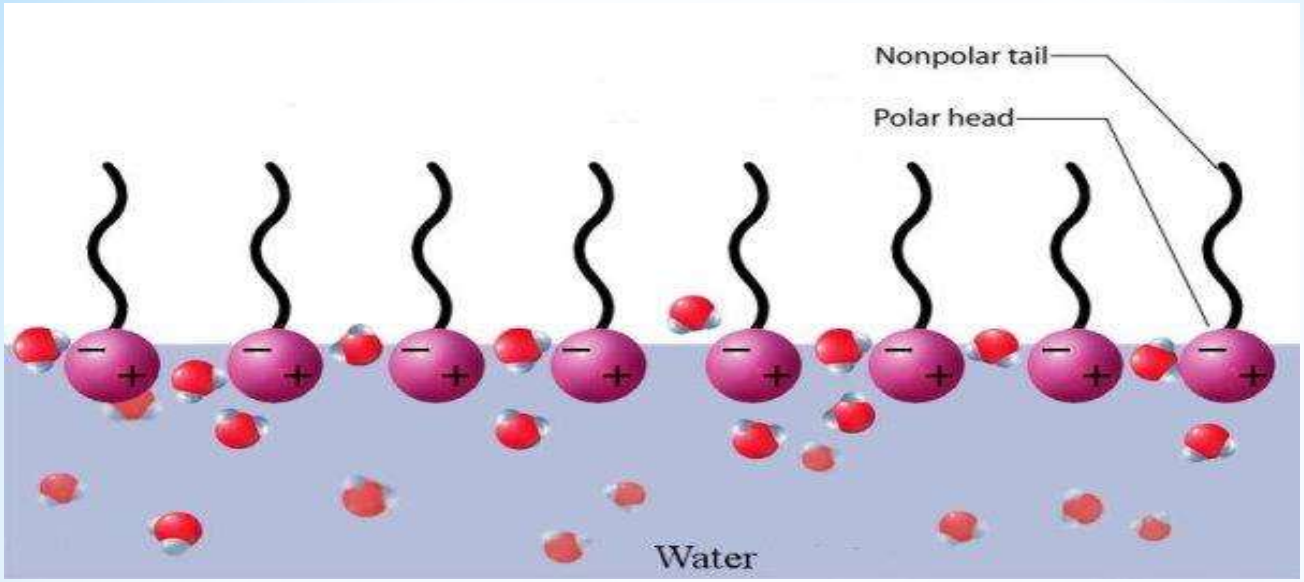
For Example Chloramphenicol-B more soluble than A & C

- Polymeric form of riboflavin 3 is 20times more D.R than riboflavin 1
- Cortisone acetate, Phenobarbital, Novobiocine amorphous form have more dissolution rate

(E). SOLUBILIZATION BY SURFACTANTS:

- They enhance dissolution rate primarily by promoting wetting and penetration of dissolution fluid into the solid drug particles.

Eg: Solubility enhancement of antimicrobial drug enrofloxacin using a series of co-solvents and surfactants. Aqueous solubility of enrofloxacin could be increased up to 26 times.



Mechanism of action of surfactants

- Microemulsions are potential drug delivery systems for poorly water-soluble drugs
- because to their ability to solubilize the drugs in the oil phase, thus increasing their dissolution rate and these are called as micro because it consists of <0.1 micron droplet diameter.

II . CHEMICAL MODIFICATION

(A). pH ADJUSTEMENT:

- The absorption of drug is largely dependent upon diffusion, which varies with pH of the individual regions within the gastrointestinal tract, the pKa of the drug and permeability also depends upon pH effects upon drug ionization.

