TECHNIQUES FOR IMPROVEMENT IN DRUG SOLUBILIZATION

CONTENTS

COMLEXATION TECHNIQUES

COMPLEXATION is the association between two or more molecules to form a no bonded entity with a well-defined Stoichiometry. The two types of complexation that are useful for increasing the solubility of drugs in aqueous media are stacking and inclusion.

Stacking complexes are formed by the overlap of planar regions of aromatic molecules, while inclusion complexes are formed by the insertion of the nonpolar region of one molecule into the cavity of another molecule (or group of molecules). The mathematical description for the equilibrium constant of a 1:1 complex, $K_{1:1}$ is defined by

$$K_{1:1} = [SL] / [S] [L] \quad \text{..... (1)}$$

Where **S** is the concentration of the free solute,

L is the concentration of the free ligand, & **[SL]** is the concentration of the solute/ligand complex.

The equilibrium constant is also commonly referred to as the stability constant or the complexation constant.

Initially, the linear region will continue until the solubility of the complex itself is reached, at which point the total solubility of the solute remains constant, as indicated by the central segment of the curve, further addition of the complexing agent can result in a reduction in of the concentration of the free solute and a leveling off of the curve at the solubility of the pure complex.

The solubilization curve for a solute molecule that complexes with two ligand molecules are more complicated. If the complexation constant for a second ligand is significantly lower than the first, a 1:1 complex will be formed at lower ligand concentration. It will then combine with a second ligand to produce a 2:1 complex. Assuming that the later is more soluble than the 1:1 complex, the solubilization curve will have two distinct slopes.

The most useful ligands for solubilization in aqueous media are highly water soluble, and produce soluble complexes.

SELF-ASSOCIATION AND STACKING COMPLEXATION:

Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of the water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule. Stacked complexes can be homogenous or mixed. The former is known as self-association and the later as complexation. Examples of substances that interact in an aqueous media by stacking are NAPHTHALENE, BENZOIC ACID, PYRENE, METHYLENE BLUE, CAFFEINE, etc.

Complexes formed between compounds containing aromatic acids or amides and comps. With aromatic nitrogens had higher stability constants than complexes made of a single compound.

INCLUSION COMPLEXES:

An inclusion complex is produced by the inclusion of a nonpolar molecule or the nonpolar region of a molecule (known as the **GUEST**) into the nonpolar cavity of another molecule or group of molecules (known as the **HOST**).

When the guest molecule enters the host molecule the contact between water and the nonpolar regions of both is reduced. Thus, inclusion phenomena are the result of the same driving force that produces the micellization, Self-association, and stacking: namely the squeezing out from water of nonpolar moieties.

The host cavity must be large enough to accommodate the guest and small enough to eliminate water so that the total contact between water and the nonpolar regions of the host and the guest is reduced.

The most commonly used host molecules are the cyclodextrins. These cyclic oligomers of glucose are relatively soluble in water and have cavities large enough to accept nonpolar portions of common drug molecules.

Solid inclusion complexes can be prepared by following methods:

a. Kneading Technique: In this technique, cyclodextrin (CD) is impregnated with water and converted to paste. Drug is then added and kneaded for specified time. The kneaded mixture is then dried and passed through sieve if required.

b. Co-precipitation: Required amount of drug is added to the solution of β-CD. The system is kept under magnetic agitation with controlled process parameters and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

c. **Neutralization:** Drug is added in alkaline solution like sodium hydroxide, ammonium hydroxide. A solution of β- Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained after few seconds under agitation is neutralized using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried.

d. **Co-grinding:** Drug and cyclodextrin are mixed and the physical mixture is introduced in a suitable mill like oscillatory mill and grinded for suitable time.

e. **Spray-Drying Method:** Drug is dissolved in suitable solvent and the required stoichiometric amount of carrier material like β-cyclodextrin is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried.

f. **Microwave Irradiation Method:** Drug and cyclodextrins mixture is reacted in microwave oven to form inclusion. It is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of product.

SOLUTE-SOLVENT COMPLEXATION

When we discuss the formation of a solution when viewed at the atomic level we need to consider three steps; The following interaction must be considered.

1) solvent-solvent intermolecular attractions

2) solute-solute intermolecular attractions

3) solute-solvent intermolecular attractions

Interaction between two solutes dissolved in an inert solvent can potentiate an increase or a decrease in solubility, but when the complexing species are solute & solvent, enhanced solubility must always result.

Solute solvent complexation can be expressed generally by –

$$nS + mL \overset{K}{\Leftrightarrow} S_nL_m$$

where, n = number of molecules of substrate (S)
m = number of molecules of complexing agent (L)
k = stability constant or binding constant greater value of k , greater the degree of complexation.

- The effects of complexation on the solubility of a solid can be represented by a phase solubility diagram.
- Phase diagram is constructed by plotting total molar concentration of solute against the molar conc. of complexing agent added.

CLATHERATES

An inclusion compound is a unique form of chemical complex in which one molecule is enclosed within another molecule or structure of molecules. This combination is characterized by the absence of ordinary chemical bonds; the essential criterion is simply that the enclosed molecule or "guest" be of a suitable size and shape, to fit into a cavity within a solid structure formed by "host" molecules. The hollow space formed by the host may be in the form of a channel, cage or layer.
The stereochemistry and, possibly, the polarity of both the host and the guest molecules determine whether inclusion can occur.

Other terms that have been used to describe these complexes are "occlusion compounds", "adducts" and "clatherates". *Barrer* divided inclusion compounds into 3 categories, based on the varying concept of the host crystal,

(a) Those that are stable both in the presence and in the absence of the guest molecule;
(b) Those in which the amount of guest may be changed but which have a critical concentration of guest molecules, below which the host structure becomes metastable and recrystallizes; and
(c) Those in which the host framework continuously readjusts itself as the content of guest molecules fluctuates.

The term "clatherate", derived from Latin: "clatheratus", meaning "enclosed by the bars of a grill". "Clatherates": this term more appropriately describes only the cage–like polymolecular inclusion compounds.

Clatherates: The individual host molecules link together to form a cage– or a cup–shaped structure, the open end of which joins with the open end of a second similar structure to form the cage. Because of the characteristic feature of these compounds, Powell named them 'clatherates'.

The cage–like framework encloses void spaces approximately 4 A° is diameter, from which the guest molecules cannot escape.
Eg: Hydroquinone clatherates are formed only by molecules, that can fit inside the cavity; molecules small enough to slip out of the cage do not form a clatherate.
Eg: Water–under certain circumstances, water molecules form a crystalline framework containing cavities in which gases or low boiling–point liquids can be entrapped. Such clatherates are termed: "gas hydrates" or "liquid hydrates".

Eg: Cycloveratril –Formaldehyde & 1,2 –dimethoxy combine to form cycloveratril. The benzene rings of cycloveratril are slightly tilted giving a non –polar configuration to the molecule.

ALTERATION IN THE pH OF SOLVENT

Definition of pH

pH is the negative logarithm to the base 10 of the hydronium ion concentration.

$$pH = -\log [H_3O^+]$$

Introduction

- For ionizable drugs, the aqueous solubility is strongly influenced by the pH of the solvent.
- Thus, the pH adjustment may be the most simple, economic and effective way of increasing the aq. solubility of the drug.

Solubilization by pH

- For a drug to be formulated in a liquid dosage form is generally required to be dissolved in an aqueous media.
- The ionized form of the drug is favored over unionized form to be solubilized in the aqueous solvent.
- **For weakly acidic drugs /salt,**
  - Lower pH → unionized form → insoluble/ precipitation
  - Higher pH → ionized form → more solubility
- **For weakly basic drugs / salt,**
  - Lower pH →ionized form →more solubility
  - Higher pH →unionized form → insoluble/ precipitation
- The relation between pH of the solvent, pKa and solubility of the drug can be given by **modified Henderson Hasslbalch equation**.

  For weakly acidic drugs,

  $$pH = pKa + \log \frac{S-So}{So}$$

  For weakly basic drugs

  $$pH = pKa + \log \frac{So}{S-So}$$

  S = overall solubility of a drug at a given pH

  So = intrinsic solubility of unionized form

  Where pKa and So are molecular parameters that neither salt selection nor formulation can alter.

  This equation helps to find out

  1. Solubility of a drug at that pH
  2. Minimum pH range that must be maintained to prevent precipitation of the drug.

Drugs showing improvement in solubility upon alteration in pH

✓ **Weak acids:**

Nimesulide: practically insoluble in water51 fold increase in solubility by increased in pH from 1.2 to 8.4

pH	Solubility mg/ml
1.2	0.70
6.2	0.86
7.4	4.10
8.4	43.90

- Same way for Aspirin, phenytoin, penicillin, cephalosporin, etc.

✓ **Weak bases:**

- Similar increase in solubility is seen in case of levemopamil HCl by decreasing pH, i.e., acidic pH
- Same way for, morphine, ephedrine, itraconazole, flavopiridol, etc.

✓ **Zwitter ion compounds:**

Pelrinone HCl

pH 3-5 → Cationic pyridinium ring formed by protonation

pH 5-8 → Sparingly soluble neutral form

pH 8-11 → anionic enolate by dissociation of a proton.

- Same way for, lorazepam, proteins and amino acids, etc.

✓ **Divalent Compound:**

The solubilization of divalent acids and bases is similar to their monoprotic counterpart. However upon the ionization of second functional group; the solubilization slop, is 2 instead of 1 i.e., **100 fold increase in solubility for a change in 1 pH unit.**

Limitation of this equation,

1. Values for **Ka,** and So reported for a p'cular drug in the literature are in **distilled water**. So, the actual values differ in different dosage forms.

   → Cosolvents like alcohol/ glycerin has effect on increasing So and decreasing Ka [(2)]**.**

2. Equation **assumes no interaction** between solute and itself or between solute and other formulation components.

   → At low concentration of solute, this assumption is valid.

Factors to be considered in selecting pH environment for adequate solubility

1) **pH must not conflict with chemical stability;**
   - In many cases the optimum pH for solubilization doesn't co-inside with the pH of stability of API or other adjuvants or the formulation.
2) **Physiological compatibility;**
   - Extreme pH may not be desired as they may cause irritation, pain discomfort or stinging upon ingestion.
     - Parentrals especially i.m. or s.c. would not dilute rapidly and causes inconvenience at the site of application.

- ✖ Ophthalmic drops should not be formulated in extreme pH environment. E.g., Pilocarpin and physostigmine is more stable and soluble at pH 5 but physiological pH of tears is 6.8
- ✖ Mucous membrane or abraded skin is sensitive to extreme pH

3) Drug activity;

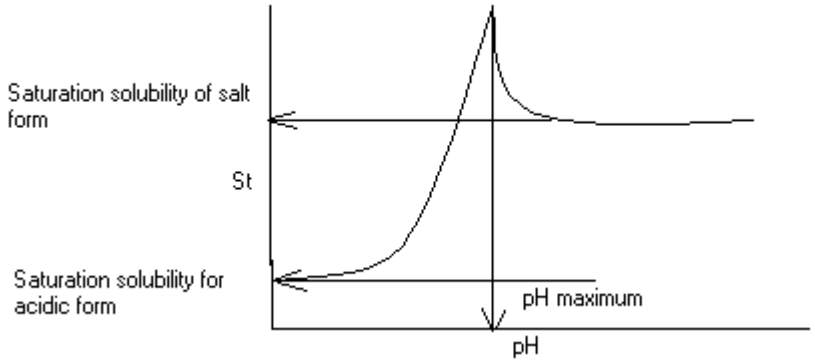
- ⌗ Drug may exist in ionized, unionized or mixture of both the forms. But, the drug may be active in only one form. E.g., Benzoic acid and mandelic acid have pronounced antibacterial activity in unionized form whereas they are most soluble in ionized form and no activity is observed in this ionized form.

4) Drug absorption;

- ⌗ The degree of ionization and lipoidal solubility of a drug are important factors to determine the rate of absorption from g.i.t.
- ⌗ Unionized form is the function of dissociation constant of the dug and pH of the environment at the absorption site.

5) Selection of buffer;

- ⌗ If the pH is critical to maintain solubility of the drug, the system must be adequately buffered.
  - The buffer must have adequate **capacity** in desired pH range.
  - Biologically **safe** for intended use.
  - **No Deleterious effect** on stability of the final product.
  - Should permit the use of **other excipients** like flavoring or coloring agents.
- ⌗ A very small change in pH may result in 30% more drug going into the solution. So, by observing pH solubility profile; it helps in selection buffer for optimum pH range.



- ⌗ Buffers used in pharmaceuticals

Formulation	**Buffers**
Tablets and capsules	Mg carbonate; sodium bicarbonate
Ointments and creams	Citrate, acetate, phosphate
Ophthalmic	Boric acid, isotonic phosphate, citrate
Parentrals	Citrate, Acetate, Tartrate, glutamate, Adipate, etc.

Combined techniques of solubilization

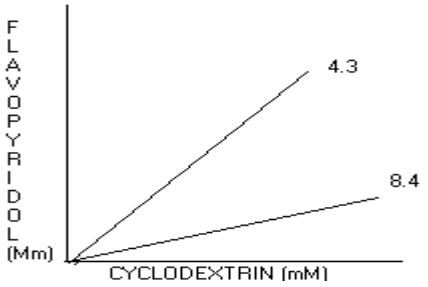
- ➢ As this solubilization by pH alteration is limited for ionizable drugs; **compromise in optimum pH is necessary to ensure stability,** physiological compatibility,

bioavailability; pH modification is adopted by combination with other solubilization processes.

