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Review Article

Techniques for Increasing Solubility: A Review of Conventional and New Strategies

Keerti Yadav[1]*, Anupam Kr. Sachan[2], Kiran[3], Sunil Kumar[3], Anubhav Dubey[4]

[1]Department of Pharmaceutics, Dayanand Dinanath College Institute of Pharmacy, Kanpur Uttar Pradesh, India.
[2]Associate Professor, Dayanand Dinanath College Institute of Pharmacy, Kanpur Uttar Pradesh, India
[3]Assistant Professor, Dayanand Dinanath College Institute of Pharmacy, Kanpur Uttar Pradesh, India
[4]Assistant Professor Department of Pharmacy, Maharana Pratap College of Pharmacy, Kanpur Uttar Pradesh, India

A B S T R A C T

Whenever a drug's success depends on its ability to disperse evenly in the liquid phase, solubility is a critical factor. Most active pharmacological compounds, on the other hand, are poorly soluble in water. The solubility of the medications is one of the most difficult parts of formulation creation. Due to a lack of water solubility, critical ingredients are left out of final medications, preventing them from reaching their full therapeutic potential. Due to poor water solubility, many novel medicines fail to launch in the market, despite their promising pharmacokinetic properties. Solubility in water limits the potential bioavailability of molecules that would otherwise have a significant impact on their physiological target. To achieve the desired (anticipat5ed) pharmacological response in the systemic circulation, aqueous solubility of a drug also affects the physical, chemical, dose stability, severs as a standard for purity, dissolution rate, rate and extent of absorption, and achieves the desired concentration of the drug in systemic circulation. When it comes to the formulation of medications, solubility is an extremely essential issue. A new API with high market demand must be developed by the formulation scientist if the molecule is to make it through the pharmaceutical development process. Solubilization techniques, such as chemical modification using solubilizers such as soluplus, povacoat, and dendrimers, as well as physical modification, complexation, and the use of surfactant, are being discussed in this review article because they are becoming increasingly important to the pharmaceutical industry by opening up new pathways for the preparation of effective and marketable drugs.

Key Words: Solubility, Critical factor, Bioavailability, Complexation, Dissolution.

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***Address for Correspondence:**
Keerti Yadav, Research Scholar, Department of Pharmaceutics, Dayanand Dinanath College Institute of Pharmacy, Kanpur Uttar Pradesh, India.

INTRODUCTION

Solubility is a substance's property in a solvent. It is the concentration of dissolved solute in a saturated solution at a given temperature. In terms of quality, it is a clear homogenous molecular dispersion. It is the highest solute concentration in a solvent at equilibrium. A saturated solution is the name given to the resulting solution. A solubility chart lists ions and how they can precipitate or remain aqueous when mixed with other particles.[1, 2]Solubility equilibrium occurs when a solid chemical substance demonstrates chemical equilibrium with a solution of that compound. Pharmaceuticals rely on solubility equilibria. Poor aqueous solubility (Class II or even Class IV BCS chemicals) causes dissolving and absorption issues. Solubility can be described quantitatively as parts, molarity, normalcy, formality, mole fraction percent solution, volume fraction, and molality.

Table1: Solubility Expression [3]

Definition	Parts of solvent required for one part of
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	From 1000 -10,000
Insoluble	Greater than 10,000

Possible Causes for Poor Oral Absorption [4] any drug is saidto be poorly soluble when:

- Aqueous solubility <100µg/ml.
- Poor dissolution: Intrinsic dissolution rate <0.1 mg/cm^2/min,
- High molecular weight: (>500), Self association and aggregation.
- High crystal energy.

Process of Solubilization [5]

Step 1: The process of solubilization involves the breaking of inter- ionic or intermolecular interactions in the solute, the separation of the interactions between the solvent and the solute molecule or ion

Step 2: A solid molecule separates from the bulk.

Step 3: Insert solid molecule feed into Solvent hole.

Biopharmaceutics classification system (BCS)

The FDA introduced the Biopharmaceutics Classification System (BCS) which divides drugs into four classifications based on permeability and solubility.Due to low solubility, Class II and IV of the system encounter dissolution as the rate limiting step for drug absorption.

Table: 2 BCS Classification of Drug. [6]

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

Factors Affecting Solubility [1, 5]

Particle size: The size of the particles has an effect on their solubility. The surface area to volume ratio increases as the size of the particles decreases. As the surface area of a particle rises, the particle's contact with the solvent becomes more intense. [5]The following equations can be used to describe the effect of particle size on solubility:

Where,

S is the solubility of infinitely large particles

$\mathbf{S_0}$ is the solubility of fine particles

V is molar volume

γ is the surface tension of the solid

r is the radius of the fine particle

T absolute temperature in degree Kelvin.

R universal gas constant.

Temperature: Temperature has an effect on solubility. Energy is absorbed by the solution process, hence the solubility will grow. warming up in the process. The solubility decreases as the temperature rises if the solution process releases energy.[8]

Molecular size: This decrease in solubility is due to the difficulty of surrounding larger molecules with solvent molecules in order to solvate substances with higher molecular weights and larger molecular sizes.