- By applying a pH change, poorly water soluble drug molecules that can be protonated (base) or deprotonated (acid) may practically dissolved in water.
- The principle of in situ salt formation has been used to enhance dissolution rate of drugs like Asprin, Pencillin from buffered alkaline tablets

(B). SALT FORMATION:

- Salt formation of poorly soluble drugs (weak acids and bases) has been used for to enhance solubility,
- Weakly acidic drugs , a strong base salt is prepared such as Na , K salts of Barbiturates
- Weakly basic drugs a strong acid salt is prepared like Hcl , Sulphate

Eg: Alkali metal salt of acidic drugs like penicillin & strong acid salt of basic drugs like atropine more water soluble than parent drug

- The solubility of salt form of the drug mainly depends on **counter ion size.**

Ex: Novobiocin, Stearates

(C). DERIVATIZATION:

- Derivatization is a technique used by which transforms a chemical compound into a product (the reaction's derivate) of similar chemical structure, called a derivative.
- Phosphate group is most commonly used group to increase aqueous solubility
- Ex: Clindamycin-Hcl (is soluble)

  Clindamycin2 phosphate(is more soluble)

- Sulphate group improve solubility and improve dissolution rate of prednisolone.
- Prodrugs as its Na salt improve the solubility of parent Glucocorticoid.