- Studies also suggest that under certain circumstances the solubilization of the ionized solute by cosolvent or surfactant is more important than the solubilization of unionized solute in determining the total solubility.

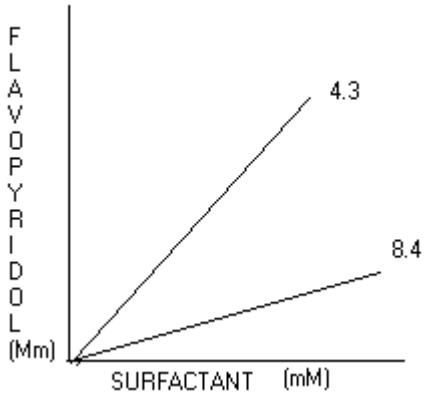
A. pH and complexation

- For weakly basic drugs like Flavopiridol, the complexation constant for ionized form [Ki = 124 M^{-1}] is less than 1/3 of that of unionized form [Ku = 445M^{-1}]
- Since the unionized species usually forms more stable complex with Cyclodextrin than its ionic counterpart, it's often assumed that the unionized species is primarily responsible for formation of complex and subsequent increase in solubility.
- But the solubility of Ionized drug complex [DiL] is six folds greater than the solubility of unionized drug complex [DuL]
- This unexpected result is **due to** 25 folds greater **solubility of ionized drug [Di] at pH 4.3** over that of free unionized species [Du] at pH 8.4.
- This shows that any pH alteration that increases the concentration of Di will also increase the concentration of DiL.
- This fact is **independent** of the value of **complexation constant**.



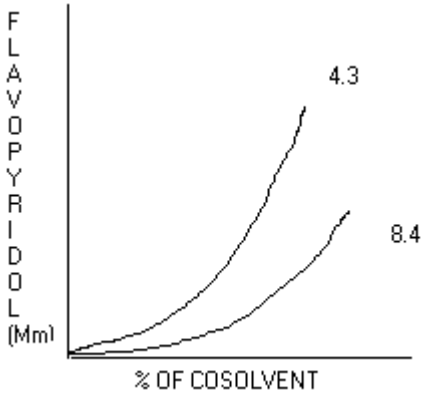
B. pH and micellization

- As we increase the concentration of surfactant (Polysorbate 20 or 80) linear increase in solubility is seen for Flavopiridol.
- But, solubility increase is much greater at pH 4.3 than that at 8.4.
- Same was observed with flurbiprofen.



C. pH and cosolvency

- An increase in concentration of co solvents produces an exponential increase in drug solubility.
- But, the drug solubility at pH 4.3 is much greater at pH 4. than that at 8.4.



D. pH and physical mixture of drug

- For poorly soluble drugs like indomethacin the self assembling property of **PVA** showed **physical mixture** of this polymer with indomethacin leading to increase in availability of free drug in solution with respect to pure drug due to solubilizing effect of the drug polymer interaction.
- The increase in **pH** of the mixture further enhances the free drug availability due to **increase in drug polymer affinity.**

Newer approach in Solubilization Solubilizing excipients

- ✓ The absorption of a drug is largely dependent diffusion, which varies with the pKa of the drug and the pH of individual regions within the gastro intestinal tract and permeability.
- ✓ While the importance of salt selection and pH adjustment has been stressed; the use of **pH altering excipients** within the drug delivery system is also of significant utility.
- ✓ Solubilizing excipients **alters pH** within the dosage forms like tablets or capsules, to a range **higher than pKa of weakly acidic drugs** increases the solubility of that drug; and those excipients which act as **alkalizing agents** may increase the solubility of weakly **basic drugs**.
- ✓ One e.g. of such a use of pH including excipients is one or more **excipients** are included in within the dosage form **whose pKa is complementary to the drug**; as the dosage form hydrates, simultaneously the electrolyte is wetted with API creating a microenvironment independent of g.i. pH**.**

SALT FORMATION

Introduction: Salt formation is frequently performed on weak acidic or basic drugs because it is a relatively simple chemical manipulation, which may alter the physicochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying the basic chemical structure.

The ideal characteristics of a salt are that it is chemically stable, not hygroscopic, presents no processing problems, dissolves quickly from solid dosage forms (unless it is formed with the intent to delay dissolution) and exhibits good bioavailability.)

- **Weakly acidic drugs , a strong base salt is prepared such as the sodium and potassium salts of barbiturates and sulphonamides.**
- **Weakly basic drugs , a strong acid salt is prepared like hydrochloride or sulphate salts of alkaloidal drugs (Atropine)**
- **Size of the counter ion influence the solubility of salt forms of the drug.**
- ***Smaller the size of the counter ion , greater the solubility of salt***
- **Novobiocin from its sodium salt , calcium salt and free acid form was found solubility in the ratio – 50:25:1**

The mathematical equations for solubility predictions of a weak acid & weak base are:

$$S_T = S_w (1+10^{(pH-pKa)}) \quad \text{----------(1)}$$

$$S_T = S_w (1+10^{(pKa-pH)}) \quad \text{----------(2)}$$

Equations (1) & (2) assure that ionized species of a solute has infinite solubility. However, an ionized solute can form salts with appropriate counter-ions. The formation of a solute is governed by the solubility product (Ksp) of the salt complex. For example, the thermodynamic equilibrium for a chloride salt, BH^+Cl^- is given by

$$BH^+Cl^-_{(solid)} \overset{K_{sp}}{==} [BH^+] + [Cl^-]$$

Where, $BH^+Cl^-_{(solid)}$ represents the solid chloride salt, BH^+ is the ionized base and Cl^- is a chloride counter ion. As a result the concentration of the ionized species will be limited by the solubility of the salt.

Some organic salts are very soluble in aqueous systems, others are not and can significantly affect the solubility of a solute.

INORGANIC SALTS were also found to have the systematic effect on the aqueous solubility. Salts were found to have the systematic effect on the behaviour of aqueous solutions & were divided into kosmotropes (polar water-structure markers) or chaotropes (water-structure breakers). This distinction was based on the degree to which ions would interact with the adjacent water molecules.

A kosmotrope like a doubly charged ion (e.g So_4^{-2}) or an ion with a high charge density. (e.g. F^-) was proposed to interact with the adjacent water molecules more strongly than would bulk water.

On the other hand, a chaotrope like a large ion with a single charge (e.g. ClO^4- or SCN^-) was proposed to interact with adjacent water molecules less strongly than would bulk water.Example: Caffeine solubility in different salts solution is shown in figure:

Different salts have different effects on the solubility: Added $NaClO_4$ or NaSCN increases the caffeine solubility, whereas added Na_2SO_4 or NaCl decreased it, and added NaBr did not show any significant effect. The effect of these salts on the aqueous solubility of theophylline & theobromine are similar.It can be seen through this work, that chaotropes increases xanthine solubility whereas kosmotropes decrease it.Because, all the investigated salts in this study were sodium salts, the differences in salt effects were attributed to their anions.

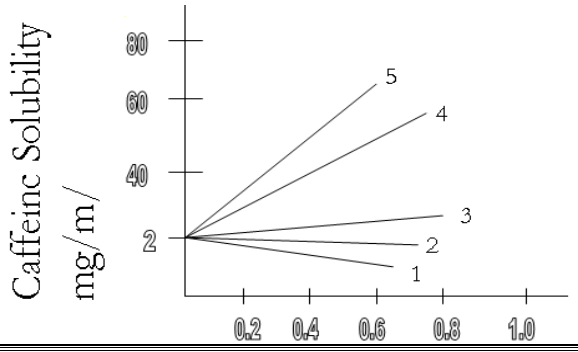


Figure 2: Caffeine solubility in different salts concentration at 25°C.

1-Na_2SO_4,
2-NaCl,
3-NaBr,
4-$NaClO_4$,
5-NaSCN

The solubility were also treated using the empirical Setschenow equation:-

log (S°/S) = k/s

Where,

S° = non-electrolyte solubility in water
S = solubility in salt solution
k = Setschenow constant
Cs = Salt concentration

The k values are positive for salts that decrease solubility & negative for salt that increase solubility.

Potentially Useful Salts: Salt formation is one of the simplest chemical reactions, involving either a proton transfer or a neutralization reaction between an acid and a base.

Theoretically, every compound possessing acidic and/or basic properties can participate in salt formation.

Many of the antibiotics administered i.v. are sodium salts. This indicates that the drug class, history of use and local tolerance and possibly regulatory acceptability influence the selection of the salt form.

Complex Salt Formation:

Organic acid salt forms of basic drugs, such as amines, frequently have higher aqueous solubilities than their corresponding inorganic salts.
Acetic acid produced solubilities higher than those observed with nay of the inorganic acids.

Solubility Predictions: A higher crystal lattice energy (crystallinity) is generally reflected by a higher melting point. An increase in melting point, usually by maximizing or encouraging crystal symmetry, reduces solubility.
Organic salts may increase aqueous solubility through decreased crystal lattice energy, lowered melting point, increased hydrogen bonding of the salt counterions with water, etc. the melting point and the degree of crystal hydration of the solid phase are the most important in determining the solubilities of the sodium salts of some drugs.
Soluble salts: Solubilization does not always improve the taste. Eg: potassium salts frequently have an unpleasant taste and leave a metallic aftertaste.
N-Cyclohexylsulfate salts of several drugs have improved taste and enhanced solubility properties.

HYDROTROPIC SOLUBILIZATION:

Hydrotropic effect, the meaning is taken as the increase in saturation solubility of a substance in water by the addition of organic salts or also non-electrolytes, which of course must be physiologically compatible for pharmaceutical application.The mode of action of the hydrotropic substances is thought to be due to either an associate formation, in low concentrations to a formation of molecular complexes or in higher concentrations to the water structure being influenced. These hydrotropic substances are able to increase the number of hydrogen bridges in the water clusters. This makes the water more hydrophobic & thus it is a better solvent for non-polar drug.

However, the use of hydrotropic substances such as sodium benzoate, nicotianamide, urea, caffeine, sorbitol, etc. is limited due to the following factors:

- Slight increase of saturation solubility with high concentration of excipients. (e.g. upto 50% nicotianamide with a triple increase in the saturation solubility)
- Isotonicity is not reached.
- Individual effects of the excipients.

The use of hydrotropic substances is at best to be considered as an additional effect in connection with the other methods.

MICELLER SOLUBILIZATION BY SURFACTANTS

- **Surfactants** are compounds that have molecular structures with two distinct regions : A polar (hydrophilic) head group and a Nonpolar (hydrophobic tail).

Traditional Surfactants

ANIONIC SURFACTANT : Hydrophilic group carries a negative charge.
e.g.:- SLS , Potassium Laurate

CATIONIC SURFACTANT : Hydrophilic group carries a positive charge.
e.g. :- Cetrimide , Benzalkonium Chloride

AMPHOLYTIC SURFACTANT (ZWITTERIONIC SURFACTANT) : Molecule carries both negative and positive charge.
e.g.:- N-dodecyl-N,N-dimethylbetaine

Non Traditional Surfactants

NONIONIC SURFACTANT : Hydrophile carries no charge but derives its water solubility from highly polar groups such as hydroxyl or polyoxyethylene groups.
e.g. :- Cetomacrogol (polyoxyethylated glycol monoethers)
Spans and Tweens (Sorbitan esters)

- **In the water, as the concentration of surfactant increases above a critical value, its molecule self associate into structures called Micelles** and the concentration at which they begin to form is called Critical Micelle Concentration (CMC) .
- In **micellar structure** , the hydrophobic tail gathers in the core and is surrounded by mantle of hydrophobic heads which are in contact with water .

Therefore a hydrophobic (nonpolar) drug which is squeezed from the water locates in the micelle core .

Since micelle is soluble in water , any drug incorporated into the micelle is also soluble in water .

- **<u>Micellar Solubilisation</u>** is defined as : The spontaneous passage of solute molecules of a substance insoluble in water into an aqueous solution of a surfactant in which a thermodynamically stable solution is formed .
- **<u>Solubilisation by Micelles</u> :** There are a number of possible loci of solubilization for a drug in a micelle, as represented in the following figure 5.

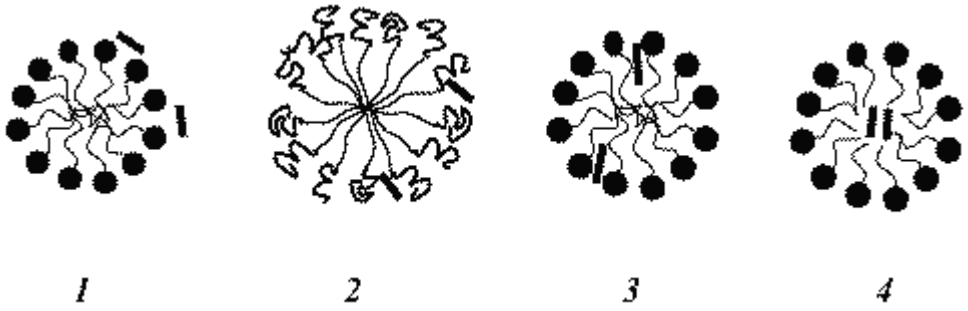


Figure 5: Possible loci of solubilization of drugs in surfactant micelles, depending on the drug hydrophobicity. The black bold lines (—) represent the drug at different sites in the micelle

May occur at a number of different sites in a micelle as evidenced by conductivity, spectorphotometric , and NMR studies :

- On the surface at the micelle-solvent interface .
- Between the hydrophilic head group .
- In the palisade layer between the hydrophilic groups and the first few carbon atoms of the hydrophobic groups that comprise the outer regions of the micelle core .
- More deeply in the palisade layer .
- In the micelle inner core .