Nature of solute and solvent: How solutes and solvents interact with each other is determined by their concentration and the temperature at which they are mixed. One gramme of lead (II) chloride dissolves in 100 grammes of water at room temperature, but 200 grammes of zinc chloride dissolves in 100 grammes of water with the same concentrations of water.[4]

Pressure: The solubility of gaseous solutes increases as pressure rises, while the solubility decreases as pressure falls.

Solubility is unaffected by pressure variations for both solids and liquids**.**

Polarity: Solubility is affected by the polarity of both the solute and the solvent molecules. As a general rule, polar solute molecules will dissolve in polar solvents, whereas non-polar solute molecules will dissolve in non-polar solvents.

Polymorphs: Polymorphism refers to a substance's ability to crystallize in more than one crystalline state. Polymorphism is the ability of an agent to crystallize in several forms. If a solid crystallizes in a variety of ways, it is feasible that it will take on numerous shapes. A polymorph's melting point can be different. Polymorphs will have varied solubility since the melting point of a solid is linked to solubility.[4]

Techniques to Overcome Poor Solubility [7-14]

Chemical Modifications:

- Salt Formation
- Co-crystallization
- Co-solvency
- Hydrotropy
- Use of novel solubilizer
- Nanotechnology

Physical Modifications:

- **Particle size reduction**
- Conventional method
- Micronization
- Nanosuspension

Modification of the crystal habit

- Polymorphs
- Pseudopolymorphs
- **Complexation**
- Physical mixture
- Kneading method
- Co-precipitate method

Inclusion Complex Formulation Based Techniques

- Kneading method
- Lyophilization/ Freeze- drying Technique

- Microwave irradiation method

Solubilization by surfactants

- Microemulsions
- Self microemulsifying drug delivery system

Drug dispersion in carriers

- Solid solutions
- Solid dispersions
- Fusion Process
- Solvent Method
- Fusion solvent method
- Spray drying
- Lyophilization (Spray Freeze Drying Method)
- Hot melt Extrusion
- Dropping Method
- pH adjustment
- Supercritical fluid process
- Liquisolid technique
- Polymeric alteration

CHEMICAL MODIFICATIONS

Salt formation:

Sometimes an API cannot be defined in its pure form due to instability difficulties. So they become salts, co-crystals, solvates, hydrates, and polymorphs. Each one affects the drug's performance attributes such as stability, bioavailability, purification, and manufacturability. Increasing the solubility of weakly soluble therapeutic candidates (weak acids and bases) has been done for decades. When a compound ionizes in solution, salts form. It works well in parenteral, liquid, and solid dose forms. Acid or basic medication transformed to salt with higher solubility. Barbiturates,Theophylline, etc. Progesterone, a water-insoluble steroid, is commercially available in peanut oil [15].

Co-crystallization: [16] Co-crystallization affects molecular interactions and may be used to improve medicinal characteristics.

A co-crystal is a "multi-component crystal formed between two chemicals that are solids at ambient conditions, with at least one component being an acceptable ion or molecule." (Source) Co-crystallization solves an API's physical, chemical, and physiological flaws. Co-solvency promotes nonpolar solute solubility by lowering interfacial tension. Analytical approaches and rational physicochemical research can be used to pick the best co-crystal. The only distinction between solvates and co-crystals is their physical condition. Solvates are formed when one component is liquid and the other is solid. Co-crystals are formed when both components are solid. Pharmaceutical The API and the co- crystal former are the two main components of co- crystals (s).

Different techniques for co crystallization 1)Solvent evaporation 2)Grinding 3)Slurry Co - Crystallization 4)Solvent drop grinding (Modification of Grinding) 5)High throughput co- crystallization [17] 6)Hot melt extrusion 7) Sonocrystallization Method.Co Crystals Characterization Parameters 1) Solubility 2) Maximum wavelength 3) Stability 4) Intrinsic dissolution 5) Bioavailability 6) Melting Point 7) Melt (Hot stage microscopy) 8) Scanning Calorimetry (DSC) 9) XRD 10) Vibrational spectroscopy.

3-Co-solvency/Solvent Blending: It improves the solubility of poorly water soluble drugs by lowering the interfacial tension between aqueous solution and hydrophobic solute. The drug is always liquid .Poorly soluble lipophillic or crystalline substances with high solubility in the solvent combination may be co-solvent candidates. It is used in parenteral dosage forms due to low toxicity of several co-solvents and their capacity to solubilize nonpolar medicines. Co-solvents include glycerol, propylene glycol, PEG 400, dimethyl sulfoxide, dimethyl acetamide, ethanol, and n-octanol. [18-19]

Advantages of co-solvency/solvent Blending

The formulation, production, and evaluation of this medicine are simple and rapid, despite its high solubilization capability for poorly soluble pharmaceuticals.

Using various solubilization techniques as well as pH manipulation, it can be used in conjunction with other methods to increase the solubility of weakly soluble substances.

Disadvantages of co-solvency/solvent Blending

It is necessary to examine the toxicity and tolerance of the solvent in relation to the concentration provided.

When diluted with aqueous medium, precipitation can occur, sometimes in an uncontrolled fashion.

Precipitates can be amorphous or crystalline in nature, and their sizes can vary.

Many of the insoluble compounds are unsuitable for co-solvents, which makes them particularly unsuitable for intravenous delivery.