III OTHER METHODS

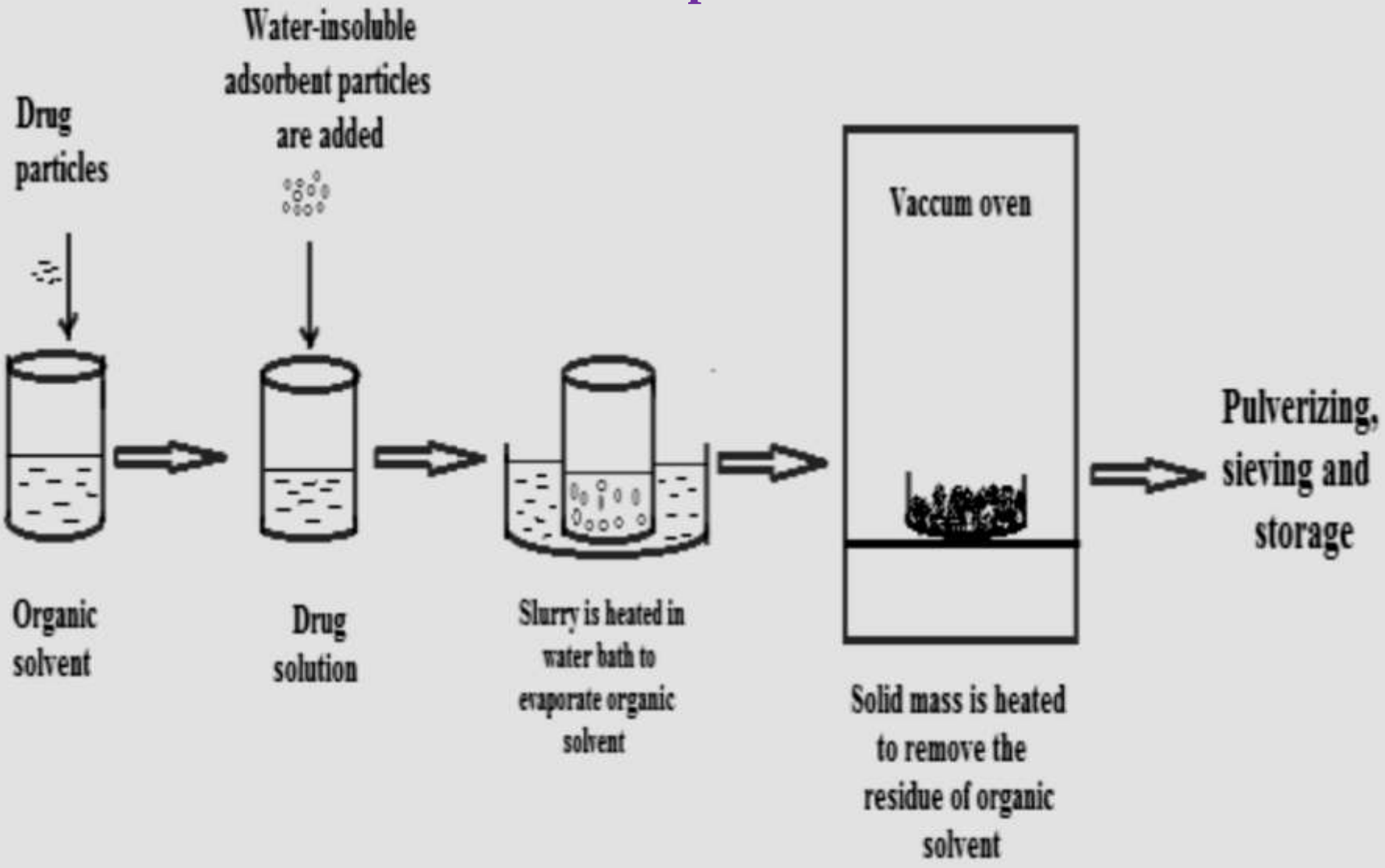
(A).SOLVENT DEPOSITION

- The solvent deposition system is a solid preparation in which a drug is deposited from a solvent on the surface of a matrix.

- This step is usually done by simple evaporation of the solvent used for distribution of the drug onto the matrix

Eg: The poorly aqueous soluble drug such as Nifedipine is formulated as solid dispersion and carrier is microcrystalline cellulose

Method of preparation of Solvent deposition:



Solvent deposition system prepared with different drugs and carrier:

S.No	Water Insoluble Drug	Solvent used	Carrier used
1	Indomethacin	Alcohol solution	Kaolin and microcrystalline cellulose
2	Piroxicam	Dichloromethane	Microcrystalline cellulose (Avicel PH 101)
3	Glibenclamide	Chloroform	Microcrystallinecellulose(Avicel PH-102)
4	Chlordiazepoxide	Dichloromethane	Starch-lactose granules

(B). HYDROTROPHY:

- Hydrotrophy is a solubilization process, whereby addition of a large amount of second solute that is the hydrotropic agent increases the aqueous solubility of first solute.

- Hydrotropic agents are ionic organic salts, consists of alkali metal salts of various organic acids.

- The mechanism by which it enhances solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea, and the poorly soluble drugs.

Hydrotropic solubilization of various poorly water-soluble drugs:

S.No	Drug	Hydrotropic Agent
1.	Progesterone, Diazepam and Griseofulvin	Nicotinamide, Isonicotinamide
2.	Paracetamol	Sodium salicylate, Nicotinamide
3.	Rofecoxib, celecoxib, melocoxib	Nicotinamide, Sodium benzoate,
4.	Riboflavin	Nicotinamide
5.	Ibuprofen	Sodium salt of Ibuprofen
6.	Nifedipine	Urea, Methyl urea, Ehhyl urea, Butyl urea, , N, N-dimethyl nicotinamide
7.	Carbamazepine	Sodium salicylate, Sodium benzoate
8.	Riboflavin	ProcaineHCl, Resorcinol, Pyrogallol
9.	Diazepam, Oxazepam, Nitrazepam,Clonazepam	Sodium salicylate

(C).USE OF SOLUBLE PRODRUG:

This is the method of enhancing solubility by improving the physico-chemical properties of the drug by boi-reversible chemical alteration.

- It involves the incorporation of polar or ionizable moiety into the parent compound to improve the aqueous solubility.
- Example : Prodrug has been successfully used to improve water solubility of corticosteroids, benzodiazepines.

(D). SELECTIVE ADSORPTION ON INSOLUBLE CARRIERS:

The drug particles are deposits on the bentonite and the rapid release of the drug from the surface of the clays occurs due to

- The weak physical bonding between the adsorbate and adsorbent
- Hydration and swelling of the clay in the aqueous media.

