**SOLUBILITY ENHANCEMENT PARAMETER AND CHEMICAL MODIFICATION**

**Sandip G. Badadhe1, Mahesh T. Markande2\*,** **Avinash R. Deshmane2, Hrishikesh S. Deokar****2**

1. Assistant Professor & HOD Department of Pharmaceutical Chemistry, Abasaheb Kakade college of B Pharmacy Bodhegaon, Dist. Ahmednagar Maharashtra, India- 414503 [badadhesandip@gmail.com](mailto:badadhesandip@gmail.com)
2. Research scholar, Abasaheb Kakade college of B pharmacy Bodhegaon, Dist. Ahmednagar Maharashtra, India- 414503

\*Corresponding Author: Mahesh T. Markande \*8208422827, maheshmarkande009@gmail.com

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**Abstract**

The oral route and solidunit dosage forms like tablets and capsules are the most convenient and accepted things. For medicament to bring ready for the oral route the drug solubility is considered significant for drug in reaching action site. When using an oral dosage form, it might be particularly difficult to synthesize medications that aren't readily soluble in water because of the impact on drug's pharmacological activity. Poor solubility of the medicine may reduce absorption and dissolving rates, therefore procedures such as salt formation, solid dispersal, co-solvency, as well as inclusion of a soliloquizing agent can increase solubility of drug. These methods don't always result in increased bio-availability of the medicine that was hoped for. Particle size reduction, pH modification, solid hydrotropy and dispersion, and other strategies are all discussed in this study in an attempt to improve solubility of medications that aren't very water-soluble and any one method can used for enhancement of solubility and bioavailability of medicament. This paper describes details about all methods for solubility enhancement their mechanism advantages and limitation or disadvantages along with criteria to select specific method suitable for particular medicament depending on their characteristics. This review article’s goal is to present solubilization approaches for achieving efficient absorption and increased bioavailability.

**Keywords:** bioavailability, Solubility Enhancement, solid dispersion, hydrotrophy.

1 Introduction

**1.1 Solubility:**

Solubility is process of solute dissolving into solvent forming homogeneous environment, which is an significant parts in achieving desired drug concentration into the standardized circulating for anticipated pharmacological impact. Inadequate permeability solubility may be the cause of the bio-availability problem.Solubility issues affect the majority of mixed solutions.   The mechanisms of solute-solvent interaction characterize the homogeneous liquid phases containing equal quantities of solvent& solute.Solubility-enhancing strategies are selected based on drug's properties, retention location, as well as needed measurement structure. Oral medication delivery is more widely accepted because of its solubility. A drug's solubility has significant impact on how it is taken orally. [1]

**1.2 The Biopharmaceutical Classification System (BCS**): It’s model used to test for properties like permeability and solubility in certain solutions. To help regulate post-approval revisions and generics, method was designed to allow approvals based purely on in vitro evidence as necessary. The system's design was based on fact that vast majority of medications are administered orally. Studies on in vivo bioequivalence might be skipped if a medicine meets specific criteria for solubility and permeability, and also dissolves readily in human body. [2]

However, the pharmaceutical industry is increasingly relying on the BCS in the process of creating new drugs. It may be used to identify medications which shouldn't be tried in clinical trials unless proper formulation procedures are applied. As an example, without using increased formulation methods to increase dispersion or dissolution rate a BCS Class II chemical (permeable but somewhat insoluble) is unlikely to be a promising clinical candidate On basis of BCS category, many strategies are in place to direct an API towards a certain drug delivery strategy. Even yet, most techniques are still fragmented in methodology, disregarding both commercial and biological aspects of the problem at hand. However, when combined with other data, the BCS may be a powerful tool in the drug development process. To increase bioavailability, some believe that FIH medication dosing patterns must be devised. This dosing formulation must be an important step on the path toward commercialization, not just band-aid solution for collecting data. [2]Table 1 highlights BCS classification along with examples.

**Table: 1** Biopharmaceutical classification system (BCS)

|  |  |  |
| --- | --- | --- |
| **Class** | **Solubility** | **Examples** |
| Class I | High solubility  High permeability | Metoprolol,  Propranolol |
| Class II | Low solubility  High permeability | Nifedipine,  Naproxen |
| Class III | High solubility  Low permeability | Cimetidine,  Metformin |
| Class IV | Low solubility  Low permeability | Taxol,  Clorthiazole |

**1.3 Solubility: -**The solubility class limit is set by highest dosage intensity of a drug substance which is subject of biowaiver request (drug substances authorization with no pharmacokinetic BE study). As per USFDA BCS advice, drug product is deemed very soluble if the maximum dosage concentration can be dissolved in 250 ml. [3]

Maximum dosage (if API is on Essential Medicines list of W.H.O) or maximum dosage resilience obtainable in market like an oral solid doses form (if API isn’t on Essential Medicines list of W.H.O) is deliberated as xtremely soluble if it is solvable into 250ml or lesser aqueous media over pH range of 1.2-6.8. Testing API's solubility in water at various pH values is necessary. A least of 3 duplicate solubility experiments are recommended for each pH condition. As per suggestions in BCS Guidance, solubility should be tested.