It is possible that the injection site will experience embolism and other local adverse effects if the medications used are particularly insoluble in water and do not rapidly redissolve following precipitation from the co-solvent mixture.

As is true of all solubilized drugs, the chemical stability of the insoluble drug is reduced when compared to when it is in its crystalline form.

Hydrotrophy: When a substantial amount of a second solute is added to an existing solute, the solubilization of the current solute increases in aqueous solution, which is known as a solubilization phenomenon. More specifically, the mechanism by which it enhances solubility is more directly associated with complexation, which involves just a modest interaction between hydrotropic agents such as sodium benzoate, sodium acetate, sodium alginate, or urea and the medications that are poorly soluble.Ionic organic salts are used as hydrotropic agents. Hydrotropic solutions do not exhibit colloidal features and include just a weak contact between the hydrotropic agent and the solute in their composition. [20]

Table: 3 Classification of hydrotropes.

Category	Example
Aromatic anionics	Sodium benzoate, Sodium salicylate, Sodium benzene sulphonate, Sodium benzene disulphonate, Sodium cinnamate.
Aromatic cationics	Para amino benzoic acid hydrochloride, Procaine hydrochloride, Caffeine.
Aliphatics and linear anionics	Sodium alkanoate.

Advantages of hydrotrophy

Hydrotropy is suggested to be superior to other solubilization 0method, such as miscibility, micellar solubilization, co solvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.

Solvent character is independent of pH, hydrotrophy has highselectivity and does not require emulsification.

It only requires mixing the drug with the hydrotrope in water and do not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

Wide variety of compounds has been reported to exhibit hydrotropic behavior. Examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, and b- naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene.

Mixed Hydrotropy [21]: It is new, simple, cost effective, safe, accurate, precise method which involves the blends of hydrotropes which gives synergistic effect on solubility of poorly water soluble drug.

Advantages of mixed hydrotropy

It may reduce the large total concentration of hydrotropic agents necessary to produce modest increase in solubility by employing combination of agents in lower concentration.

The use of hydrotropic solubilizers as permeation enhancers.

Application of hydrotropic solubilisation in nanotechnology (bycontrolled precipitation).

Use of novel solubilizer: The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. Conventional solubilizer Polysorbates, PEG 400 Sepitrap, [22] Soluplus [23] Povacoat, dendrimers, is improve the solubility of hydrophobic API.

Sepitrap as novel Solubilizer In less than 5 minutes, 80 % of solubilizers are desorbed from Sepitrap^{TM} (Microencapsulated solubilizer for solid dosage application) and therefore is available to solubilize the drug substance. The ratio of sepitrap and drug (2:1) is good for enhancing dissolution rate and at the same time does not affect tablets characteristics and can be used without any formulation constraints. [24]

Dendrimers [25] are recognized for their three-dimensional, monodispersed, highly branching, macromolecular nano-scopic architecture with number of reactive end groups generated by reiterative reaction sequences. Dendrimers are static unimolecular micelles whose structure is stable at high solvent concentrations. Dendrimers' micelle-like behaviour led to its use to solubilize hydrophobic medicines. Dendrimers increase hydrophobic contacts, hydrogen bonding, and electrostatic interactions between dendrimer terminal functional groups and hydrophobic groups. Polyamidoamine (PAMAM) and polypropyleneimine (PPI) dendrimers are the most frequent.

PAMAM dendrimers appear to be the most studied in solubilization. Brabander and Meijer discovered an important family of dendrimers called poly (propylene)imine dendrimers (PPI).They resemble PAMAM dendrimers (except repeating units).

Nanotechnology: Refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometres (nm) or less. For many new chemical entities of very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has very low effective surface area for dissolution and next step taken was nanonisation [26]. The methods of preparation like milling, high pressure homogenization, vacuum deposition, and high temperature evaporation may be used.

Advantages of nanotechnology

It results in production of the nano or micro sized spherical particles with smooth surfaces and narrow particle size distribution and high specific surface areas, consequently increasing the dissolution rate and solubility.

Disadvantage of nanotechnology

The agglomeration problem is inherent and difficult to overcome.

PHYSICAL MODIFICATIONS:

Particle size reduction Solubility of drug is often intrinsically related to drug particle size. As particle size become smaller, surface area to volume ratio increases. Larger surface area allows grater interaction with the solvent which causes an increase in solubility. The bioavailability of poorly soluble drugs is often related to drug particle size. Increased surface area by reducing particle size improves the dissolution properties and allows a wider range of formulation approaches and delivery technologies. [27, 28]

Advantages of particle size reduction

It is efficient, reproducible, economic means of solubility enhancement.

Increase the rate of solution in case of chemical substances, because reduction of particle size increases the surface area for the action of solvent.

Allows rapid penetration of solvent.

Disadvantages of particle size reduction

Due to high surface charge on discrete small particles, thereis strong tendency for particle agglomeration.

Physical, mechanical stress may induce degradation of activecompound.

Thermal stress which occurs during comminution may present problems in processing of thermosensitive agents.

Developing solid dosage form with a high pay load without encouraging agglomeration and sterile intravenous formulation is technically challenging.