- The total solubility S_T of a solute in a surfactant system is :

$$S_T = S_W + K (C_{surf} - CMC)$$

Where ,

K = Solubilising Capacity

$C_{surf} - CMC$ = Micelle concentration

C_{surf} = Total conc. of surfactant

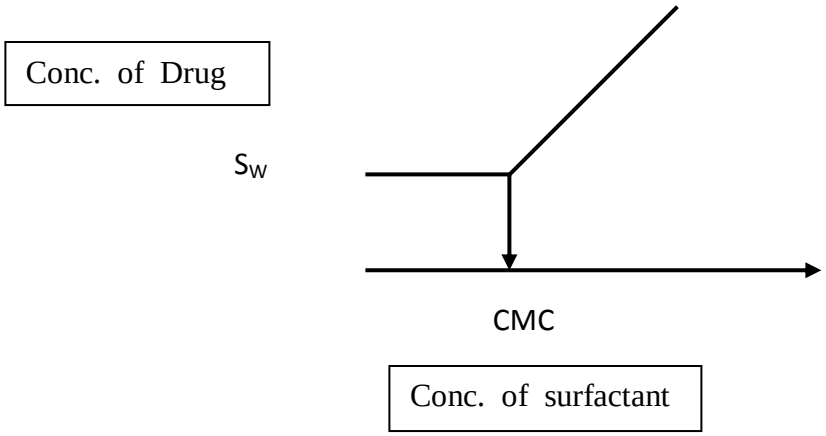
The solubilisation capacity reflects the number of surfactant molecules required to solubilize a solute molecule .

Solubilization process above CMC may be considered to involve a simple partition phenomenon between an aqueous and micellar phase . The reaction between surfactant conc. and drug solubilisate is given as :

$$C_{tot} = C_S + PC_SC_M$$

C_S = Drug solubility in absence of surface active agent .

P = Distribution coefficient of drug between micelle and bulk phase .



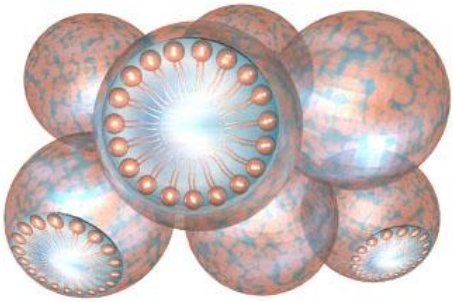
- A Point to be taken care of : When a mixture of two surfactant with widely differing HLB value used , solubilisation of solute decreases whereas when surfactants having small HLB differences used solubilisation increases .
  e.g. : As observed in case of Vit A and Vit D .

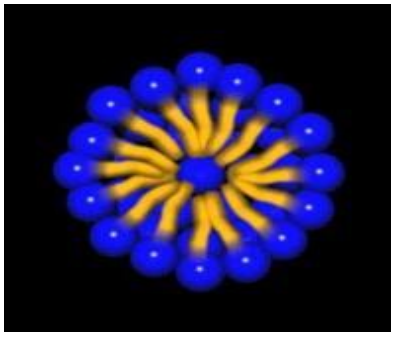
- **Micellar Solubilisation of Drugs can be studied by :**
  Semiequillibrium Dialysis .
  Eluent Gel Permeation Chromatography .
- **CMC of surfactant can be measured by :**
  Fluorescence Probing .
  Equillibrium Surface Tension .
  Light Scattering Techniques

Solubilizing Capacity of surfactant follows the following order :
Anionic < Cationic < Nonionic , the effect being attributed to a corresponding increase in the area per head group , leading to looser micelles with less dense hydrocarbon cores which can accommodate core solute .

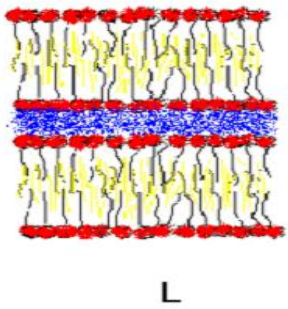
Types of Micelles :

Spherical Micelles :

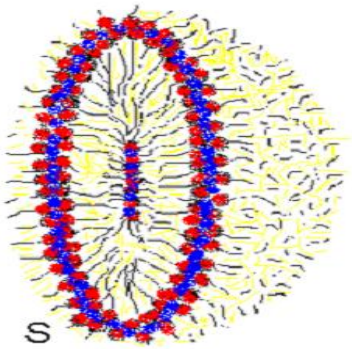




Rod Shaped Micelles (cylindrical , ellipsoids) :
Hexagonal Micelles :
Lamellar Micelles (L) and Spherulite Micelles (M) :

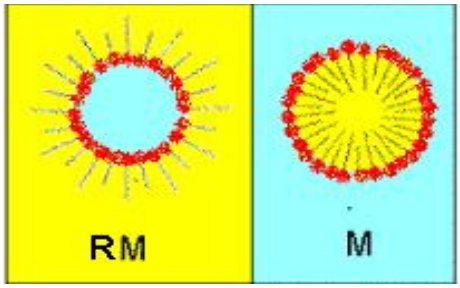


L

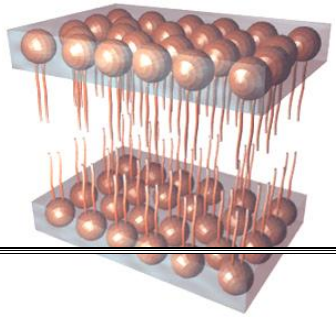


S

Vesicles :
Spherical structure , consisting of lamellar micelles arranged in one or more concentric spheres . Can solubilize both lipid soluble and water soluble agents .
Reverse Micelles or Inverted Micelles :



:
Formed in nonaqueous solvent . Dipole-Dipole interactions hold the hydrophilic head of the surfactant molecules together in the core and in certain cases H bonding b/w head groups can also occur .



Bilayer Structure :

- **Market preparations containging surfactants :**

Most widely used surfactant are Polysorbate 80 and Cremophor EL .
Others used are Nonoxinols and Octoxinols (Macrogols) , Polyoxyl 35 Castor Oil Polyoxyl Stearates and Polysorbates .

Trade Name	***API***	***Manufacturer***	***ROA***	***%W/V Surfactant***
MVI	Multivitamin	Armour	IV infusion	1-1.7% Polysorbate 20
Taxol	Paclitaxel	BMS	IV infusion	Cremophor EL
Librium	Chlordiazepoxide	Roche	IV (diluent)	4 % Polysorbate 20

- **Newer Approaches in Micellar Systems :**

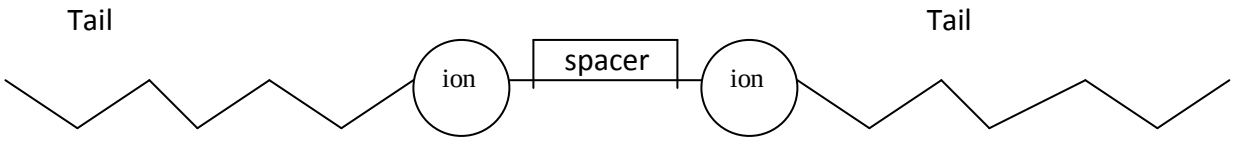
  - ***Vitamin C Based Micellar System :***
    - Alkanoyl –6- o Ascorbic Acid Esters are easily obtained from Vitamin C .
    - It produce self – assembled aggregates in water solution with an inner hydrophobic pool surrounded by an external hydrophilic shell .
    - In virtue of their amphiphilic nature , ascorbic acid based supramolecular system can dissolve relevant amount of hydrophobic poorly water soluble chemicals such as drugs , vitamins and so on and at the same time they provide a suitable shield against oxidative deterioration of valuable materials.
    - Vitamin C Based Surfctants may contribute an interesting class of amphiphilic compounds both for their biocompatibility and for the antiradical activity.
    - Poorly water soluble drugs tried were Phenacetin (analgesic and antipyretic).

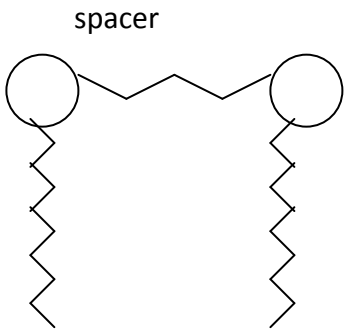
  - ***Mixed Micelles :***
    - Mixed Micelles may show high solubility enhancement than simple micelles.
    - Ex : Solubilisation of Vit. K_1 < Solubilisation of Vit K_1 by bile salt micelles by phosphatidylcholine bile salt mixed micelles.
    - Here bile salt act as a carrier for lipid and unsaturated fatty acid with lower MP promote absorption by affecting the permeability of membrane .
    - Another example of mixed micelles is combination of Anionic and Cationic Amphiphilic ZWHG (Zwitter Ionic HeteroGemini Surfactant) and SDS (Sodium Dodecyl Sulfate) . It showed improved solubilisation .

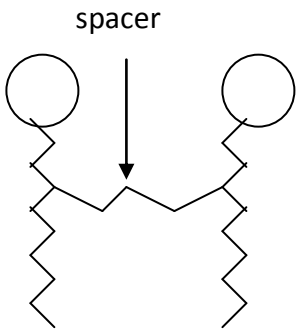
  - ***Sterically Stabilised Micelles (SSM) and Sterically Stabilised Mixed Micelles (SSMM) :***
    - SSM composed of Poly(ethyleneglycol – 2000) – grafted distearoyl phosphatidylethanolamine (DSFE – PEG)
    - SSMM composed of DSFE – PEG and egg phosphatidyl choline (PC)
    - Both have recently been introduced as novel lipid based carriers for water insoluble drug .
    - Improved solubilisation by SSMM .

- PEG conjugated to the polar head of a phospholipid renders the polar head group larger and the molecule is more soluble .
- Attractive for drug delivery due to :
  1. Being composed of phospholipids , are biocompatible and nontoxic .
  2. Because of presence of phospholipid it results in large hydrophobic core : solubilise high conc. of water insoluble drug molecules / micelles .
  3. They have lower CMC than conventional micelles .
  4. Hydrophilic PEG renders the micelle sterically stable protecting drug from MPS uptake .
  5. Due to low CMC , SSM are thermodynamically more stable than conventional detergent micelles upon dilution .
  6. Passive targeting of drug .
  7. Actively targeted delivery by phospholipid micelles is also possible by conjugating a specific targeting agent on the distal part of PEG .
  8. Penetration is simpler than other lipid carriers such as liposomes and emulsions .

- ***Gemini (Dimeric) Surfactants :***
  - A Gemini Surfactant (GS) consists of two conventional surfactant molecules chemically bonded together by a spacer.
  - The two terminal HC tails can be short or long .
    The two polar head groups can be cationic , anionic or nonionic .
    The spacer can be short or long , flexible or rigid .
  - GS can self assemble at much lower conc. and are superior in surface activity as compared to conventional surfactants .
  - GS are very attractive for :
    Catalysis
    Adsorption Applications
    New Synthetic Vectors for Gene Transfection
    Analytical Separation
    Solubilisation Process
    Nanoscale Technology
    Biotechnology Enhanced Oil Recovery
    Paint Additives







- ***Surface Active Excipient :***
  - Gelucire 44/14 is a surface active excipient that can solubilize poorly soluble drug .
  - Cosolvents Dimethylacetamide (DMA) and DimethylSulfoxide (DMSO) were added but had a little advantage from the view point of improving solubility.
  - Fluorescent measurement confirmed the micelle formation by Gelucire .
- ***Mixed Linker System :***
  - Lipophilic Linker and Hydrophilic Linker increase the ability of surfactant to solubilize the organics .
  - They act as powerful tools to improve the efficiency of surfactants .
  - Advantages :
    - ❖ Improve effectiveness of surfactant .
    - ❖ Level of surfactant in formulation can be reduced .
    - ❖ Thus lowering the cost of formulation and increasing profitability .
  - Increasing the solubility enhancement of Anionic DOWFAX surfactant by mixed linker system .
  - Lipophilic Linker : Long Chain Fatty Alcohols
    Hydrophilic Linker : AMA
  - Highly synergistic in nature .
  - Both have to be used together .
    Using any one of them is not effective .
  - 1:1 Molar Ratio is desired .

MICRONIZATION

- → Micronization is reduction of particle size up to micron level
- → Any problem related with the bioavaibility of drug may be related with dissolution of drug and solubility of drug is affecting dissolution of drug.
- → In order to get better dissolution need to increase solubility and micronization is used as one of the solubilizing tool to increase solubility
- → By micronization we get uniform and narrow particle size distribution which is essential for developing uniform dosage form
- → As micronization occurs surface area increases with decreasing particle size and solubility increases and observed solubility increased with decreasing particle size in accordance this equation :-

log $S/S_O = 2(\gamma/2.303RTr)$

Where,

S = the observed solubility

S_0= Inherent equilibrium solubility

γ= surface Energy of particle

R = Gas constant

T = Absolute Temperature

r = Radius of the particles.