The oral route of drug administration is the mainly important

method for administering drugs for systemic effects. When a

new drug is discovered, one of the first questions, a

pharmaceutical company asks is whether or not the drug can be

successfully administered by the oral route, for its intended

effect. The development of dosage forms specially for the

prolonged release purpose has been a challenge to formulation

scientists, because of many free factors governing the

absorption of the drug from the gastrointestinal tract (Khan et

al., 2001) and competitive objectives, that is, any action taken

to improve one objective or set of objectives may cause another

objective or set of objectives to degrade (Sachan et al., 2006).

For example, modifying the solubility of the drug substance to

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**1.4 BSC Importance**

The goal of BCS is to identify medications that could be appropriate for a waiver of in vivo bioequivalence investigations for products of such drugs. The goal of B.D.D.C.S is anticipating drug nature and possible drug-drug interfaces in intestines, liver, and maybe kidney and brain, as well as in other organs.

**1.5 Solubility importance**

Oral ingestion is the most convenient and commonly

employed route of drug delivery due to its ease of administra-

tion, high patient compliance, costeﬀectiveness, least sterility

constraints, and ﬂexibility in the design of dosage form. As a

result, many of the generic drug companies are inclined more

to produce bioequivalent oral drug products

Because of its affluence of administering, higher patient acquiescence, cost-effectiveness, minimal sterility limitations, and freedom into designing of dosage form, oral consumption is most often utilized method of drug delivery. In wake of this, several generic pharmaceutical firms are now more motivated to manufacture bioequivalent oral medication formulations. [6]

The lower oral dosage bioavailability of procedures, with other hand, is key obstacle into their development. Factors such as drug perviousness, dissolution rate, first-pass metabolism, presystolic sensitivity& metabolism for effluxing mechanisms influence oral bioavailability. Weak solubility and inadequate permeability are often cited as primary reasons of limited oral bioavailability. Other dosage forms, such as parenteral formulations, depend heavily on solubility as well [7].

A drug's solubility is a critical characteristic in determining its systemic circulation concentration and, therefore, the pharmacological reaction it will produce. [8]

And over 45% of the new chemicals made in pharma companies are almost impossible to dissolve in water. Inadequate bioavailability and mucosal toxicity are the result of these weakly water-soluble medicines' delayed absorption. Solubility is the most critical rate-limiting property for oral medicines to obtain the necessary concentration into systemical circulatory for pharmacological response. Solubility Formulation scientists have a significant task in addressing the issue of solubility. [9]

As a result, the bioavailability of weakly water-soluble medicines in the gastrointestinal fluid softens due to poor solubility and low dissolution rates. To improve bioavailability, especially for class II compounds (higher permeability and lower solubility), enhancing solubility and dissolution rate in gastrointestinal fluids may help.[6] Table 2 describes solubility expression.

**Table 2** Solubility Expression Chart

|  |  |
| --- | --- |
| **Definition** | **Parts of solvent required for one part of solute** |
| Very Soluble | Less than 1 |
| Freely soluble | From 1-10 |
| Soluble | From 10-30 |
| Sparingly Soluble | From 30-100 |
| Slightly Soluble | From 100-1000 |
| Very Slightly Soluble | From 1000-10000 |
| Insoluble | Greater Than 10000 |

**2 METHODS FOR OVERCOMING POOR SOLUBILITY [10-17]**

**2.1 Chemical Alterations**:

2.1.1. Salt Formation

2.1.2. Cocrystallization

2.1.3. Co-solvency

2.1.4. Hydrotropy

2.1.5. New solubilizer use

2.1.6. Nanotechnology

**2.2. Physical Alterations:**

2.2.1. Reduction in Particle size

2.2.1.1. Conventional technique

2.2.1.2. Nanosuspension

2.2.1.3. Micronation

2.2.2. Crystal habit modification

2.2.2.1. Pseudo polymorphs

2.2.2.2. Polymorphs

**2.3. Complexation**

2.3.1. Kneading technique

2.3.2. Co-precipitate technique

2.3.3. Physical mixture

**2.4. Inclusion Complex Formulation Centered Methods**

2.4.1. Kneading technique

2.4.2. Freeze- drying /Lyophilization Method

2.4.3. Microwave irradiation technique

**2.5. Solubilization by surfactants**

2.5.1. Microemulsions

2.5.2. Self micro emulsifying drug delivering system

**2.6. Drug dispersion in carriers**

2.6.1. Solid dispersions

2.6.2. Solid solutions

i. Fusion Procedure

ii. Solvent Technique

iii. Fusion solvent technique

iv. Spray drying

v. Hot melt Extrusion

vi. Lyophilization (Spray Freeze Drying Method)