Conventional method of particle size reduction Different mechanisms involved in conventional method of particle size reduction are cutting, compression, impact, attrition, combined impact and attrition. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an economic, reproducible, and efficient means of solubility improvement. However, the mechanical forces natural to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also considered when processing thermo sensitive or unstable active agents. Only by using traditional methods of solubility enhancement it is not possible to increase the solubility of poorly soluble drugs upto desirable level.

Micronization: It is a high energy particle size reduction technique that can convert coarse particles into particles of less than 5 μ in diameter. Micronization results in uniform and narrow particle size distribution essential for developing uniform dosage form. As micronization occurs surface area increases with decreasing particle size and solubility increases. The properties of the micronized drug substance such as particle size, size distribution, shape, surface properties, and agglomeration behavior and powder flow are affected by the type of micronization technique used. Mechanical communition, spray drying and supercritical fluid (SCF) technology are the most commonly employed techniques for production of micronized drug particles. According to the Noyes–Whitney postulations, the administration of a drug in micron size is a prominent method to improve bioavailability of poorly water soluble drug substances.

Techniques for Micronization

- Jet milling /fluid energy mill or micronizer
- Rotor stator colloids mills
- Microprecipitation & microcrystallization
- Controlled crystallization
- Supercritical fluid technology
- Spray freezing in to liquid

Advantages of micronization

Gives uniform particle with increase in surface area and narrow particle size distribution.

Disadvantages of micronization

High energy process, which causes disruption in the drug crystal lattice and this, may result in presence of disordered or amorphous regions in the final product.

Amorphous regions are thermodynamically unstable and are susceptible to recrystallization upon storage particularly in hotand humid conditions.

Nanosuspension: This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is biphasic systems consisting of nano sized drug particles in aqueous vehicle stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. [29] Nanosuspension is produced by bottom up technology and top down technology. Top down technology involves various methods such as nano edege, nanojet technology, milling tech (Nanocrystals).

Advantages of nanosuspension

In nanosuspension the particle size of drug is reduced which increases the surface area which in turn increases solubility, dissolution rate, and ultimately bioavailability.

Nanosuspension results in permeability enhancement.

Nanosuspension results in increases in bioadhesion and duration of action of residence.

Nanoformulation exerts advantage of high drug loading.

Avoidance of organic solvent.

Disadvantages of nanosuspension

Suffers from problem of instability due to agglomeration, crystalgrowth, Ostwald ripening.

Modification of the crystal habit

- Polymorphs
- Pseudopolymorphs

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability. Similarly amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase in surface area. Order for dissolution of different solid forms of drug Amorphous

>Metastable polymorph >Stable polymorph

Complexation: Is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometry. [30] Two type of complex:

Stacking complexes: It is driven by association of non-polar area of drug and complexes agent this results in exclusion of the non-polar area from contact with water. Stacking can be homogeneous or mixed, but results in clear solution.

Inclusion complexes: It is formed by the inserting the nonpolar molecule, region of one molecule into the cavity of another molecule or group of molecules. Cyclodextrine and their derivatives commonly used in complexation.

Solid ternary complexes can be formed with

Carboxylic acid [31] – eg. citric acid, tartaric acid

Water soluble polymer[32] – Soluplus,[23] Povacoat,Kollidon,

Amino acid [33]- Arginine, tryptophan, leucine, phenylalanine, methionine, and isoleucine

Sugar alcohol[34] – Mannitol

Ternary agent helps in binding of drug and with complexing agent. Most probably use of acidic ternary compound in case of basic drug or vice versa that is use of basic ternary compound with acidic drug is done to form solid ternary complex. Water soluble polymer may be used in specific concentration for example 0.5% or 1% by preparing its aqueous solution. Drug, B-CD and amino acid such as L- Lysine and Arginine ternary complexes may be prepared at 1:1:2 molar ratios, or weight ratio or other suitable ratio.

Physical mixture: in this the CDs or suitable polymer and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product. It is simple trituration method.

Kneading method: This process involves soaking CDs or other appropriate polymers in water or hydro alcoholic solutions to form a paste. The medicine is then added and kneaded for a period. The kneaded dough is dried and sieved.

Co-precipitate method: Medications are added into the CDs or polymer solution in the appropriate amount. Magnetic agitation of the compound under controlled conditions. The entire complex has been darkened. The precipitate is vacuum filtered and dried at room temperature to prevent the loss of inclusion complex structure water from the inclusion complex structure. This is a highly industrialised procedure.

Inclusion Complex Formulation Based Techniques:

Inserting guest molecules or nonpolar areas into holes of other molecules (known as inclusion complexes) (known as host). Cyclodextrins are hosts. Host cavity must be big enough for visitor but small enough to drain water. Included in the preparation are kneading, co-precipitation, neutralisation and co-grinding.[35]

Kneading method: discussed in complexation

Lyophilization/Freeze-Drying Technique: By freezing and then drying the solution, the solvent system can be removed from the solution without harming the sample. The unique properties of water as a solvent, gas, diluent, plasticizer, stabiliser, and more are critical to the lyophilization process. Instead of evaporating them, the drug and carrier are molecularly combined in a shared solvent.