→ Equation indicates that solubility inversely proportional to the particle Radius

→ But if we further decreases the particle radius (smaller than micron level)then it may decreases solubility because any changes on particle it may affect the static charge present on the particle and which may decreases the solubility

→ And second thing is that whenever we concerned solubility with particle size , surface area is most imp criteria because there are many cases in which particle size of different component is same but the surface area is different due to it's bulk density where the volume of that component is same but weight is different which affecting solubility

→ E.G. griseofulvin, chloramfenicol, tetracycline salts shows 50% more absorption rate after mcronizer.

→ Therefore this extreme decrease in particle size is not achieved by simple size reduction technique comminution but can be achieved by :-

1) jet milling :-

- ⇨ is done by fluid energy mill or micronizer
- ⇨ principle: impact and attrition
- ⇨ but not used for thermolabile drugs because of heat generation and do not give extreme reduction of the particle size.

2) solid solution & eutectic mixtures :-

- to overcome above problem this method is used.
- Unique method of micronization
- When two component solution is cooled to R.T. after melting –resulting in to
  - Simple eutectic mixture.
  1. solid solutions
  2. Continuous solid solution.
- First involves formation of eutectic mixture of drug (which solid at R.T.) & a pharmacological carrier. Therefore when two components of eutectic mixture crystallize simultaneously and size reduction of minor component i.e. drug occurs- get microstructure- with improved dissolution rate of poorly soluble compound.
- Therefore when the eutectic mixture is placed in water, the soluble carrier sub. Dissolves rapidly and extremely fine particles of drug released.
- E.g. PEG-fenofibrate eutectic mixture.
- But, Goldberg argued that increased dissolution rate of drug in presence of carrier is caused by formation of solid solution of drug with carrier not by eutectic mixture.

- The purpose of this investigation was to compare the dissolution rate of eutectic mixture composed of drug and carrier with dissolution rate of alone.
- e.g. chloramphenicl-urea mix.
  Griseofulvin-succinic acid solid solution.

3) Microprecipitation & microcrystallization:-

- Defined as dissolution of a solid material in a small amount of good liquid solvent followed by addition of large amount of poor solvent, results in precipitation of dissolved solid.
- Similarly when the poor solvent is added to the solute dissolved in the good solvent, the process is known as salting out.
- Disadvantage of using liquids a antisolvents is that the particles often form a clay like cake which filters poorly and the resulting particles display broad particle size distribution
- This can be solved by the process like Controlled Crystallization and Gas antisolvent method.

4) Controlled crystallization:-

- It is the process of micronization without any milling process.
- First drug dissolved in organic solvent and precipitate by a solvent change method or microcrystallization in presence of HPMC (stabilizing hydrocolloid) & other protective agent like PVP –used as thickening agent which increases viscosity of medium. so, that particle can not move , so no crystal growth seen there.
- By rapid pouring the solution of HPMC in water, in to the drug solution under stirring in a relationship (v/v), the previously molecularly dispersed drug was associated to small particles and stabilized against crystal growth simultaneously.
- This dispersion was spray dried, resulting in drug powder with a uniform particle size distribution and a drug load up to 98%.

The mean particle size of the drug was lower than 5μm in most cases and consequently in the respirable range. Where as the fraction of jet milled drugs is more.

- E.g. Beclomethasone,Betamethadione,Triamcinolone

5) Supercritical fluid technology :-

- Supercritical fluids are gases & liquids above their critical points.
- Near the critical points, supercritical fluids possess liquid like densities and gas like transport properties.
- The solubilizing power of supercritical fluids is sensitive to small changes in operating conditions, and is possible to fine tune the pressure and temperature to tailor the solvent capacity of supercritical fluids for a particular process.
- -this property is used for precipitation and crystallization processes was developing for pharmaceutical materials, and this activity has steadily increased over recent year.

Choice of Supercritical fluid :-

Critical temperature of a supercritical solvents increase as the molecular weight of the solvent increases or as the polarity or intermolecular hydrogen bonding of the solvent increases.

- ⇨ For pharmaceutical applications, the most widely used supercritical fluid is carbon dioxide.($sfco_2$) because of its

  (1) low critical temperature.(31.18º)

  (2) Attractiveness for heat sensitive materials including product sourced from biological.

  (3) Non inflammable

  (4) Non toxic

  (5) Having GRAS (generally regarded as safe) status

  (6) Inexpensive.
- ⇨ This solubility & selectivity of material can be increased tremendously by choosing the appropriate SCF.
- ⇨ E.g. for non polar molecule –nonpolar solvent such as co_2, ethane or ethylene. And for polar molecule - polar solvent such as floroform are preferred for polar compound & these containing functional croup that can hydrogen bond with acidic proton of the solvent.

a) Rapid expansion of supercritical solution(RESS) or Supercritical fluid nucleation (SFN) :-

- ✘ This is unique and innovative method.
- ✘ The solute is first dissolved in SCF which is subjected to rapid expansion (decompression) by passing through a nozzle at supersonic speed which leads to supersaturation of solute and subsequent precipitation of solute with narrow PSD.
- ✘ Here, during decompression, the density and solubilizing power of the SCF decreases dramatically, resulting in a high degree of solute supersaturaion and subsequent precipitations.
- ✘ The morphology and size distribution of the precipitated material is a function of
  -Pre-expansion concentration

  -Expansion conditions.
- ✘ The Pre-expansion concentration is dependent on the choice of supercritical fluid
  - Nature of solute

  - Addition of co solvents

  -Operating pressure

  -Temperature.
- ✘ – The higher the pre-expansion concentration, the smaller the particles and narrower will be particle size range

b) Gas antisolvent recrystallization :-

- Utilizing a same principle of microcrystallizaion, the low solubility of pharmaceutical compound in supercritical solvents can be exploited by using SCF in gaseous form as antisolvents.
- It is possible to induce rapid crystallization by introducing the antisolvent gas in to a solution ctg dissolved solute.
- Rapid addition of a supercritical fluid results in a sudden reduction in the density of the liquid, a sharp rise in the supersqaturation within the liquid mixture and the consequent formation of small and uniform particles.
- One of the requirements for this approach is that the carrier solvent and the SF antisolvent must be at least partially miscible.
- Supercritical ethane provide smaller and more voluminous powder particle as compared to supercritical carbon dioxide as anitsolvent.

c) precipitation with compressed fluid antisolvent :-

- Micronization of organic compound is possible.
- Here gaseous CO_2 is used.
- E.g. micronization of paracetamol and tartaric acid
- Liquid solutions of tartaric acid in acetone, ethanol and methanol/ethanol mixture have been sprayed into supercritical CO_2 used as antisolvent.
- The physical properties of resultant particles are affected by the pressure and temperature of the co_2 phase.

  -Flow rate

  -Formation parameters such as polymer concentration and nature of the polymer.

6) Spray freezing in to liquid :-

- E.g. protein can be micronized using this method.
- Stable protein microstructure particles can be produced by spray freezing in to liquid N_2 .
- Protein crystals are dissolved in water & then delivered to 4.65 :m inner diameter nozzle at 5000 Psi, which was submerged below the surface of liq. N_2.
- Then these frozen slurries were lyophilized in a lyophilizer with a condenser temp. of -67c & pressure of 100 mTorr.
- By this get high surface area particle with size of 0.1-1 :m.

7) Spray freeze dried (SFD):-

- Get reduction of particle size to 0.2-12:m
- Reduction with help of cryogenic process.
- Involves atomization of a e.g. protein solution in to liquid mist, which is then freezes up on contact with cryogenic process.

8) Co-grinding/Co-micronization:

- Cogrinding of a poorly water-soluble drug with water-soluble polymers like hydroxyl propyl methyl cellulose (HPMC), poly vinyl alcohol (PVA) etc in the presence of small

amount of water is extremely effective to improve its apparent solubility with maintenance of drug crystallinity to some extent.

- Small particles produced by milling or micronization have increased surface area and expected to have enhanced dissolution rate. However, energy added to reduce particle size results in increased Van der Waal's interactions and electrostatic attraction between particles leading to reduce effective surface area due to agglomeration thus decreasing dissolution rate.
- Co-micronization of drugs by using excipients like microcrystalline cellulose can be used as an alternative to reduce or eliminate cohesive and electrostatic forces. This approach increases apparent surface area available for drug dissolution by creating an ordered mixture, thereby causing a reduction in particle-particle agglomeration or by reducing Van der Waal's interactions.
- Increase in true surface area of the ordered powdered mixture is expected due to the inherent surface roughness and porosity of microcrystalline cellulose-Drug mixture

9) High- Pressure Homogenization:

- DissoCubes manufacture involves dispersing a drug powder in an aqueous surfactant solution and passing through a high-pressure homogenizer, subsequently nanosuspensions are obtained.
- The cavitation force experienced is sufficient to disintegrate drug from microparticles to nanoparticles. The particle size is dependent on the hardness of the drug substance, the processing pressure and the number of cycles applied.

The possible interesting features of nanosuspensions are :

i. Increase in saturation solubility and dissolution rate of drug

ii. Increase in adhesive nature, thus resulting in enhanced bioavailability

iii. Increase the amorphous fraction in the particles, leading to a potential change in the crystalline structure and higher solubility

iv. Possibility of surface modification of nano-suspensions for site-specific delivery

v. Possibility of large-scale production, the prerequisite for the introduction of a delivery system to the market.

- However, only brittle drug candidates might be broken up into nanoparticles by this technique.
- A few points has to be considered, such as chemical instability of fragile drugs under the harsh production conditions, Ostwald ripening in long-term storage, toxicity of surfactants, redispersibility of the dried powder, batch-to-batch variation in crystallinity level and finally the difficulty of quality control and the stability of the partially amorphous nanosuspensions.

SOLID SOLUTION

Defination "A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent. Since the 2 components crystallize together in a homogenous

one phase system, solid solutions are also called as **molecular dispersions or mixed crystals OR MELTS**

- Melts and coprecipitates are solid dispersion that provide a means for reducing particle size to a molecular level. so solid solutions show greater aqueous solubility and faster dissolution than eutectics and solid dispersions .
- In all these cases, the solute is frequently a poorly water soluble drug acting as the **guest** and the solvent is a highly water-soluble compound or polymer acting as a **host or carrier**.
- The use of dispersion method to obtain physically modified form of a drug which are much more rapidly soluble than pure compound
- It is often called as mixed crystal because the two components crystallize together in a homogenous system.

COMPOSITION OF THE SOLID SOLUTION

- Poorly water soluble drug
- Carrier (polymer or polymer blends)
- Solvent (to dissolve the phase if necessary ,depends on the methodology used)
- Additives (cosolvents or glycerol)
- Recrystallization inhibitors

REASONS OF SOLUBILITY ENHANCEMENT IN SOLID SOLUTION

- Reduction Of Particle size.
- The resulting enhanced surface area produces higher dissolution rate & bioavailability
- Carrier material have solubilization effect on the drug.
- Carrier material enhances wettability & Dispersibility.
- Formation of the metastable dispersions.

CLASSIFICATION

(1) According to the extent of miscibility of two components.

(a) Continuous solid solution (isomorphous , unlimited, complete)

(b) Discontinuous solid solution (limited , restricted , partial , incomplete) solid solution .

(2) According to molecular size of two molecules / crystalline structure of solid solution

(a) Substitutional solid solution

(b) Interstitial solid solution

CONTINUOUS SOLID SOLUTION

- In this type of solid solution the two components are miscible in the solid state in all proportion.
- The total lattice energy of continuous solid solution at various compositions theoretically should be greater than that of bond between the different components at solid state.

DISCONTINUOUS SOLID SOLUTION

- In contrast to the continuous solid solution, there is only a limited solubility of a solute in a solid solvent in this group of solid solution
- As given in the fig. the regions of solid solution is represented by α and β

- Each component shown is capable of dissolving the other components to a certain degree above the eutectic temperature
- As the temperature is lowered, the solid solution regions become narrower

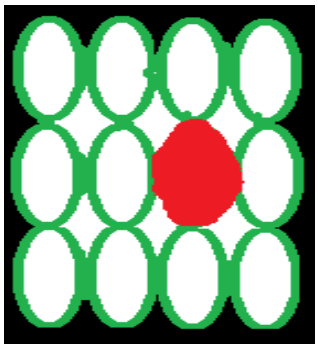
SUBSTITUTIONAL SOLID SOLUTION

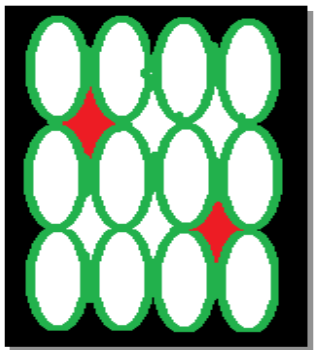
- In this type of solid solution the solid molecule substitutes for the solvent molecule in the crystal lattice of the solid solvent. it can form a continuous or discontinuous solid solution
- The size and steric factor of the solute molecule were shown to play a decisive role in the formulation of solid solution, the size of the solute and the solvent molecule should be as close as possible

- EXAMPLES
  (1) Anthracene – acenaphthalene
  (2) Ammonia – potasium thiocyanate

INTERSTITIAL SOILD SOLUTION

- In this type of solid solution, the solute (guest) molecule occupies the interstitial space of the solvent (host) lattice usually forms only discontinuous (limited) solid solution
- The size of solute is critical in order to fit into the interstices.
- The polyethylene glycol is a universal solvent for the formation of stable or metastable limited solid solution EXAMPLE -Solid solution of digitoxin, methyl testosterone, prednisolone acetate & Hydrocortisone acetate in matrix of PEG – 6000.