Vii. Dropping Technique

VIII. Supercritical fluid procedure

IV. PH adjustment

V. Liqui-solid method

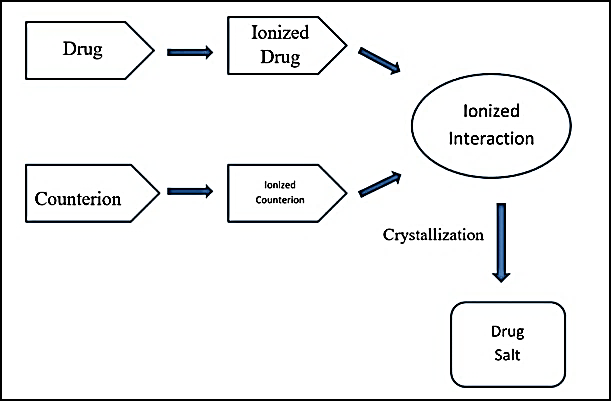
VI. Polymeric alteration

**2.7. Novel solubility augmentations comprise**

**2.1. Chemical Alterations / Modifications:**

**2.1.1.** **Salt formation:**

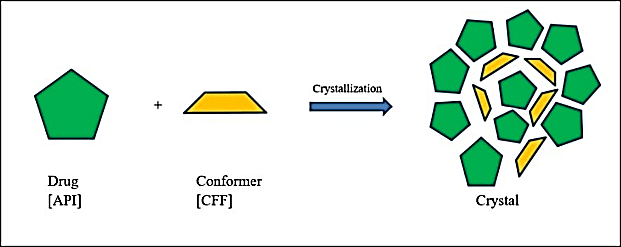
API may not be possible to be created through its pure state because of various instability issues. This results in the formation of solid formations like salts, co-crystals and so on. Different physiochemical features are imparted by several of them and they all have an impact on performance qualities such as bioavailability, stability, purification and manufacture ability in their own unique manner. For many decades, forming salts from inactive, weakly soluble chemicals (weak bases and bases) is an approach to improve solubility. When a substance is ionized in solution, salts are generated. Parenteral or other fluid formulas as well as solid dose forms may benefit from it. An acidic or basic medication is transformed into a more solubilizing salt. A few examples: Aspirin, Theophylline, and barbiturates. Progesterone, water-insoluble steroid which is dissolved in peanut oil, is one example of this technique that is readily accessible in the market. [18] Figure 1 is about salt formation mechanism.



**Figure:** 1Salt formation

**2.1.2.** **Co-crystallization:**

Co-crystallization modifies molecular interaction thus is regarded viable approach to improve medicinal characteristics. "Multicomponent crystal that is created between two substances which are solids at ambient circumstances, in which at least 1 constituent is an allowable ion or molecule," is a more precise description of a "co-crystal." There are several physical, chemical, and physiological limitations to API co-crystallization. The co-solvency process reduces the interfacial tension, which aids in dissolving of anon-polar solutes. Analytical methods and reasonable physicochemical studies may be used to choose the best suitable co-crystal, including tests of stability& solubility. There is no distinction amongst solvates and co-crystals other from physical condition of the components. It's called solvates when one component is liquid another is solid; on either side, it's called co-crystals when both components exist in solid form. Pharmaceutical API and co-crystal former are 2 primary components of co-crystals (s). [19] Figure 2 is mechanism of crystallization.



**Figure2** Mechanism of crystallization

Numerousco-crystallizationmethods

1)Grinding

2)Solvent evaporation

3)Solvent drop grinding (GrindingModification)

4)Slurry Co-Crystallization

5)Hot melt extrusionHigher

6) Throughput co-crystallization

7) Soncrystallization Method.

Co-Crystals Characterization Strictures

1) Max wavelength

2)Solubility

3) Steadiness

4) Bioavailability

5)Inherent dissolution

6) Melt (Hot phase microscopy)

7) Melting Point

8) X.R.D

9) Differential  Scanning Calorimetry (D.S.C)

10) Vibrational spectroscopy.

**2.1.3)** **Co-solvency/Solvent Blending:**

There is less interfacial tension among aqueous phase as well as hydrophobic solute, which helps weakly water-soluble medication become more solubilized with inclusion of water-miscible solvent. Whenever a medication is prescribed, it is in form of a liquid. It is possible to use cosolvent method for poorly soluble chemicals that are lipophilic or extremely crystalline. Due can obvious low toxicity of many co-solvents and the better capacity of co-solvents to solubilize nonpolar pharmaceuticals, it has found its primary employment in parenteral dosage forms. Dimethylsulfoxide,propylene glycol, ethanol,dimethyl acetamide, n-octanol, and glycerol are most often utilized cosolvents. [20, 21]

**2.1.3.1. Co-solvency/solvent Blending advantages:**

1. Simple and quick formulation, production, and evaluation of formulations with large solubilization capability for poorly soluble pharmaceuticals
2. Solubilization procedures and pH adjustments may be used in conjunction with this method to further enhance solubility of weakly soluble substances.

**2.1.3.2. Co-solvency/solvent Blending disadvantages:**

1. It is important to examine degree of solvent used when determining level of toxicity and tolerance.
2. When water is added to a solution, precipitation may occur uncontrollably. They maybe amorphous or crystalline, and their sizes could differ.
3. For intravenous administration, several insoluble substances are unsuitable for cosolvents. Embolism and local negative impacts at injection site are possible risks for medicines that are particularly insoluble in water therefore so don't rapidly redissolve following precipitation from co-solvent combination.
4. A crystallized version of insoluble medication has worse chemical stability than its solubilized counterpart.