Advantages of lyophilization/freeze-drying technique

Lyophilization/freeze drying technique is considered worthyto get a porous, amorphous powder with high degree of interaction between drug and suitable polymer.

Thermolabile substances can be successfully made into complex form by this method.

Disadvantages of lyophilization/freeze-drying technique

Use of specialized equipment.

Time consuming process, and yield poor flowing powdered product.

Microwave Irradiation Method: Involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60 ^{o}c in the microwave oven. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate is separated by whatman filter paper, and dried in vacuum oven at40 ^{o}c for 48 hrs.

Solubilization by surfactants:

Surfactants are polar and nonpolar compounds. They have a hydrocarbon segment attached to a polar group. Any of these polar groups can be anionic or cationic. Small polar molecules can concentrate in the micelle's hydrophobic centre. This process is vital in industrial and natural processes. Surfactants reduce surface tension and promote drug solubility by promoting lipophilic drug dissolution in aqueous media. Surfactants also stabilise medication suspensions. When surfactant concentration exceeds critical micelle concentration (CMC,Micelle formation happens at low concentrations (0.05–0.10 percent for most surfactants), encasing pharmaceuticals within micelles. This process is known as micellization, and it increases poorly soluble drug solubility.

Microemulsions:

In an optically clear pre-concentrate, a hydrophilic surfactant and a hydrophilic solvent dissolve a poorly water soluble medication. The surfactant must be HLB and non-toxic. It generates a transparent emulsion of small uniform oil droplets that contain the solubilized poorly soluble medication. Micro-emulsions have been used to enhance the solubility of numerous medications that are practically insoluble in water. The bes formulation is an oil-in-water microemulsion, which will boost solubility by dissolving molecules with low water solubility into an oil phase. Because surfactant-induced permeability alterations can increase oral bioavailability, they can also increase oral bioavailability. [14]

Advantages of micro emulsions: Simplicity of preparation, clarity, ability to be filtered and incorporate a wide range of drugs of varying solubility.

Self-emulsifying drug delivery systems: Utilizes the concept of in situ emulsion creation in the digestive tract. The mixture of oil, surfactant, co-surfactant, one or more

hydrophilic solvents, and co-solvent that forms the self-emulsifying drug delivery system is a transparent isotropic solution (SEDDS). Self-emulsifying drug delivery systems (SEDDS) and self microemulsifying drug delivery systems (SMEDDS) are isotropic solutions of oil and surfactant that, with gentle agitation in the presence of water, generate oil-in-water microemulsions. On oral administration, these new colloidal formulations act like oil-in-water microemulsions.

Drug dispersion in carriers [36]: Solid solution is blend oftwo crystalline solids that exist as a new crystalline solid. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, it is expected to yield much higher rates of dissolution than simple eutectic systems. **Amorphous precipitation:** Amorphous precipitation occurs when drug precipitates as an amorphous form in inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystallineforms of the drug.

Applications of solid dispersions It is possible that such a technique be used: [37]

Obtaining a homogenous dispersion of a minute amount of medicine in solid state is the goal of this procedure.

- To keep the medication from becoming unstable.
- The ability to administer liquids (up to 10% of the total volume) or gaseous substances in a solid dose.
- To create a fast-acting main dose in a sustained-release dosage form for administration.
- To minimize the amount of time that medications such as morphine and progesterone are inactive before they enter the system.
- To develop a prolonged release regimen for soluble medications by including carriers those are poorly soluble or insoluble.
- To turn polymorphs in a particular system into isomorphous solids by combining them.

Advantages of solid dispersion [38]

1. It has a high rate of dissolution and is easy to use.
2. Increase the rate at which medications are absorbed.
3. Increase the dissolvability in water of a poorly water-soluble medication in a pharmaceutical formulation.
4. Transform the drug's crystalline structure into an amorphous state by heating it.
    - Prepare rapid disintegration oral tablets.
    - Mask the taste of the drug substance.
    - Avoid degradation or decomposition of drugs. Transformation of the liquid form of the drug into a solid form (Ex. Clofibrate and Benzoyl benzoate can be incorporated into PEG-6000 to give a solid.)
    - Avoidance of polymorphic changes and there by bioavailability problems,

Disadvantages of solid dispersion [38]

- Instability of solid dispersion.
- Moisture and temperature have deteriorating effect on soliddispersion.
- It shows crystallinity and decrease in dissolution rate withaging.

Limitations of solid dispersion system

Unpredictability of solid dispersion behaviour due to ignorance of material properties.

The amorphous condition may crystallise during processing (mechanical stress) or storage (temperature and humidity stress).

Moisture can affect the storage stability of amorphous medicines by increasing drug mobility and crystallisation.

Most polymers employed in solid dispersions absorb moisture, causing crystal formation, phase separation, or conversion from amorphous to crystalline state during storage, reducing solubility and dissolution rate.

Methods of preparing solid dispersions

Fusion Process [39]: The carrier is heated to a temperature just above its melting point and the drug is incorporated into thematrix. The mixture is cooled with constant stirring to homogeneously disperse the drug throughout the matrix. Other factors that may play a role include solubilizing effect conferred by the carrier itself, improved wetting or decreased surface hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form of altered thermodynamic properties.