SUBSTITUTIONAL **INTERSTITIAL**

METHODS OF PREPARATION

I) Melting or Fusion method (Hot Melt Extrusion Technique)
II) Electrostatic Spinning Method
III) Fluidized Bed Coating System
VI) Supercritical Fluid Technique
V) Novel ultra-rapid freezing particle engineering process.

Melting or Fusion method

- The congealed melts may be clear and glassy or crystalline in nature.
- The rate of dissolution decreased as degree of crystallinity increased.

- Congealed melts were prepared by first heating the carrier in an aluminium dish over an oil bath to 5 °C above the melting point of the carrier.
- The drug was then dissolved into the molten carrier and stirred for 2min to ensure a homogenous dispersion.
- 2 methods of cooling were employed
- Process A involved the flash cooling of dispersion by immersion of aluminium dish contg. the molten mass in a bath of dry ice and acetone.
- The preparation of the congealed melt by process B involved gradual cooling of the oil bath under ambient conditions over period of several hours.
- Dispersions from both processes were passed through a 20 mesh screen,and 20-40 mesh fractions was retained for dissolution studies
- Ground samples of the dispersion were employed for the scanning electron microscopic evaluation of the surface crystalline properties and the finer fractions in 60 to 100 mesh range was retained for x-ray analysis.
- The ratios of carrier to the drug were 2:1 w/w for all samples with exception
- Sugar based congealed samples of betamethasone acetate or methyl prednisolone acetate were prepared with dextrose, galactose or sucrose as water soluble carrier.
- The final solid mass was crushed, pulverized and sieved.
- To facilitate faster solidification, the homogenous melt was poured in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by blowing air or water on the opposite side of the plate.

Hot melt extrusion technique

- The advent of high through-put screening in the drug discovery process has resulted in compounds with high lipophilicity and poor solubility.
- Hot-melt extrusion is an efficient technology for producing solid molecular dispersions with considerable advantages over **solvent-based processes such as spray drying and co-precipitation**.
- Hot-melt extrusion has been demonstrated to provide sustained, modified, and targeted drug delivery.
- Improvements in bioavailability utilizing the hot-melt extrusion technique demonstrate the value of the technology as a potential drug delivery processing tool.
- It has been reported that melt extrusion of **miscible components** results in **amorphous solid solution** formation, whereas extrusion of an **immiscible component** leads to amorphous drug dispersed in crystalline excipient.
- The process has been useful in the preparation of solid dispersions in a single step.
- (An extruder consists of 2 distinct parts: a **conveyer system** that transports the material and sometimes imparts a degree of distributive mixing; and a **dye system** that forms the materials into the required shape.
- The drug carrier mix is filled in the hopper and is conveyed, mixed, and melted by the extruder. The die then shapes the melt in the required form such as granules, pellets, films, or powder that can be further processed into conventional tablets or capsules.
- The ADVANTAGES of hot-melt extrusion include
    1. Lower temperature
    2. Shorter residence time of the drug carrier mix (<2 minutes),
    3. Absence of organic solvents,
    4. Continuous operation possibility,

5. Minimum product wastage,
6. Good control of operating parameters, and
7. Oxygen and moisture may be excluded almost completely for substances prone to oxidation and hydrolysis.

DISADVANTAGES

1. Thermal process (drug/polymer stability)
2. Flow properties of the polymer are essential to processing.
3. Limited number of available polymers
4. the method of preparation
5. reproducibility of physicochemical properties
6. formulation into dosage forms
7. the scale up of manufacturing processes

Electrostatic spinning method

- In this process, a liquid stream of a drug/polymer solution is subjected to a potential between **5 and 30 kV.**
- When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, **fibers of submicron diameters** are formed.
- As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandril.
- The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength
- Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and nonbiodegradable) polymers are useful in controllable dissolution properties.
- Fabrics generated by water-soluble carriers could be used in oral dosage formulations by direct incorporation of the materials into a **capsule.**
- **Itraconazole/HPMC nanofibers** have been prepared using this technique.
- Electrospun samples dissolved completely over time, with the rate of dissolution being dependent on the type of formulation presentation and the drug: polymer ratio.

Spraying on sugar beads using a fluidized bed coating system

- The approach involves a fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granules ready for tableting or drug-coated pellets for encapsulation in one step. The method has been applied for both controlled- and immediate-release solid dispersions.
- Itraconazole (Sporanox oral capsules) coated on sugar sphere, hydroxypropylmethylcellulose (HPMC) in an organic solvent of dichloromethane and ethanol.
- A solid solution of drug in HPMC is produced upon coating (cosolvent evaporation) and controlled drying of coated beads in a closed Wurster process. As this thin film dissolves in water or gastric fluid, the molecularly dispersed itraconazole is released at supersaturated concentration. HPMC acts as a stabilizer to inhibit recrystallization of the itraconazole. The supersaturated solutions of itraconazole are sufficiently stable to allow for absorption and distribution.

- Modifications to the above method, wherein the use of organic solvents is avoided, have been reported. These alterations involve the use of hot-melt fluid bed technique,

Supercritical fluid technology

- **SEDS** process was used to form solid solution particles and 2 different types of carriers, Mannitol and Eudragit E 100.
- One-phase solid solution was obtained when coprocessed with Eudragit E 100 but was not obtained for the mannitol coprecipitate. This result emphasized the role of excipients used in the process.
- Solid solutions of several drugs have been produced using the SEDS technique with hydroxypropylcellulose, ethylcellulose, and polyvinylpyrrolidone as carriers
- In the **PGSS p**rocess, a melt of the drug and the carrier saturated with supercritical CO2 is rapidly cooled by adiabatic expansion of CO2, whereupon the solid dispersion precipitates in the form of microparticles.
- This rapid cooling and expansion of CO2 produces fine particles with a narrow particle size distribution and, thereby, avoids the comminution step
- Solid dispersions of nifedipine and felodipine54 and fenofibrate55 were prepared with PEG 8000 using the PGSS process.
- The solid dispersions consistently showed better dissolution rates than the micronized drugs.

Novel ultra-rapid freezing particle engineering process

- **An ultra-rapid freezing (URF) technology has been developed to produce high surface area powders composed of solid solutions of an active pharmaceutical ingredient (API) and a polymer stabilizer for enhancement of dissolution rates of poorly water-soluble drugs.**
- A solution of API and polymer excipient(s) is spread on a cold solid surface to form a thin film that freezes in 50 ms to 1s.
- The solvent's physical properties and the thin film geometry influence **the freezing rate** and consequently the final **physico-chemical properties** of URF-processed powders.
- **Danazol (DAN)/polyvinylpyrrolidone (PVP) powders**, produced from both acetonitrile (ACN) and tert-butanol (T-BUT) as the solvent, were amorphous with high surface areas (approximately 28-30 m^2/g) and enhanced dissolution rates.

SOLID DISPERSION

It is defined as “a dispersion of one or more ingredients in an inert carrier or matrix in solid state prepared by the melting (fusion) method, solvent method or melting-solvent method “ The solid dispersion may also called as solid state dispersions.

- Dispersions obtained through the fusion process are often called as **melts,** and those obtained by solvent method are called as **co precipitates** or **co evaporates**.

- Solid dispersions are prepared to:
    1. To improve drug **solubility.**
    2. To improve drug stability.
    3. To mask the bitter taste of drug.

4. To obtain required release profile.

CLASSIFICATION OF SOLID DISPERSION

- Simple eutectic mixture.
- Solid solution.
- Glass solution and glass suspension.
- Amorphous precipitations in a crystalline carrier.
- Compound or Complex formation.
- Combinations of previous five types.

1) Simple eutectic mixture

- These are prepared by rapid solidification of fused melts of two components that shows complete liquid miscibility but negligible solid-solid solubility. Thermodynamically, such a system is intimately blended physical mixture of two crystalline components. Thus x-ray diffraction pattern of a eutectic constitutes an additive composite of the two components.
- If one component of eutectic has low entropy of fusion, i.e. , if S^f/R (where R is the universal gas constant) is less than 2 , the resulting eutectic crystallization will exhibit coupled growth or simultaneous growth of both components. This simultaneous growth of both phases results in eutectic mixture having well-defined microstructure.

If both components have large melting entropies two components grow independent of each other, and resulting eutectic is a simple physical mixture of two types of anisotropic/faceted crystals.

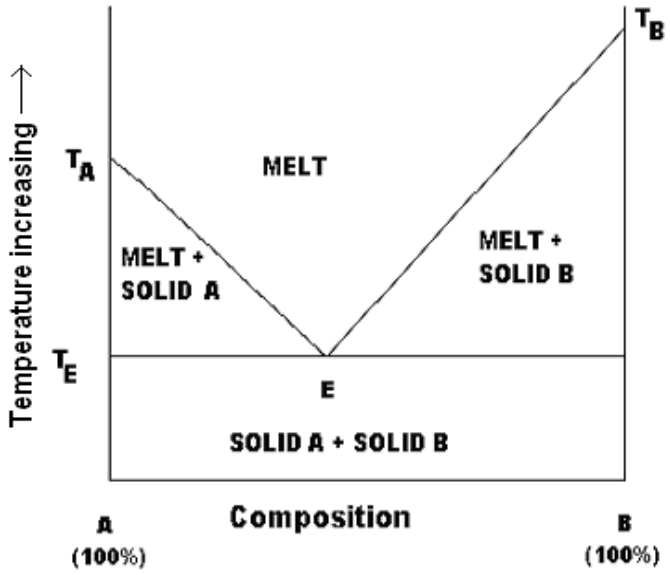


Fig. 1 - Phase diagram of simple eutectic mixture with negligible solid solubility

- According to tamman's rule, the low melting component of a eutectic mixture forms the major phase. Moreover, it has been noted that when melts with eutectic composition are cooled, the two phase begin to crystallize spontaneously and eutectic crystallization rate accelerates at the contact between the two phases, and proceeds with the minor phase of the eutectic growing in the interstitial space of the primary

phase. This process leads to a marked reduction in **particle size** of the minor component.

2) Glass solution and glass suspension.

- A glass solution is a homogenous system in which a solute is is dissolved in glassy system.
- A glass suspension refers to a mixture in which precipitated particles are suspended in glassy solvent.
- The glassy state is characterized by **transparency and brittleness** below the glass transition temp. (Tg). Glasses do not have sharp melting points, instead they softened progressively on heating. The lattice energy, which represents a barrier to rapid dissolution is much lower in glass solution than in solid solution.

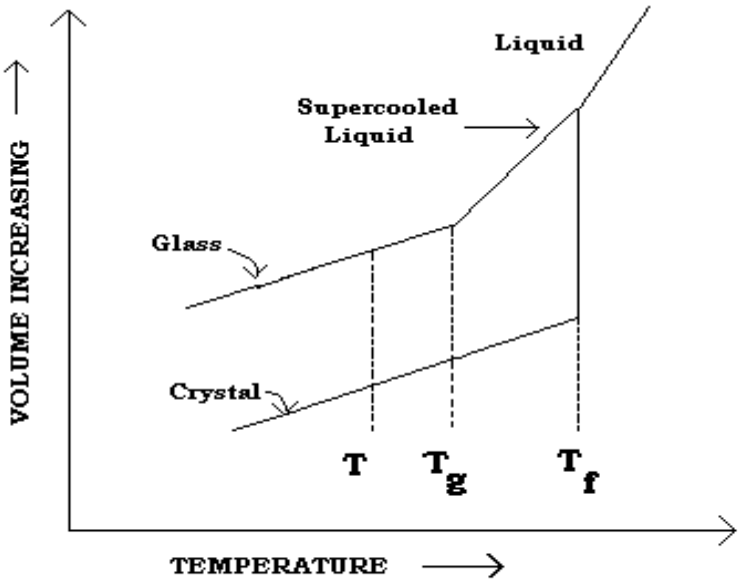


Fig. 2 - Relation between the glassy, liquid and solid state.

- As shown in the graph, liquid is cooled through the freezing point, Tf , it may either freeze into a crystalline solid, with a discontinuous change in volume, or it may be continue as liquid below this temperature.

If the liquid is further cooled rapidly, a change in slope of volume-temp. curve occurs and the new slope often nearly the same as that of the corresponding curve for the crystal.

The temperature at which the curve changes the slope is called the **glass transforming temperature, Tg** . Below Tg , the curve is no longer an equilibrium curve. Therefore a glass or glass solution is **metastable.**

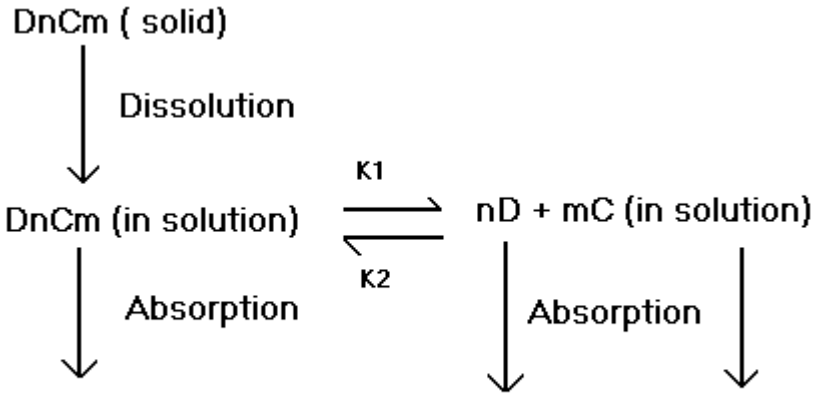
NOTE : It is interesting to note that any liquid or supercooled liquid whose viscosity is greater than 10^{13} poise is generally called as glass.