**2.1.4.** **Hydrotrophy:**

Hydrotrophy is phenomena of solubilization in which an enhancement into aqueous solubility of an existing solute is caused by large-scale addition of second solute. Hydrotropic agents such as sodium acetate, sodium benzoate, urea, sodium alginate weakly interact with poorly soluble medicines during complexation, which is process by which it enhances solubility. Ionic organic salts are hydrotropic agents. There are no colloidal qualities in hydrotropic solutions, which have a weak connection among hydrotropic agent as well as solution's solute. [22] Examples of hydrotropicagent :sodium salicylate, sodium benzoate,sodium acetate as mention in table 3 and figure 3 describes solubilization phenomenon of hydrotrophy..

**Table 3** Classification of Hydrotropes

|  |  |
| --- | --- |
| Category | Example |
| Aromatic anionic | Sodium benzoate, Sodium salicylate, Sodium benzene sulphonate, Sodium benzene disulphonate, Sodium cinnamate. |
| Aromatic cationic | Para amino benzoic acid hydrochloride, Procaine hydrochloride, Caffeine |
| Aliphatic and linear anionic | Sodium alkanoate |

**2.1.4.1.** **Hydrotrophy Advantages:**

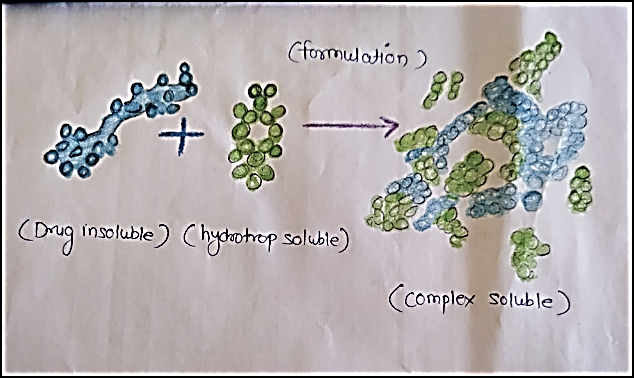
1. Solubilization techniques like miscibility, micellarsolubilization, co-solvents, as well as salting in have been shown to be inferior to hydrotropy since it does not need emulsification and solvent character is pH independent.

2. It doesn't matter what pH the solution is, hydrotrophy is very selective, & emulsification isn't necessary.

3. To prepare an emulsion, the medication and hydrotrope are simply mixed in water, and no organic solvents or chemical modifications are required.

4. Hydrotropic behavior of wide range of substances has been documented.[22]

As an instance, ethanol, aromatic alcohols, such as catechol ,pyrogallol and resorcinol, as well as salicylates, alkaloids like nicotine& caffeine, ionic surfactants like diacids, SDS (sodium dodecyl sulfate) and dodecylate- doxi-dibenzene are all examples of aromatic alcohols.



**Figure 3** solubilization phenomenon of Hydrotrophy

**2.1.5.** **Novelsolubilizer Uses:**

To increase dissolvability of poorly soluble medicines, several materials may be used.

Ex. PEG400 Sepitrap, Conventional solubilizer Polysorbates , [23] dendrimers, Soluplus [24] Povacoat ,advances hydrophobic APIsolubility.

**Sepitrap as novel Solubilizer**:

Eighty percent of solubilizers in sepitrap TM (Microencapsulated solubilizer for solid dose administration) are desorbed in less than five minutes and may now be used to solubilize the medication. To increase dissolvability, 2:1spectral: drug ratio is ideal since it doesn't impair tablet properties and may be employed without any restrictions.

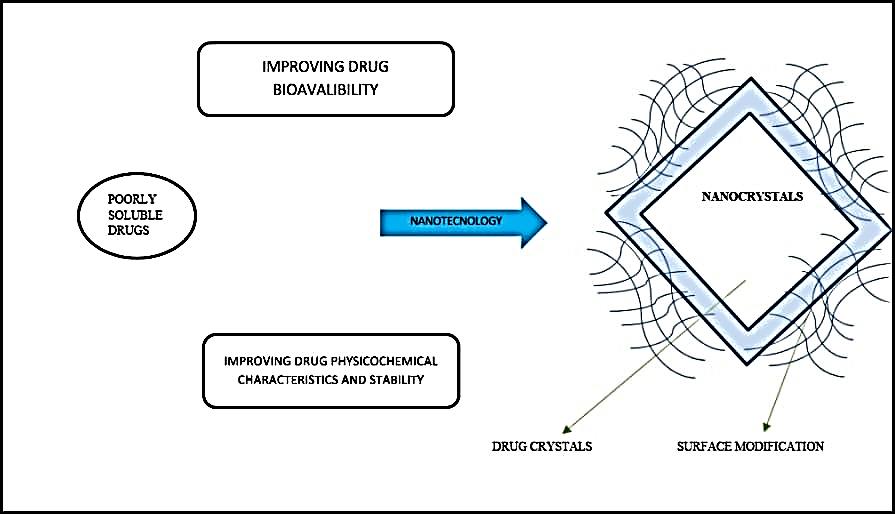
**2.1.6.** **Nanotechnology:**

The term "nanotechnology" refers to research also utilisation of elements and systems at nanometer (nm) scale or below. Micronization alone is not enough to improve oral bioavailability for many novel chemical entities with poor solubility [25]. Next step attempted was nanonization, which has much larger functional interface region for dissolving. High-pressure homogenization, milling, vacuum deposition, & high-temperature evaporation may all be utilized in preparation. Nanocrystals of poorly soluble drugs described by figure 4.