(E). COSOLVENCY:

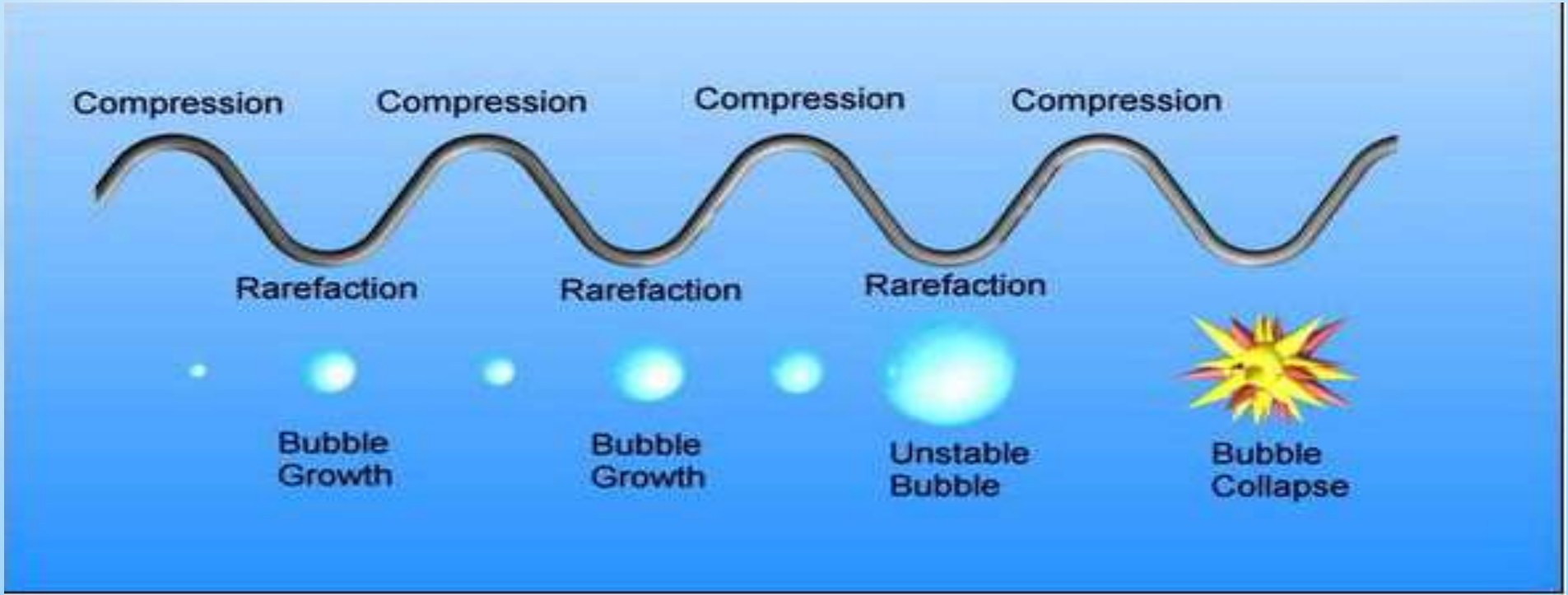
- Non polar molecules and weak electrolytes have poor water solubility
- It can be improved by improved by changing the polarity of the molecule and this can be achieved by addition of another solvent.
- Mainly cosolvency works by reducing the interfacial tension or surface tension between the aqueous solution and hydrophobic solute.

Examples of co-solvents are PEG-300, propylene glycol,ethanol.

(F). SONOCRYSTALLIZATION:

- Ultrasound energy to modify the nucleation of a crystallization process is known as sonocrystallization
- The energy of ultrasound fashions consecutive compression and expansion.
- In sonocrystallization ultrasound used in the range of 20K Hz-5M Hz.

PROCESS OF SONOCRYSTALLIZATION



(G). SOLUBILIZING AGENTS:

Solubility of poorly soluble drugs can be enhanced by using various solubilizing agents

Eg: PEG-400 is improving the solubility of hydrochlorthiazide85.

Solubilizer	Solubilizate
Polyoxyethylene monoalkylether	Essential oils
Sucrose monoesters	Vitamin-A,D,E
Fatty acid ester	21-acetoxy pregnenolone, Barbitol,Caffine
Polyoxyethylene sorbitan	Acetamenaphtone

CONCLUSION

- By this I conclude that, Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and also the basic requirement for the formulation and development of different dosage form of different drugs.
- Because of dissolution problem of many drugs, the bioavailability of them gets affected and hence dissolution enhancement becomes necessary. It is now possible that to increase the dissolution of poorly soluble drugs with the help of various techniques as mentioned above.

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Thank you ...