3) Amorphous precipitations in a crystalline carrier.

- Instead of forming simple eutectic mixture in which both drug and carrier crystallize simultaneously, the drug may also be precipitated out in amorphous form in a crystalline carrier.
- Since the amorphous form is the highest energy form of the pure drug, it produce faster dissolution and absorption rates than the crystalline form whether the crystals are or are not dispersed in a carrier.
- It is postulated that a drug with high supercooling property has more tendency to solidify as an amorphous in the presence of a carrier.e.g. Sulphathiazole in crystalline urea.

4) Compound or complex formation:

- In strict sense, the modification of a dosage form by compound or complex formation (DnCm) between a drug (D) and an inert soluble carrier (C) should not classified under the application of solid dispersion systems. Nevertheless, due to their frequent occurrence during preparation of solid dispersions by slandered methods, it seems worthwhile to review them here briefly.
- The dissolution and absorption of a drug into the body from a complex or a compound are schematically shown in scheme 1. It is a clear from scheme 1 that the avaibility of a drug depends on the solubility, the dissociation constant, and the intrinsic absorption rate of the complex.



Scheme 1

- It is believed that in comparison either pure, insoluble, solid drug, the rate of dissolution and GI absorption can be increased by the formation of a soluble complex with a low association constant.

5) Combinations and miscellaneous mechanism:

- Quite often a solid dispersion does not entirely belong to any of the groups discussed previously, but is made up of combination of different groups. Therefore, observed increase in dissolution and absorption rate may be the combination of different mechanisms.

  e.g. Sulfathiazole dispersed at high concentration in PVP may exist as
  - individual molecule
  - sulfathiazole-pvp complex molecule
  - amorphous and polymorphic molecule
  - amorphous sulfsthiazole-pvp complex.

METHODS OF PREPARATION OF SOLID DISPERSION:

- Melting / fusion method.
- Solvent method.
- Melting-solvent method.

1) Melting / Fusion method:

- A physical mixture of an active agent and water soluble carrier is heated until it is melted. The melt is rapidly solidified in ice bath with rigorous stirring , pulverized and sieved.
- Rapid congealing is desirable because it result in supersaturation of drug as result of an entrapment of solute molecule in solvent matrix by instantaneous solidification. The solidification process can be achieved:
  → on stainless steel plates attached to a cooling system to favor rapid heat loss.
  → spray congealing from modified spray drier on to a cold metal surface.
- Product from spray congealing can be obtained in pellet form without grinding step that may alter crystalline modification.
- The main **advantage** of direct melting method are its simplicity and economy. The **disadvantage** is that many substance either drug or carrier, may decompose or evaporate during the fusion process at high temp.

  e.g. succinic acid, used as carrier for Griseofulvin, is quite volatile and may also be partially decomposed by dehydration near its melting point.

2) **Solvent method**.

- Physical mixtures of two solid components are dissolved in a common solvent and than solvent is removed by evaporation. The choices of solvent and evaporation rate are critical to the quality of dispersions. A mixture of solvent may be used.
- The main **advantage** of the solvent method is that the thermal decomposition of drugs or carriers can be prevented because of the low temp. is required for the evaporation of the organic solvents. However, the **disadvantages** associated with this method are,
  - higher cost of preparation
  - the difficulty in completely removing of solvent
  - the possible adverse effect of negligible amount of solvent
  - the selection of common volatile solvent
  - the difficulty of reproducing crystal form.

3) Melting-Solvent method.

- It has been found that **5-10% w/w** of liquid compound could be incorporated in PEG 6000 without significant loss of its solid property. Hence it is possible to prepared solid dispersion by, first dissolving drug in a suitable liquid solvent and than solution is incorporated directly in to the melt of PEG (70 °C) without removing liquid solvent.
- Such a unique method possesses the advantage of both the melting and solvent method. Unfortunately, from a practical standpoint, it is only limited to drugs with a low therapeutic dose, e.g. below 50mg

MECHANISM FOR INCREASING SOLUBILITY:

- Reduction of particle size.
- Solubilization effect of carrier material on drug.
- Improved wettability and dispersibility of drug.
- Formation of metastable dispersion.

ADVANTAGE & DISADVANTAGE OF SOLID DISPERSION

Advantage:

1. Rapid dissolution rates that may be results in an increase in the rate and extent of the absorption of the drug.
2. Reduction of presystematic metabolism may be due to the saturation of the enzyme responsible for biotransformation of the drug.
3. Transformation of liquid form of the drug to a solid form.
4. Avoid polymorphic changes and thereby bioavaibility problems.
5. Protection of certain drugs by PEG against decomposition by saliva to allow buccal absorption.

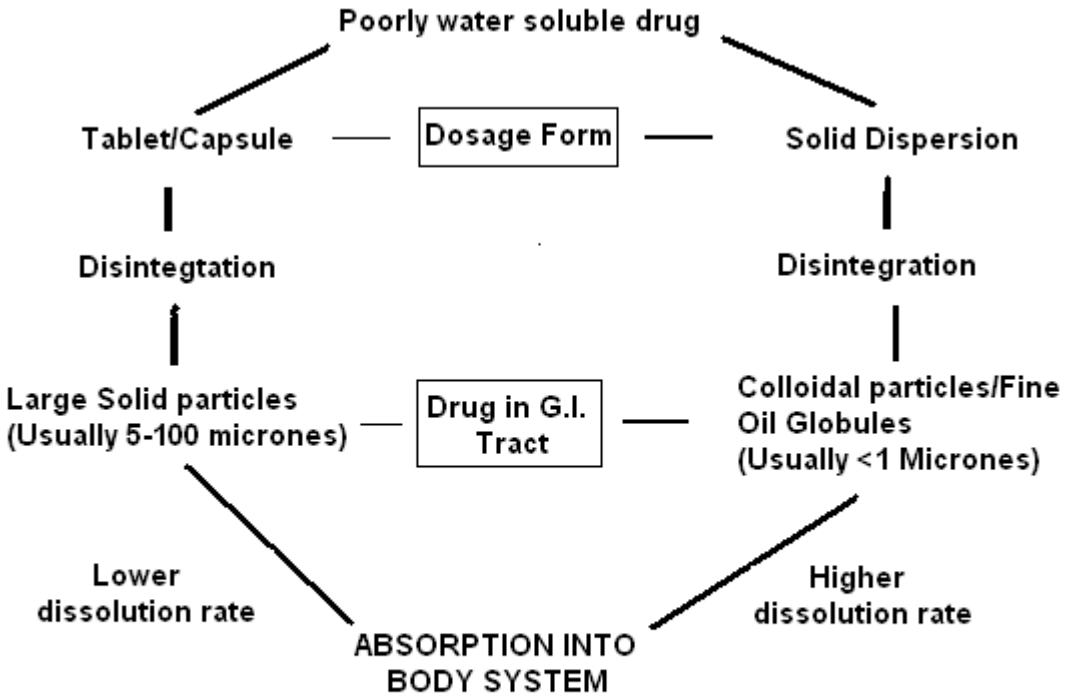


Fig. 3 A Schematic representation of the bioavaibility enhancement of a poorly water soluble drug by solid dospersion compared with conventional tablet or capsule

Disadvantage:

1. Instability**.** Several systems have been shown changes in crystallinity and a decrease in dissolution rate with drug.
2. Moisture and temperature have more deteriorating effect on S D than physical mixture. Some S D may not lend themselves to easy handling because of tackiness (Drug-PEG).

LIMITATION OF SOLID DISPERSION

- Method of Preparation.
- Reproducibility of Physicochemical Properties.
- Dosage Form Development.
- Scale up of Manufacturing Processes.
- Stability.

Materials used as carrier for solid dispersion:

Sugar	Dextrose Sucrose, Sorbitol, Maltose, Xylitol, Mannitol, Lactose
Acids	Citric acid, Succinic acid
Polymeric material	PVP, PEG, HPMC, MC, Hydroxyl ethyl cellulose, Cyclodextrin, Hydroxyl propyl celllose, Pectin.
Insoluble or Enteric material	HPMCP, Edragit RL, Edragit RS, Eudragit L-100, Eudragit S-100
Surfactant	Polyethylene stearate, Poloxamer 188, Renex, Tweens, Spans.

Criteria for selection of drug:

The drug components should meet the following requirements,

1) It should have thermal and air stability.
2) It should be soluble in easily available solvent.
3) It should have recrystallizing property from organic solvent after undergoing molecular micronisation.
4) It should have relatively law Vapour pressure.

Criteria for selection of solvent:

The solvent should meet the following requirements,

1) Nontoxic in nature.
2) Evaporate readily at room temperature and atmospheric pressure.
3) Chemically inert.

FAST DISSOLVING PRODUCTS

Definition:-

"Fast dissolving system can be defined as a dosage form for oral administration, which when placed in the mouth disintegrates rapidly or dissolves and can be swallowed in the form of liquid."

Synonyms:-

- ★ Fast dissolving drug delivery system.
- ★ Fast dissolving/disintegrating tablets. (FDDTs)
- ★ Mouth dissolving tablets. (MDTs)
- ★ Orally disintegrating tablets. (ODTs)
- ★ Orodissolvingtablets.

REQUIREMENTS OF FAST DISSOLVING TABLETS:-

An ideal FDTs should

- Require no water for oral administration, yet dissolve/disperse/disintegrate in mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Be harder and less friable.
- Leave minimal or no residue in mouth after administration.
- Exhibit low sensitivity to environmental conditions (temperature and humidity).
- Allow the manufacture of tablet using conventional processing and packaging equipments.

ADVANTAGES OF FAST DISSOLVING PRODUCTS:-

- Administered to the patients who can not swallow, such as elderly, stroke victims, bedridden patients, patients affected by renal failure and patients who refuse to swallow such as pediatric, geriatric and psychiatric patients.
- Rapid drug therapy intervention.
- Achieve increased bioavailability/rapid absorption through pregastric absorption o drugs from mouth, pharynx and esophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extention and life cycle management.

- **Composition:-**

Processing ingredients	Purpose
Hydrolyzed and nonhydrolyzed gelatin	As supporting matrix
Mannitol/Lactose	As bulking agent
Sodium starch glycollate/croscarmellose sodium	As superdisintegrant
Citric acid OR osdium bicarbonate	Acidic OR alkaline ingredients

- Advantage:-Tablets produced by this technique show fast disintegration and enhanced dissolution.

METHOD OF PREPARATION OF FAST DISSOLVING PRODUCTD

Sublimation:-

The sublimation method for preparing highly porous and rapidly dissolving tablets was described by Roser and Blair.

- The process includes addition of sublime salt to the tableting components, compressing the blend and removing the salt by the process of sublimation.

Composition:-

Processing ingredients	Purpose
Lactose/Trehalose	Diluent
Ammonium carbonate, ammonium bicarbonate, amm.acetate, camphor, naphthalene	Sublime salt

procedure using sublimed salt:-

The active ingredient, a diluent (e.g. a lactose & trehalose), a sublime salt (e.g. ammonium carbonate, ammonium bi-carbonate & ammonium acetate), a binder and other excipients are blended and the tablets are prepared. Then, the volatile salt is removed by sublimation, by exposing the tablets to reduced atmospheric pressure for a time sufficient to completely remove the salt.

- water can also be used s pore forming material for preparation of highly porous fast dissolving tablets.

procedure using water:-

A mixture of active ingredient and a carbohydrate(e.g. sucrose, glucose, xylitol or mannitol)was wetted with suitable amount of water and compressed into tablets. The water is evaporated, producing highly porous tablets with good mechanical strength.

advantages:-Tablets prepared by this method dissolve rapidly (20 sec.) and possess sufficient hardness

Lyophilization/freeze drying:-

- Introduction:-freeze drying or lyophilization process is one of the first generation techniques of preparing MDT, in which water sublimes from the product after freezing. On wetting water penetrates through pores of network resulting in rapid disintegration and/or dissolution of the dosage form.
- ideal drug characteristicsfor this process:-

  1)The drug has relative water insolubility with fine particle size and good aqueous stability in suspensions.

  For waret soluble drugs, there may be chances of formaton of eutectic mixture, resulting in freezing point depression and formation of glassy solid on freezing which might collapse during sublimation.

  - solution: ---The addition of cryoprotectants likee mannitol, crystal forming material, induces crystaliity and imparts rigidity to amorphous material and can prevent collapse of structure.
  - The soluble drugs can also be complexed with ion exchange resins to prevent collapse of structure and mask the bitter taste.

Advantages :-

1) The product obtained by this process dissolves more rapidly than other available solid products.

2) Pharmaceutical substances can be processed at nonelevated temperature, thereby eliminating adverse thermal effects. Thus the process is suitable for heat sensitive drugs and biological
3) Lyophilization results in preparations which are highly porous with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailabilityexample:-fact dissolving products of spionolactone, nicergoline and troleandomycin show increased absorption and bioavailability in comparision to their conventional formulation.
4) The enhanced dissolution characteristic of the formulations is because of the appearance of glassy amorphous structure to the bulking agents and sometimes to drug also by freeze drying pocess.

Disadvantages:-

1) High cost of the equipments and processing limits the use of freeze drying process.
2) Tablets prepared by this technique are fragile and possess low mechanical strength which make them difficult to handle and they also ehibit poor stability on storage under stressed conditions.

Note:-

A mixture of mannitol and one natural um (e.g. acacia guar or xanthan gum) as a carrier material in formulation of lyophilized fast dissolving tablets give good stability in blister pack even when stored at high humidity conditions.