**2.1.6.1.** **Nanotechnology Advantages:** Micro-sized or Nano spherical particles having smooth surfaces, narrow particle sizes, as well as high specific surface areas are produced, enhancing dissolving rate and solubility of substance.

**2.1.6.2.** **Nanotechnology Disadvantages:**

Efforts to solve issue of agglomeration are difficult since it is inherent.



**Figure 4** Nanocrystals of poorly soluble drugs

**2.2. PHYSICAL ALTERATION / MODIFICATIONS:**

**2.2.1.** **Particle size reduction:**

The size of a drug particle may have a significant impact on the medication's solubility. The surface - to - volume proportion rises as particle size decreases. Increased solubility is result of increased solvent interaction due to increased surface area. The smaller drug particle, less bioavailable it is. Decreased particle size enhances dissolving capabilities while opening up broader choice of formulation strategies and administration methods. Increased surface area [26, 27]

**2.2.1.1.** **Particle size reduction advantages**:

1. This method of increasing solubility is effective, repeatable, and cost-effective.
2. In chemical substances, enhance pace of dissolution since particle size reduction improves solvent's surface area of action.
3. Enables solvent to penetrate quickly.

**2.2.1.2.** **Particle size reduction disadvantages:**

1. Because of higher surface charges of discrete tiny particles, particle agglomeration has a strong tendency.
2. Mechanical and physical strain might lead to the breakdown of active substances.
3. In addition, the thermal stress that happens during communication may have an impact on process of thermosensitive substances.
4. Technically, building a solid dosing formulation with higher payload that does not encourage agglomeration and sterile intravenous formula is difficult task.

**a) Conventional technique of particle size reduction:**

Cutting, compression, impact, attrition, mixed impact, and attrition are some of the processes used in the traditional technique of particle size reduction. Mechanical stress is used to disaggregate the active component in traditional particle size reduction procedures as transmission and spray drying. Solubility may be improved economically, reliably, and efficiently by reducing particle size. Mechanical forces inherent in communication such as grinding and milling can cause considerable physical stress that might lead to deterioration of medicinal products. When working with thermosensitive or unstable active agents, it's important to keep in mind the potential for thermal stress throughout the comminution and spray drying processes. Poorly soluble pharmaceuticals cannot be made more soluble to a satisfactory level by employing just established techniques of solubility augmentation.

**b) Micronization:** To reduce the size of coarse particles to fewer than 5μ, a high-energy particle size reduction approach is used. In order to provide a consistent dosage form, a narrow and homogenous particle size distribution is obtained by micronization. Solubility and surface area increase when the particle size decreases due to micronization. By using a specific process for producing micronized drug substances (e.g. spherification), the characteristics of the micronized medicinal material may be altered. The most widely used methods for creating micronized medication particles are mechanical mixing, spray drying, and supercritical fluid (SCF) technologies. Drugs that are difficult to dissolve in water may be improved in bioavailability by administering them in micron size, as per Noyes–Whitney hypothesis.

**Micronization Techniques**

a) Fluid energy mill/Jet milling or micronizer

b) Microcrystallization & Microprecipitation

c) Rotor stator colloids mills

d) Meticulous crystallization

e) Spray freezing into liquid

f) Supercritical fluid technology

**Micronization Advantages**

1. Increased surface area and narrower particle size dispersion result in more homogenous particle.

**Micronization Disadvantages**

1. It is possible that crystal structure of medication may be disrupted by high-energy procedure, resulting in amorphous or disordered areas.
2. Amorphous areas were thermodynamically unsteady & vulnerable to recrystallization, especially in hot and humid circumstances, when they are held in storage.
3. **Nanosuspension**:

Drugs that are difficult to dissolve both in oil and water might benefit from this method. It is possible to administer pharmacological nanosuspension through oral, topical, parenteral, or pulmonary routes, all of which employ surfactant-stabilized water vehicles containing nano-sized drug particles.

Including a mean particle size around 200 to 600 nm, solid particle in nanosuspensions are usually smaller than one micron in diameter. [28] Bottom-up and top-down approaches are used to create nanosuspension. Nano edege, nanojet technologies, and milling technology are all examples of top-down technology.

**Nanosuspension Advantages**

1. As a result, solubility, dissolving rate, and eventually bioavailability are increased in nanosuspension because drug particles are decreased in size.
2. Permeability is increased as a consequence of nanosuspension.
3. Bioadhesion and residence time are lengthened by nanosuspension.
4. High drug loading is one of the advantages of nanoformulation.
5. Organic solvents should be avoided. Nanosuspension's drawbacks Because of agglomeration, crystal formation, and Ostwald ripening, it is unstable.