Disadvantages

Exposure of drugs to elevated temperatures, particularly if the carrier is a high-melting solid and the drug is thermoliable.

Solvent Method: They are dissolved in an organic solvent. This solvent is vaporised at high temperatures. Subsequent to the removal of the solvent, super saturation occurs, followed by precipitation of the contents. The co precipitate is then vacuum dried to remove any solvent remaining on the particle. The solvent must be removed completely. Differential thermal analysis (DTA), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA) are highly sensitive techniques that can show total solvent elimination.[40]

Fusion-Solvent Method: Carrier(s) is/are melted and the drug(s) is/are incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal is eliminated. Method is useful for drugs with high melting points or that are thermolabile.

Spray Drying: The carrier and the active ingredient are dissolved, suspend in a suitable solvent. This solvent is evaporated by drying it to apply a stream of heated air to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates and solid dispersion is formed quickly.

Lyophilization (Spray Freeze Drying Method)

This is the polymer industry's choice. But it was Disperse and Huttenrach that used this method to drugs. Melt extrusion sections include: Warming and mixing the feed materials in a heated barrel, with an exit outlet and optional die to form the extruding mass. The heated extruder barrel feeds the active components and carrier.

The "fluid-like state" is created by heating the screws that carry the active component. Extruder screw shear allows for close and homogeneous mixing. A die shapes the melt into granules, pellets, films, or powder. Hot melt extrusion heats the drug/carrier mix for roughly a minute, allowing processing of thermolabile medicines. [44]

Hot-melt Extrusion: The polymer industry prefers this technology. But it was Speiser and Huttenrach that used this technology for pharmacological purposes. Sections of a melt extrusion include:A heated barrel with extruder screws to convey and mix the fed materials, and an exit outlet with an optional die to shape the extruding mass. The active components and carrier are fed continuously into the heated extruder barrel. The "fluid-like state" is achieved by conveying the active component and carrier through heated screws. The strong shear of extruder screws facilitates close and homogenous mixing. An optional die moulds the melt into granules, pellets, films, or powder. The drug/carrier mix is only heated for about a minute in hot melt extrusion, which allows processing of thermolabile drugs. [44]

Dropping Method: Re - solidified drug-carrier mixture is pipetted into solid dispersion, which hardens into spherical particles. The particle size and form are affected by the viscosity of the melt and the pipette size. Considering that viscosity is strongly temperature dependant, it is critical that the melt solidify spherically when dropped on the plate. [45]

PH ADJUSTMENT

Poorly water-soluble drugs may be made water-soluble by altering the pH. The buffer capacity and tolerability of the chosen pH must be taken into account when attempting to access solubility this way. Therefore, alkalizing excipients may enhance the solubility of weekly acidic medications, whereas solubilized excipients increasing pH inside the dosage form to a range greater than or equal to pKa may increase the solubility of weekly basic drugs.[19]

Advantages of pH adjustment

- Simple to formulate and analyze.
- Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages of pH adjustment

- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability.
- Tolerability and toxicity both local and systemic related with the use of a non-physiological pH and extreme pH should be considered.
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

SUPERCRITICAL FLUID PROCESS:

Supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide. It is safe, environmentally friendly, and economical. A SCF exists as a single phase above its critical temperature and pressure. SCFs have properties useful to product processing because they are intermediate between thoseof pure liquid and gas. Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure or both around the critical points. Unique processing capabilities of SCFs, long recognized and applied in the food industry have recently been adapted to pharmaceutical applications. Commonly used supercritical solvents are carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), Rapid Expansion of Supercritical Solutions, Gas Antisolvent Recrystallization, Precipitation with Impregnation or infusion of polymers with bioactive materials, Compressed Fluid Antisolvent, Solution enhanced Dispersion by Supercritical Fluid, solution enhanced dispersion by SCF (SEDS), aerosol supercritical extraction system (ASES) and supercritical antisolvents processes (SAS) [46]

Advantages of supercritical fluid process

The low operating conditions (temperature and pressure) makeSCFs attractive for pharmaceutical research.

Once the drug particles are solubilized within SCF, they may be recrystallized at greatly reduced particle sizes. Current SCF processes have demonstrated the ability to create nano suspensions of particles 5-2,000nm in diameter.

The flexibility and precision offered by SCF processes allows micronization of drug particles within narrow ranges of particle size, often to sub-micron levels.

LIQUISOLID METHODS

Carrier materials with porous surfaces, like cellulose, absorb and adsorb liquids. This means that the liquid is initially absorbed into the interior of the particles, which are then saturated, and the liquid is then transferred to the external surface. This process occurs both before and after the drug is dissolved in liquid. Once the coating material has been added, the liquisolid system gains the necessary flow properties due to its high adsorptive capacity and large specific surface area. Coating materials include cellulose and silica powders, both crystalline and amorphous. [45]

Advantages of Liquisolid Methods

- Provides acceptably flowing and compressible powderedforms of liquid medications.
- Method improves the solubility, bioavailability of orally administered water insoluble and is applicable in industry.
- Useful for the formulation of oily drugs/liquid drugs.
- Drug release can be modified by using different carrier and additives like PVP, PEG 60000, Hydroxy Propyl Methyl Cellulose and Eudragit etc.
- A number of poorly soluble drugs can be formulated in to the system.
- This system is specifically for the powdered liquid medications.
- Production cost is low compared to that of preparation of soft gelatin capsules.