Addition of disintegrants:-

Addition of disintegrants in fast dissolving tablets lead sto quick disintegration of tablets and hence improves dissolution.

Examples:-

i. Microcrystalline cellulose(MCC)
ii. Cross linked carboxymethyl cellulose sodium
iii. Cross linked PVP
iv. Partially substituted hydroxypropyl cellulose (HPC)

MECHANISM:-

Various Disintigrants though water insoluble absorb and swell due to capillary action .there for they are considered as effective disintigrants in the preparation of foot dissolving tablets. agar powder is also used as disintegrant in developing fast disintegrating tablets.

Mechanism:- Upon contact with water agar powder absorbs water and swells without becoming gelatinous at ordinary temperatures.

Fast disintegration of tablets can also be achieved by incorporating effervescent disintegrating agents which generate CO2.This phenomenon also resulted in partial taste-masking of unacceptable taste of the ddrug. EFVDAS is an effervescent drug delivery system used by Elan in the development of pharmaceutical products.e.g. paracetamol, ibuprofen, cimetidine and naproxen)

Advantages:-good hardness,quick disintedration.

Mass extruction:-

This technique includes softening of the active blend using solvent mixture of water soluble PEG, using methanol an expulsion of softened mass though extruder or syringe to get a cylinder of the product into segments using heated blade to form tablets. The dried cylinder can also be used to coat granules having bitter taste masking.

Direct compression:-

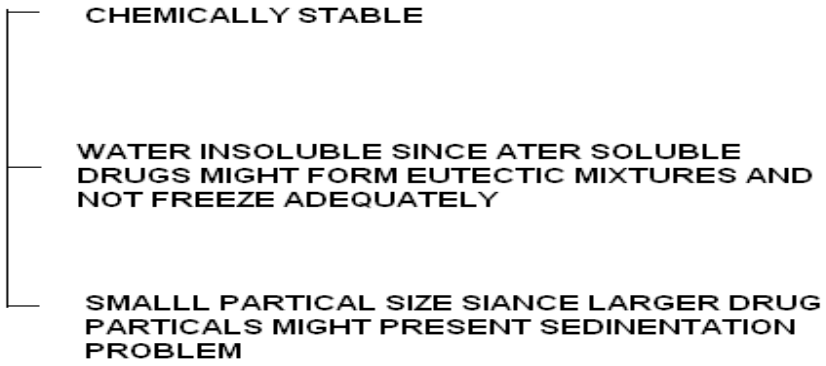
Easiest way to manufacture tablets is direct compression. low manufacturing cost, conventional equipments, limited number of processing steps lead this technique to be a preferable one. High doses can also be accommodated and final weight of tablet can easily exceed thatof other production methods.

PATENTED TECHNOLOGIES

Zydis technology:

The matrix consists of water soluble polysaccharides and polymer (gelatin, dextran, alginates) provide rapid dissolution and to allow sufficient physical strength to withstand handling.

- Patented by:.-R.P.Scherer
- Ideal requirement for drug:-



- Ingredients used in processing and purpose:-

Water:-used during the process to produce porous units for rapid disintegration.

Various gums:-to determine both sedimentation problem of dispersed drugs.

Glycerin:- to prevent the shrinkage of zydis unit during the process and in long term storage

Preparation:-

- In zydis technology drug is physically trapped in the solution of carrier material (preferably gelatin)to obtain dispersion,
- Dispersion is packed in preformed pockets of blister pack by automatic means.
- Then freeze dried to produce the final dosage form.

Amount of the drug that can be incorporated:-

- Less than 400mg --- for insoluble drugs
- Less than 60mg --- for soluble drugs.

Packaging:-

Zydis technology results in tablet with weak mechanical strength so they are marketed in blister pack which allows removal of product without damaging it.

Advantage:-Most compounds in zydis formulation are claimed to be

bio equivalent to their existing solid oral dosage forms and disintegration time is less than 3 seconds.

ORASOLV TECHNOLOGY

Patented by:-CIMA LAB.

Processing technique used:-direct compression.

The system essentially makes tables that contain the taste masked active ingredients and an effervescent disintegrating agent which on contact with saliva, rapidly disintegrates and releases the taste masked active ingredient.

Preparation: - The tables are prepared by direct compression technique at low compression force in order to minimize oral disintegration and dissolution time. Conventional blenders and tablet presses are used to produce the tablets.

Packaging:-The tables produced are soft and friable and are packed in specially designed pick-and place system.

Paksolv^{r}_packaging system developed by CIMA labs consisting of specialized tablet transfer, packaging materials and designs to pack the soft, friable tablets to protect it from attrition and breakage during transportation.

- There are six orasolv formulations marketed worldwide. These formulations can accommodate single or multiple active ingredients and tablets containing more than 1.0g of drug have been developed.

  Disintegration time:- <30 sec.

Advantage:-The orasolv formulations are not very hygroscopic.

Example:-orasolv famotidine tablet.

DURASOLV TECHNOLOGY:-

Patented by:-CIMA labs

- The tablets made by this technology contain drug, fillers and lubricants.

Preparation:- Durasolv tablets are prepared by using conventional tabletting equipments and have good rigidity(friability less than 2%)

Advantages:-Durasolv formulations have higher mechanical strength due to application of higher compaction pressure.

Packaging:-Durasolv product is so durable that it can be packaged into conventional packaging systems like blisters, pouches or bottles.

Amount of drug: - Durasolv is one of the appropriate technologies for products requiring low amounts of active ingredients.

FLASHDOSE TECHNOLOGY:-

Patented by:-Fuisz.

Flash dose technology utilizes a unique spinning mechanism to produce ***floss*** like crystalline structure, much like cotton candy.

What is floss? "Floss means self-binding shearform matrix."

Types of shrarform matrices.

There are two types of shearform matrices.

1. Single floss or Unifloss→consisting of a carrier, and two or more sugar alcohols, of which one is xylitol.

2. Dual floss→consists of a first shearform carrier material termed base floss, contains a carrier and at least one sugar alcohol generally sorbitol and a second shearform binder matrix termed binder floss contains a carrier and xylitol.

How to prepare shearform matrices?

It can be prepared by flash heat processing.The In flash heat process, the feed stock (carbohydrates including sugars and polysaccharides) is simultaneously subjected to centrifugal force and to a temperature gradient, resulting in discrete fibers. The preformed matrices obtained are partially crystallized and have good self-binding and flow properties. Crystallization can be performed by using crystallization enhancers (e.g. ethanol, PVP, water and radiant energy) at a concentration of about 10% and crystallization modifiers (e.g. surfactants which include, lecithin, propylene glycol, spans, tweens & PEG) up to 10% by weight of tablet composition.

The so formed matrices are complex crystalline structures with high specific surface area and result in rapid dissolution rate of the drug.

Procedure:-The shear form matrix is blended with drug (usually taste masked) and other tabletting ingredients, and compressed into tablets using conventional tabletting equipments.

Advantage:- The tablets produced dissolves rapidly in the saliva of the mouth

Disadvantage:-. Flash dose tablets are soft, friable and hygroscopic dosage forms, which require specialized packaging.

Example:-Nurofen meltlets, a new form of ibuprofen as melt-in-the-mouth tablets, prepared using flash dose technologys

WOWTAB TECHNOLOGY: -

Patented by: -Yamanouchi Pharmaceutical Co.

- Wow means "***Without Water.***"

PROCESSING INGREDIENTS	PURPOSE
Low mouldability saccharide. (e.g. lactose, glucose, sucrose, mannitol, xylitol)	Rapid dissolution
High mouldability saccharide. (e.g. maltose, sorbitol, oligosaccharides)	Good binding property.

- The ratio of high to low mouldability saccharide used is 2 to 20% by weight.

Preparation:-

Method 1

The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablets.

Method 2

The low mouldability saccharide is granulated with high mouldability saccharide, and the resultant granules are mixed with active ingredient and subjected to compression using conventional tabletting equipment.

Amount of active ingredients used →50% w/w or less; preferably 20% w/w of the tablet.

Packaging:-

The wowtab product is suitable for both conventional bottle and blister packaging.

Advantage:-

The wowtab formulation is stable to environment due to its significant hardness than Zydis or Orasolv.

FLASHTAB TECHNOLOGY:-

Patented by:-Prographarm laboratories.

Preparation:-

This technology involves the preparation of a rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystals.Drug microgranules may be prepared by using the conventional techniques like coacervation, micro-encapsulation, extrusion-spheronization or simple pan coating method. The microcrystals or microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets.

Advantage:-

The tablets produced are reported to have good mechanical strength.

Disintegration time :-< 1 min.

ORAQUICK TECHNOLOGY:-

The oraquick fast dissolving tablet formulation utilizes a patented taste masking technology by K V Pharmaceutical Company, who claim that its taste masking technology i.e.microsphere technology (micromask) has superior mouth feel over taste masking alternatives. The taste masking process does not utilize solvents of any kind and therefore leads to faster and more efficient production. Tablet with significant mechanical strength without disrupting taste masking are obtained after compression. oraquik claims quick dissolution in a matter of seconds with good taste masking. There are no products yet in market using oraquick technology but KV Pharmaceutical has products, having different classes of drugs such as analgesics, cough &cold, psychotics &anti-infective, in developmental stage.

COSOLVENCY

- The addition of a water-miscible or partiallay miscible organic solvent (i.e. cosolvent to water) is a common and effective way by which to increase solubility of a nonpolar drug. The technique is known as ***cosolvency*** (aka ***solvent blending***).
- **MECHANISM :** Co-solvent decreases the water-water interaction in turn decreases the ability of water to "squeeze out" a non-polar organic solute in the cosolvent system.
  Cosolvent decrease intermolecular H-Bonding interactions of water, a new solvent system is formed that has lower overall polarity than a purely aqueous system and favours the dissolution of a non-polar solute.
  i.e. cosolvency predominantly affects the enthalpy of mixing (intermolecular interaction).
- Aqueous solubilisation via cosolvency is dependent on both the solute and cosolvent physical properties.
  i.e solubilisation is directly related to the polarity (octanol/water partition coefficient) of the drug and the polarity of the cosolvent.
  More nonpolar the cosolvent , the more nonpolar the cosolvent system, the better the solubilisation of a non-polar drug.

- $\text{Log } S_{mix} = \text{Log } S_W + \sigma f_C$

  Where $\text{Log } S_{mix}$ = Molar solubility of solute in mixture
  $\text{Log } S_W$ = Molar solubility of solute in water
  σ = Solubilisation power of cosolvent
  f_C = Cosolvent composition

σ depends upon polarity of the drug and cosolvent.

- **Commonly used Cosolvents :**

Cosolvent	Log $K_{o/w}$	Solubility Parameter (δ)	Surface Tension	Dielectric Constan (ε)
Water	-4.00	23.4	72.0	81.0
Glycerol	-2.60	16.5	64.9	42.5
Propylene Glycol	-1.40	12.6	37.1	32.0
PEG 400	-1.30	11.3	46.0	13.6
Dimethyl Sulfoxide	-1.09	12.0	38.0	46.7
Dimethyl Acetamide	-0.66	10.8	35.7	37.8
Ethanol	-0.31	12.7	22.2	24.3
n-Octanol	2.94	10.3	20.5	10.3

n-octanol is added as reference, since compounds with large octanol / water partition coefficients have poor aqueous solubility (i.e. interact more favourably in octanol than in water).

- **Multiple Cosolvents :**
  It can provide a valuable method for solubilising a poorly water soluble drug when a dosage form necessitates limits on the amount and type of cosolvent that can be used. Ex : A linear increase in the solubility of spironolactone was observe when the amount of PG or Glycerol is added to fixed PEG – 400 concentration.
- **Advantages :**
  - Simple and high degree of ↑se in solubility compared with other methods.

- No toxicity problems when compared with surfactants when given parenterally .
- Over complexing agents it doesn't require identification of a suitable substance that will form the complex .
- Prodrug formation and Salt formation require new drug entities as well as additional animal studies to confirm their efficacy and safety

- **Disadvantages :**
  - Toxic effects on renal , central , nervous , hepatic , and CVS system as well as cell lysis and local tissue irritation .
  - High viscosity leads to syringibility problems in parenteral drugs .
  - High tonicity leads to cell lysis or tissue necrosis .
  - Poor taste for oral dosage form .
  - May decrease the solubility of polar or ionic components of a formulation such as buffer material .
- **Stability :**
  - ✓ Cosolvent may increase the stability of drug .
  - ✓ *Chemical Stability :* If drug is susceptible to hydrolysis , cosolvent may reduce the degradation of the drug by reducing the conc. of water in formulation .
    Replacement of all or part of the water with a cosolvent may enhance the stability of the drug .
  - ✓ *Physical Stability :* Cosolvency is an effective and simple method for improving drug solubility and can thereby prevent physical incompatibilities in liquid dosage form that are related to poor solubility .