**2.3. Complexation:**

A stoichiometrically defined non-bonded entity is formed when 2 or many molecules come together.[29]

**Two kinds of complex:**

**Building up complexes:** This is a method in which non-polar areas of drugs & agents in complexes are linked together to prevent water from entering those non-polar areas of the drugs. There is a clear answer regardless of whether the stack is homogenous or heterogeneous.

**Inclusion complexes**: They are generated when a nonpolar molecule, area, or molecule is inserted in cavity of some other particle or grouping of molecules. It is usual to employ cyclodextrine and its derivatives in complexation.

**2.4. Incorporation of Formulation-Related Complexity:**

When a nonpolar molecule or area of one molecule (known as the guest) is deposited into a cavity of another (or group of molecules), an inclusion complex is generated (known as host). Cyclodextrins are common host molecules. The host's cavity must be big enough to accept the visitor and tiny enough to remove water. We have a variety of ways to make solid inclusion complexes: mixing, co-grinding and spray drying are a few. Microwave irradiation and kneading technique coprecipitation are two more. [30]

**2.4.1.. Kneading method:** deliberated in complexation

**2.4.2. Lyophilization / Freeze-Drying Method:**

In this method, solution's solvent system is removed by first freezing and then drying solution under low pressure, which contains both medicine and CDs or another appropriate polymer. The specific qualities of water as well as its function as a solvent, gas, diluent, plasticizer, and stabilizer play a large part in lyophilization. Drug and carrier molecules are molecularly mixed into one solvent for this method.

**2.4.2.1. Lyophilization / freeze-drying method advantages**

1. This method is thought to be worthwhile for obtaining an amorphous, porous powder with high degree of drug-polymer interaction.
2. It's possible to make complexes out of thermolabile compounds using this approach.

**2.4.2.2. Lyophilization / freeze-drying method disadvantages**

1. Utilization of specialist tools.
2. A time-consuming method that yields powder that is difficult to disperse.

**2.4.3. Microwave Irradiation Method:**

A microwave oven is used to conduct microwave irradiation reaction among medication and the complexing agent. Combination of organic& water solvent is added to the round bottom flask and medication and CD are dispersed. In the microwave oven, the mixture is heated to 60 degrees Celsius and reacted for one to two minutes. A sufficient quantity of solvent system is introduced to aforesaid reaction mixture once reaction is complete in order to eliminate any remaining free drug and CD that have not been complexed. Whatman filter paper is used to separate the precipitate, which is then dried in vacuum oven at 40 degrees Celsius for 48 hours.

**2.5. Solubilization by surfactants:**

Molecules containing polar and nonpolar sections are known as surfactants. A polar group is usually linked to a hydrocarbon segment in most surfactants. There are four types of polar groups: anionic, cationic, zwitterionic, and nonionic. The hydrophobic core of micelles may gather tiny polar molecules when they are introduced. In both industrial and natural processes, solubilization is critical. Surface tension may be reduced by the use of surfactants, which improve the solubility of lipophilic medicines by boosting their dissolution in aqueous media. Drug suspensions may also be stabilized by using surfactants. A micelle is formed whenever concentration of surfactants exceeds with their crucial micelle accumulation (CMC, which is typically in range of 0.05–0.10% with most surfactants). Micelles entrap the drugs within the micelles, which is known as micellization and primarily outcomes throughout increased solubilization of poorly soluble drugs.

**2.5.1. Microemulsions:**

As an optically clear, thermodynamically stable transparent and translucent preconcentrate comprising a blend of hydrophilic surfactant & hydrophilic solvent, micro emulsion dissolves a weakly water soluble medication. HLB and non-toxicity are the deciding factors in the surfactant choosing process. After coming into contact with water, these formulations self-emulsify and generate an oil-in-water mixture that contains solubilized, water-resistant medication. A variety of medications, many of which are essentially insoluble in water, have been made more soluble using microemulsions and proteins for oral and parenteral administration. The oil-in-water (o/w) microemulsion is best formulation for increasing solubility by dissolving molecules with poor water solubility in an oil phase. Because of the altered permeability caused by the surfactant, they may also improve oral bioavailability by lowering droplet size (100nm). [31]

**Advantages of microemulsions:**

1. Filterability and ability to integrate broad variety of medications with differing solubilities are all advantages of this formulation.

**2.5.2. Self-emulsifying drug delivery systems:**

Concept of emulsion creation in situ in intestines has been used. It's called a "self-emulsifying drug delivery system" because of clear, isotropic solution formed by the oil, surfactant, co-surfactant, hydrophilic solvent, and co-solvent combination (SEDDS). Upon modest agitation in presence of water, oils and surfactants in isotropic solutions create oil-in-water microemulsions, which are the basis for self-emulsifying drug delivery systems & self microemulsifying drug delivery systems. These new colloidal compositions act like oil-in-water microemulsions when administered orally.