Disadvantages of liquisolid method:

- It requires recipients of high adsorption properties and high specific surface area.
- It is not applicable to high dose insoluble drugs (>100 mg).

POLYMERIC ALTERATION

Polymorphs are distinct crystalline forms of a medication that have varied characteristics. There are many polymorphs with varying physicochemical parameters such as melting point vapour pressure shelf life dissolution rate morphology morphology density bioavailability. Metastable crystalline polymorphs have higher energy, surface area, solubility, bioavailability, and efficacy than stable, unstable, and unstable polymorphs. To maximize bioavailability, drugs should be converted from crystal to metastable or amorphous forms over their shelf life.

CONCLUSION:

Orally administered medications' solubility is one of the rate-limiting parameters in achieving the necessary concentration in systemic circulation for pharmacological response, which is one of the most important factors to consider. For formulation scientists, the problem of solubility is a crucial obstacle to overcome. It is possible to successfully apply the strategies mentioned in this review, either individually or in combination, to increase the solubility of hydrophobic medications in order to increase their oral bioavailability; nevertheless, the effectiveness of the improvement is primarily dependent on the method used. When it comes to resolving the solubility concerns of hydrophobic pharmaceuticals, Nanosuspension, Super Critical Fluid, Cryogenic, and Inclusion Complex Formation are the most appealing approaches to use among the many available solubility.

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Declarations -

Conflict of Interest -The authors declare no potential conflicts of interest.

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REFERENCES

1. Awuchi, C. G., Amagwula, I. O., Priya, P., Kumar, R., Yezdani, U., & Khan, M. G. (2020). Aflatoxins in foods and feeds: A review on health implications, detection, and control. *Bull Environ Pharmacol Life Sci*, 2020; *9*(9):149-155.
2. Akhgari A, Shakib Z, Sanati S, A review on electrospun nanofibers for oral drug delivery. Nanomedicine Journal 2017; 4:197–207.
3. Alldredge BK, Corelli RL, Ernst ME, Guglielmo BJ, Jacobson PA, Kradjan WA, Williams BR (2013) Koda-kimble and Young's applied therapeutics: the clinical use of drugs. Wolters Kluwer Health Adis (ESP).
4. Alubaidy A, Venkatakrishnan K, Tan B, Nanofibers reinforced polymer composite microstructures. Adv Nanofiber 2013;7:165–184. https://doi.org/10.5772/57101
5. Bhanja S, Ellaiah P, Martha S, Sahu A, Padhy S, Preparation and evaluation of solid dispersions of poorly soluble drug repaglinide. Asian Journal of Biochemical and Pharmaceutical Research 2011; 3:201–221.
6. Bindhani S, Mohapatra S ,Recent approaches of solid dispersion: a new concept toward oral bioavailability. Asian Journal of Pharmaceutical and Clinical Research 2018; 11:72–78. https://doi.org/10.22159/ajpcr.2018.v11i2.23161
7. Broadhead J, Edmond Rouan S, Rhodes C, The spray drying of pharmaceuticals. Drug development and industrial pharmacy 1992; 18: 1169–1206. https://doi.org/10.3109/03639049209046327
8. Buckton G, Beezer AE (1992) The relationship between particle size and solubility. International journal of pharmaceutics 1992; 82:R7–R10. https://doi.org/10.1016/0378-5173(92)90184-4
9. Sahana, S. Purabi saha, Roshan kumar, Pradipta das, Indranil Chatterjee, Prasit Roy, Sk Abdur Rahamat. *A Review of the 2019 Corona virus (COVID-19) World Journal of Pharmacy and Pharmaceutical science*, 2020; *9*(9):2367-2381.
10. Chavan RB, Thipparaboina R, Kumar D, Shastri NR, Co amorphous systems: A product development perspective. International journal of pharmaceutics 2016; 515:403–415. https://doi.org/10.1016/j.ijpharm.2016.10.043
11. Chiou WL, Riegelman S (1971) Pharmaceutical applications of solid dispersion systems. Journal of pharmaceutical sciences 1971; 60:1281–1302. https://doi.org/10.1002/jps.2600600902
12. Davis ME, Brewster ME, Cyclodextrin-based pharmaceutics: past, present and future. Nature reviews Drug discovery 2004; 3:1023–1035. https://doi.org/10.1038/nrd1576
13. Dengale SJ, Grohganz H, Rades T, Löbmann K, Recent advances in co-amorphous drug formulations. Advanced drug delivery reviews 2016; 100:116–125. https://doi.org/10.1016/j.addr.2015.12.009
14. Bind, A., Das, S., Singh, V. D., Kumar, R., Chourasia, A., & Saha, P. Natural Bioactives For The Potential Management Of Gastric Ulceration. *Turkish Journal of Physiotherapy and Rehabilitation*, *32*, 3.
15. Duong AD, Ruan G, Mahajan K, Winter JO, Wyslouzil BE, Scalable, semicontinuous production of micelles encapsulating nanoparticles via electrospray. Langmuir 2014; 30: 3939–3948. https://doi.org/10.1021/la404679r

16. El-Nabarawi M, Khalil I, Saad R, Impact of hydrophilic polymer solubilization on bioavailability enhancement of repaglinide by solid dispersion. Inven Rapid Pharm Tech 2016; 3:1–12.