- **Applications :**

DOSAGE FORM	***API***	***%W/V OF COSOLVENT***	***TRADE NAME***	MANUFACTURER	***MOST WIDELY USED COSOLVENT***
Oral (Elixir)	---	3-78 % ethanol	---	---	Ethanol PG
Parenteral	Nitroglycerine	30 % ethanol	Tridil	Amer Critical Care	Ethanol PG Glycerin PEG – 400 Dimethyl Acetamide
	Digoxin	10 % ethanol 40 % PG	Lanoxin	B – W	
	Diazepam	10 % ethanol 40 % PG	Valium	Roche	
	Phenytoin	10 % ethanol 40 % PG	Dilantin	Parke – Davis	
Ophthalmic	Chloramphenicol	PEG 300	Chloroptic (Allergen)	---	PG , PEG 300 Ethanol is too irritating to be used in the eye
	Na Sulfacetamide	PG	Sulten - 10	Bausch & Lomb	
Dermal (Topical)	Erythromycin	55 – 77 % ethanol & PG	---	---	Ethanol Isopropranol

	Clotrimazole	PEG 400	Lotrimin solution	---	PG Glycerin PEG 400
Mouth & Throat Prep^{n} (Topical)	Benzocaine	70 % Ethanol	Aerbesol	White Hall	Glycerin Ethanol PG PEG
	Lidocaine	PEG , Ethanol	Xylocaine Oral aerosols	Astra	

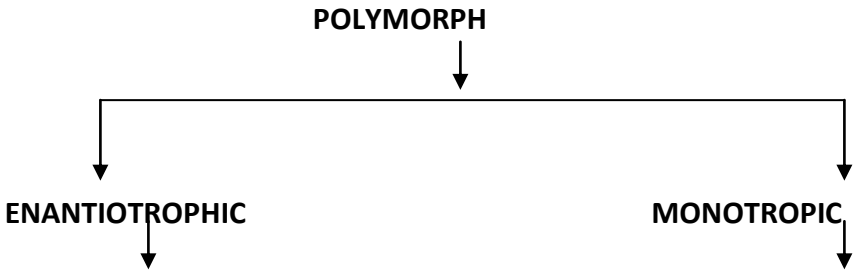
- Ethanol is most used cosolvent .
  Possess excellent solvent properties for non – polar drugs .
  More favourable taste as compared to others .

- Preparation containing 100 % cosolvent are not given IV ously but amy be acceptable for IM injection .

POLYMORPHISM

DEFINITION: Polymorphism is the ability of an element or compound to crystallize in more then one crystalline form.

- Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc.



One polymorphs form can change reversibly into another at a definite transition temperature below the melting point.

No reversible transition is possible for monotropes.

- Once the drug has been characterized under one of this category, further study involves the detection of metastable form of crystal. **Metastable forms** are associated with higher energy and thus higher solubility.
- Similarly the **amorphous form** of drug is always more suited than **crystalline form** due to higher energy associated and increase surface area.
- Some drugs can exist in amorphous form (i.e. having no internal crystal structure). Such drugs represent the highest energy state and can be considered as super cooled liquids. They have greater aqueous solubility than the crystalline forms because they require less

energy to transfer a molecule into solvent. Thus, the order for dissolution of different solid forms of drug is

Amorphous >Metastable polymorph >Stable polymorph

Melting followed by a rapid cooling or recrystallization from different solvents can be produce metastable forms of a drug.

PSEUDOPOLYMORPHISM

- The stoichiometric type of adducts where the solvent molecule are incorporated into the crystalline lattice of the solid are called as the solvates and the trapped solvent as solvent of the crystallization.
- The solvent can exist in diff. crystalline forms called as pseudopolymorh. This phenomena is called as pseudopolymorphism.
- When the solvent in the association with the drug is water, the solvate is known as Hydrates. Hydrates are most common solvate form of the drugs.
- Generally, the **anhydrous form** of a drug has greater solubility than the **hydrates**. This is because the hydrates are already in interaction with water and therefore have less energy for crystal breakup in comparison to the anhydrates (i.e. thermodynamically higher energy state) for further interaction with water. On the other hand, the **organic (nonaqueous) solvates** have greater solubility than the **nonsolvates**.

❖ **IMPORTANCE OF POLYMORPHISM UNDER SOLUBILIZATION AND SOLUBILIZED SYSTEMS**

- What changes or effects can it have on a material ?
- It is well recognized that the polymorphs can significantly impact the overall characteristics of pharmaceuticals.
- The different arrangement of molecules in the crystalline lattice can alter the physical properties of the solid such as
    - Melting Point, Heat Capacity, Conductivity, Color, Bulk Density, Hardness, Morphology, Hygroscopicity, Dissolution rate, Solubility.
- Changes in solubility and intrinsic dissolution rate will change the bioavailability and effect plasma levels of API and drug absorption/metabolism properties.

EXAMPLES

1) Ritonavir Story

- Discovered at Abbot Laboratories., Filed New Drug Application, (NDA)., & got FDA Approval for Norvir a semisolid capsule formulation consisting of a near saturated solution of API in 1996.
- 18 months later product lots begin to fail the dissolution test with drug substance starting to precipitate out of the formulated product.
- Precipitate was identified as a new polymorph, (Form II).
    - Form II was found to be thermodynamically more stable than Form I.
    - Form II was less soluble than Form I.
    - Now capsules were super-saturated with respect to Form II.
    - Form II spreads to the manufacturing plant and attempts to formulate capsules

fail.

2) Phenylbutazone

- It contains four different polymorphs: I, II, III, IV.
- Solubility results shows that form I is more soluble as compared to others in phosphate- ph 6.95 buffer at 36 ^{0}C.

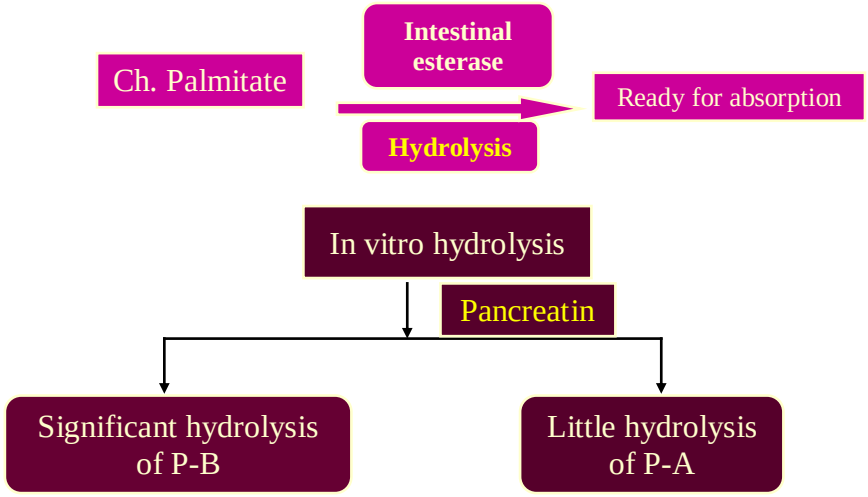
Forms	Peak Solubility (mg/100 ml)
I	288.7
II	279.9
III	233.6
IV	213.0

3) Cilostazol

- In case of Cilostazol, an anti thrombotic agent, the only crystalline form reported has renowned poor solubility in acidic, basic, and aqueous media.
- To improve solubility and bioavailability, an investigation into potential polymorphic form of the drug was initiated. During this study, an amorphous and two polymorphic forms were discovered.
- Theoretical solubility ratio calculated using calorimetry data indicated that at 37°C, Form B should be 4 times more soluble than form A and form C should be 2 times more soluble than form A

4) Effect of polymorphs on dissolution rate & oral absorption

- Chloramphenicol palmitate- 3 polymorphs A, B, C.
- Polymorph B- Absorption significantly greater than A.



P-B is more soluble than P-A. This solubility difference results in diff. in ester hydrolysis rate & ultimately diff in oral absorption.

6) **Suspension solubility:**

In aq. Vehicle, metastable form of polymorphs will get converted into stable form and will produce caking.

EXAMPLES:

1. **Cortisone acetate aq. Suspension**
   - Cortisone acetate exists in 5 diff polymorphs. The crystal growth occurs as form 2 is more soluble than form 5. Forms 5 is more stable one, and hence get caked out on storage. Also, four out of five are unstable in presence of water and convert to fifth one (stable one).Heating, grinding under water and suspension in water all these methods do not prevent the above conversion. Therefore the remedy will be:
     - This conversion should first be allowed and than final suspension should be prepared**OR**
     - Use the comp. which would not allow the growth of crystals.

     e.g. Methyl cellulose, Pectin, PVP, Gelatin, Sodium alginate, Sodium CMC
2. **Ampicillin oral suspension**
   - Aq. Solubility of anhydrous form is 20% more than that of trihydrate form.
   - In vivo expts. were done with dogs and human beings, where anhydrous and trihydrate form of the drug were given as oral suspension or capsules. The anhydrous form produce higher and easier peak in the blood serum than trihydrate form. This was more pronounced in suspension formulations.

Trends in solubility of polymorphs

A large no. of literature reports on solubility or dissolution of polymorphs were reviwed and data were analyzed for trends in solubility ratio of polymorphs.

- Overall, solubility ratio of polymorphs of 55 compounds (81 solubility ratio due to the existence of multiple forms for same comp.) were complied and examined for trends. Anhydrate/hydrate solubility ratio were complied for 17 compounds (24 ratios due to existence of multiple forms).
- Solubility ratio is the ratio of solubility of metastable polymorph to the solubility of most stable form.
- For the majority of comp. solubility ratio were reported in temp. range of 20-40 C when more than two forms were reported in a study, the solubility ratio of each form was calculated relative to the least soluble form.

  e.g., Diflunisal has 4 polymorphic form (I,II,III,IV) . Form IV had the lowest solubility, the ratio were calculated as I / IV, II /IV, III /IV.
- Overall, the average solubility ratio for polymorphs surveyed here is 1.7 (excluding premafloxacin or 2.0 with its inclusion). A similar trend also observed for anhydrate/ hydrate solubility ratio, but this ratio appears to be more spread out and higher than the typical ratio for nonsolvated polymorphs.

MULTIFLUID NOZZLE SPRAY DRIER

- Allows cospray drying with hydrophilic carrier
- Uniform particle size
- Two fluid +one compressed air + product to be dried
- Artemisin + maltodextrin

Ref: JPS volume 98 Number 1 january 2009

LIPID BASED DRUG DELIVERY SYSTEM

- Useful for highly non polar drugs
- Non polar drugs higher solubility in oils, long chain fatty acids.

MOLECULAR ENCAPSULATION

- MOLECULAR ENCAPSULATION with cyclodextrin
- Cyclodextrin molecule is versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophilic drugs as guests,the outside of the host molecule is relatively hydrophilic.
- molecularly encapsulated drug has greatly improved aqueous solubility.

SELECTIVE ADSOPTION

- Highly active adsorbent inorganic clay like bentonite enhance dissolution rate of poorly water soluble drugs like
- griseofulvin,
- indomethacin,
- prednicolone

Rapid release due to

Weak physical bonding between adsorbent-adsorbate
Hydration
Swelling of clay in the aqueous media

SUPERSATURATED DRUG DELIVERY SYSTEM

- Solubility limited oral bioavailability
- Gao and morozowich give super saturation strategy to formulating a number of poorly water soluble drugs in to supersaturable DRUG DELIVERY SYSTEM (SEDD)
- Generate high supersaturated free drug concentration in GIT.

e.g.antitumor paclitaxal(solubilty < 1µg/ml)

PRODRUG

Definition : A prodrug is a chemically modified inert drug precursor which upon biotransformation liberates the pharmacologically active parent compound .

It is also called proagent , bioreversible derivative , or latentiated drug .
The design approach is also refered to as drug latentiation .

Prodrugs have been used to both decrease and increase the aqueous solubility of a drug substance .
Decreasing the solubility is desired in order to mask an unpleasant taste .
Ex : Palmitate Ester of Chloramphenicol
Bitter taste of chloramphenicol is masked .
Increasing the solubility of a drug may be necessary for drug substances :

1. With solubilities too low to allow formulations of solutions intended for parenteral or ophthalmic use .
2. Or if the low solubility comprises bioavailability following oral administration .

Examples :

1. Disodium salt of phosphate ester of 3-hydroxy methyl phenytoin
   Solubility is 4500 times more than phenytoin . Solubility was increased using cosolvent (PG & Ethanol) method but then it caused irritation while given through IM route .
   In prodrug form , there is no irritation following IM administration .

2. Corticosteroid phosphate esters (betamethasone , prednisolone , dexamethasone)
   Solubility of corticosteroid phosphate esters is more compared to succinate esters .
   Available as injection .
   Regeneration is complete with phosphate esters.

3. Sodium succinate ester of Tocopherol .

4. Sodium succinate ester of Chloramphenicol .

5. L-Lysine ester of Diazepam .

Prodrug Of Omeprazole .

1. Pharmacokinetics and Biopharmaceutics by Brahmankar : “Prodrugs”

VITAMIN AS A SOLUBILIZER

Ubiquinone containing water soluble formulation for ophthalmic use .

In this preparation , Vit E [TPGS : Tocopherol PEG Succinate] is added along with Ubiquinone Q 10 .

Vitamin E act as antioxidant and effective solubiliser for ubiquinone itself which in its absence would be totally insoluble in an aqueous environment .

REFERENCE

Solubility and related properties by Kenneth c.James. Pg –: 253 –271.

Remington: the science and practice of pharmacy vol.1 pg:-169-202.

Pharmaceutics – The Science of Dosage Form Design Edited by M.E. **Aulton**

Physical Pharmacy by Alfred **Martin**

The theory and Practice of industrial Pharmacy by Leon **Lachman**

P'ceutical Dosage form and Drug Delivery System by Howard C. **Ansel**

Solubility & related properties By **James K.C.** pages – 251-260

Pharmacokinetics and Biopharmaceutics by Brahmankar : "Prodrugs"

Pharmaceutics : The Science Of Dosage Form Design by M . E . Aulton :"Solubility and Dissolution Rate"