**2.6. Drug dispersion in carriers**:

Two crystalline solids are mixed together to form novel crystalline solid called a solid solution. In a homogeneous one-phase solution, 2 elements crystallize together, resulting in mixed crystal. The dissolution rate should be substantially greater than in simple eutectic systems because of this. [32]

Amorphous precipitation:

Whenever drug precipitates in an inert carrier, it becomes amorphous. Dissolution rates in this system are often substantially higher than in crystalline versions of medication because of high energy state.

**Uses of solid dispersions**: [33]

1. To uniformly disperse a trace quantity of a medication in solid form.
2. To make unstable medication more stable.
3. Dispense liquid (upto 10%) or gas chemicals in solid dosages.
4. For creating sustained-release formulation of fast-acting main dosage.
5. To minimize amount of medicines such as progesterone& morphine that are metabolized before they reach bloodstream.
6. Utilizing poor insoluble or soluble carrier to provide prolonged release strategy for soluble medications.
7. Polymorphs may be transformed into solid isomers in a given system.

**Benefits of solid dispersion** [34]

It dissolves quickly.Increase the rate of medication absorption.

Improve the water dissolvability of a pharmaceutical's weakly water-soluble medication.

Reducing crystalline structure of medication into an undefined amorphous state.

Make fast-dissolving oral suppositories.Disguise flavor of medicine.

It is important to keep medications from degrading or decomposing. Conversion from liquid to solid form of medication (Ex. Benzoyl benzoate & clofibrate could be combined with PEG-6000 for obtaining solid.)

8. Preventing polymorphic alterations and, as result, issues with bioavailability

**Drawbacks of solid dispersion** [35]

1. Solid dispersion is unstable.
2. Solid dispersion is harmed by moisture and temperature.
3. A reduction in dissolving rate may be seen in crystallinity of material.

**Techniques of making solid dispersions**

**i) Fusion Procedure**:

The medication is integrated in matrix by heating carrier to temperature slightly above its melting point. As mixture cools, medication is continuously stirred to ensure uniform distribution throughout the matrix. In addition, the carrier's solubilizing action, better wetting or reduced surface hydrophobicity, complexation as well as crystallization of drug in metastable polymorphic form with changed thermodynamic characteristics may all play a role.[36]

Drawbacks:

i) Increasing temperature at which pharmaceuticals are exposed, especially if carrier is solid with high melting point as well as drug is thermolabile.

**ii) Solvent Technique:**

It is dissolved in an organic solvent that contains carrier as well as active component. A high temperature or vacuum may be used to remove this solvent. An increase in supersaturation causes precipitation of the contents when solvent is eliminated. This leaves a solid residue. Afterwards, co precipitate is vacuum-dried to remove any solvent that may have remained on particle. Even the tiniest traces of solvent must be removed. In order to prove that all of the solvent has been removed, a variety of techniques may be utilized, including DTA, DSC, TGA, spectroscopy, gravimetry and a variety of other less sensitive methods. [37]

**iii) Fusion-Solvent Technique:**

An emulsion of the drug(s) as well as carrier(s) is/are created by melting the carrier(s). It is unnecessary to remove solvents from carrier if it can contain particular amount of liquid while preserving its solid qualities. Useful for medications with higher melt point or those that are thermodynamically unstable

**iv) Spray Drying:**

In an appropriate solvent, carrier and active component are dissolved and suspended. When stream of warm air is used to remove solvent, solvent is vaporized by allowing it to dry. Solid dispersion is created fast because of huge surface area of droplets.

**v) Lyophilization:**

(Spray Freeze Drying Technique) Preparation of solid dispersions has been made easier using this technique.

**vi)** **Ambient temperature:**

Spray freeze drying at low temperature to prevent overheating medications that are sensitive to heat (SFD). To create frozen micronized powder, feed liquid comprising APIs and excipients that are not or only weakly soluble in water is atomized in cryogenic liquid at room temperature and then dried. The amorphous nature and huge surface area of this procedure make it superior to more typical methods for solid dispersions. [38-39]

**Vii) Hot-melt Extrusion:**

In the polymer sector, this is technique of choice, but first people to employ this technology for medicinal purposes were speiser and huttenrach. Sections of a melt extrusion are as follows: Extruding mass may be shaped by an optional die at extrusion port, which has an aperture for raw materials to be fed into the heated barrel. When using an extruder, a steady stream of active ingredients and carriers are delivered into its heated barrel at regular intervals. An active substance and carrier combination is turned into a "fluid like condition" when heated screws are used to transfer it. Higher shear of extruder screws provides for an intimate and homogenous mixing of the materials. It is possible to shape the melt into pellets,granules, powder or films by using an exit port that includes an optional die. Hot melt extrusion approach has benefit of simply heating the drug/carrier combination for approximately one minute, making it possible to process drugs that are moderately thermo-labile. [40]

**Viii) Dropping Technique:**

Once the drug carrier mix is pipetted, it is deposited onto the plate, where it hardens into spherical pieces. The pipette's size and the melt's viscosity may both affect particles' size and form. Because viscosity is so temperature dependant, it's critical to get melt to solidify into sphere when it's dropped on plate. [41]

**IV. SUPERCRITICAL FLUID PROCESS:**

Non-volatile solvents may be dissolved by supercritical fluids (SCFs), which have a crucial stage of carbon dioxide. A safe, ecologically sustainable and cost-effective option is available to you. When it reaches its crucial pressure and temperature, a SCF is a single phase. SCFs offer qualities that are advantageous for product processing since they are transitional between liquid and gas. It is also important to note that variations in operating temperature, pressure, or both may have a significant impact on the density, transport qualities (like viscosity & diffusivity), as well as other physiological characteristics (like dielectric constant and polarity). SCFs have long been used in food sector because of their unique processing characteristics, which have lately been modified for medicinal use. Coalescing solvents such as carbon dioxide and nitrous oxide are among the most often utilized supercritical solvents. Several SCF processing techniques have been developed to address specific parts of such problems, like precipitation using compression antisolvent sprocess, rapid expansion of Supercritical Solutions, Gas antisolvent , recrystallization, precipitation and impregnation or infusing of polymers containing bioactive ingredients, Compressed Fluid Antisolvent, Solution increased Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF, aerosol supercrystallization (SAS). [42]

**Benefits of supercritical fluid procedure**

1. SCFs are well-suited for pharmaceutical research because of their low operating temperatures and pressures.

2. Solubilized drug particles may then be re-crystallized at more small particle size after they have been dissolved in S.C.F. Current S.C.F methods has showed capacity to generate nano suspensions with particles 5-2,000nm in diameter.

3. It is possible to micronize medicine particles to sub-micron levels using SCF methods because of its flexibility and precise control over particle size.

**V. LIQUISOLID TECHNIQUES:**

As soon as drugdissolved liquid is mixed in an absorbent carrier material, such as cellulose, liquid is initially absorbed inside of particles afterwards saturation through internal structure is captured, the liquid is adsorption on external& internal surfaces of porous carrier particles takes place. A high-adsorbent covering material with a substantial particular surface area provides liquisolid system with suitable flow characteristics.. It is possible to cover with cellulose and silica particles, both microcrystalline and amorphous. [43]

**Benefits of Liquisolid Methods**

1. Provides powdered versions of liquid pharmaceuticals that are easily flowable and compressible.
2. Develops bioavailability& solubility of water insoluble medications when taken orally.
3. For the production of viscous or liquid pharmaceuticals, this is an excellent choice.
4. Different carriers and additives, such as PVP, PEG 60000, Hydroxy Propyl Methyl Cellulose and Eudragit, may be used to alter drug release.
5. It's possible to incorporate a variety of poorly soluble medications into the system.
6. The powdered liquid pharmaceuticals are the focus of this particular approach.
7. When compared to the cost of preparing soft gelatin capsules, the production cost is minimal.

**Drawbacks of liquisolid method:**

1. Adsorption characteristics and particular surface area are essential.
2. High doses of insoluble medicines are exempt from this rule. (>100 mg)

**2.7) Novel solubility augmentationscomprise**

**Spherical Agglomeration:** As part of crystallization process, spherical crystallization method uses an agglomeration approach to condense crystals into spherical shape. Reduces tablet size by removing significant quantities of fillers and enhances flowability and compression properties of active pharmacological constituents by reducing quantity of fillers in formulation.

**Melt Sono Crystallization** – Pharmacological characteristics of Rosiglitazone (R.S)-5-4-(2[methyl (pyridine-2-yl)amino]ethoxy benzyl] may be altered by application of particle engineering techniques. insulin sensitizer thiozolidione-2-4-dione, Melt sono crystallization (MSC) acts through binding withpPAR receptor into fat cells and enhancing insulin sensitivity.

**The Prodrug Approach** – To achieve intended pharmacological impact inside body, prodrugs must be changed in vivo from an inactive, bioreversible by-product of an active drug molecule. Prodrug development may be difficult, but it is viable option for improving the unpredictable features of medications already in research or already on market.

**Nanotechnology Approaches** – Increasing the solubility and dissolution rate of pharmaceuticals may be accomplished by preparing them as nanoparticles with large specific surface areas. Fluid bed coating is used to fix nanoparticles onto polymer carriers so that they may be administered in a solid dose form. This may be done either orally or intravenously, depending on how nanoparticles are created.

**Conclusion:**

We conclude in this review paper that a compound's solubility is critical and plays a significant role in medication formulation and development. Compounds or medications with low solubility may benefit from any or all of the approaches listed above, whether applied alone or in combination. Increased solubility also improves patient compliance and enhances the absorption of a less soluble medication. The choice of any approach to improve solubility is dependent on the type, and features of medication, like its chemical nature, pharmacokinetic behavior, physical characteristics, etc.

icle we conclude that the solubility of the

drug is the most critical factor in the formulation

development that controls the therapeutic efficacy of the

drug. The various techniques described above can be used to

enhance the solubility of the drug. The choice of the method

will be based on its effectiveness as well as safety in terms of

biocompatibility of the excipient used. A lot of research has

been carried out in this area and some improvements in

solubility and dissolution rate has to be made generally.

Researcher working on solubility enhancement may use

following techniques Chemical modification methods like

Salt formation, Co-crystallization, Co-solvency, Hydrotropy,

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