17. Gadadare R, Mandpe L, Pokharkar V, Ultra rapidly dissolving repaglinide nanosized crystals prepared via bottom-up and top-down approach: influence of food on pharmacokinetics behavior. AAPS Pharm SciTech 2015; 16:787–799. https://doi.org/10.1208/s12249-014-0267-8

18. Kumar, S., Kumar, A., Kumar, R., Kumar, V., Kumar, N., & Tyagi, A. Phytochemical, Pharmacognostical and Pharmacological Activities of Carica papaya. *International Journal for Research in Applied Sciences and Biotechnology*, 2022; *9*(2):310-315.

19. Goonoo N, Bhaw-Luximon A, Jhurry D, Drug loading and release from electrospun biodegradable nanofibers. Journal of biomedical nanotechnology 2014; 10:2173–2199. https://doi.org/10.1166/jbn.2014.1885

20. Guardado-Mendoza R, Prioletta A, Jiménez-Ceja LM, Sosale A, Folli F (2013) The role of nateglinide and repaglinide, derivatives of meglitinide, in the treatment of type 2 diabetes mellitus. Archives of medical science: AMS 9: e936. https://doi.org/10.5114/aoms.2013.34991

21. Guo B, Liu H, Li Y, Zhao J, Yang D, Wang X, Zhang T (2014) Application of phospholipid complex technique to improve the dissolution and pharmacokinetic of probucol by solvent-evaporation and co-grinding methods. International journal of pharmaceutics 2014; 474:50–56. https://doi.org/10.1016/j.ijpharm.2014.08.006

22. Gupte M, Ma P, Nanofibrous scaffolds for dental and craniofacial applications. Journal of dental research 2012; 91:227–234. https://doi.org/10.1177/0022034511417441

23. Hartgerink JD, Beniash E, Stupp SI, Self-assembly and mineralization of peptide-amphiphile nanofibers. Science 2001; 294:1684–1688. https://doi.org/10.1126/science.1063187

24. Hatorp V, Clinical pharmacokinetics and pharmacodynamics of repaglinide. Clinical pharmacokinetics 2002; 41:471–483. https://doi.org/10.2165/00003088-200241070-00002

25. Huang M, Hou Y, Li Y, Wang D, Zhang L, High performances of dual network PVA hydrogel modified by PVP using borax as the structure-forming accelerator. Designed monomers and polymers2017; 20:505–513. https://doi.org/10.1080/15685551.2017.1382433

26. Kabanov AV, Batrakova EV, Alakhov VY, Pluronic block copolymers as novel polymer therapeutics for drug and gene delivery. Journal of controlled release2002; 82:189–212. https://doi.org/10.1016/S0168-3659(02)00009-3

27. Karagianni A, Kachrimanis K, Nikolakakis I, Co-amorphous solid dispersions for solubility and absorption improvement of drugs: Composition, preparation, characterization and formulations for oral delivery. Pharmaceutics 2018; 10: e98. https://doi.org/10.3390/pharmaceutics10030098

28. Kumar, S., Kumar, A., Kumar, R., Kumar, V., Kumar, N., & Tyagi, A. Phytochemical, Pharmacognostical and Pharmacological Activities of Carica papaya. *International Journal for Research in Applied Sciences and Biotechnology*, 2022; *9*(2):310-315.

29. Kassem AA, Abd El-Alim SH, Basha M, Salama A (2017) Phospholipid complex enriched micelles: a novel drug delivery approach for promoting the antidiabetic effect of repaglinide. European journal of pharmaceutical sciences 2017; 99:75–84. https://doi.org/10.1016/j.ejps.2016.12.005

30. Kaushal AM, Gupta P, Bansal AK (2004) Amorphous drug delivery systems: molecular aspects, design, and performance. Critical Reviews in Therapeutic Drug Carrier Systems 21. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v21.i3.10

31. Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, Cho JM, Yun G, Lee J (2014) Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian journal of pharmaceutical sciences 2014; 9:304–316. https://doi.org/10.1016/j.ajps.2014.05.005

32. Khajavi R, Abbasipour M, Electrospinning as a versatile method for fabricating coreshell, hollow and porous nanofibers. Scientia Iranica 2012; 19:2029–2034. https://doi.org/10.1016/j.scient.2012.10.037

33. Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J (2020) Epidemiology of type 2 diabetes–global burden of disease and forecasted trends. Journal of epidemiology and global health 10: e107. https://doi.org/10.2991/jegh.k.191028.001

34. Dubey, A., Yadav, P., Verma, P., & Kumar, R. Investigation of Proapoptotic Potential of Ipomoea carnea Leaf Extract on Breast Cancer Cell Line. *Journal of Drug Delivery and Therapeutics*, 2022; *12*(1):51-55.

35. La SB, Okano T, Kataoka K, Preparation and characterization of the micelle-forming polymeric drug indomethacin-incorporated poly (ethylene oxide)–poly (β-benzyl L-aspartate) block copolymer micelles. Journal of pharmaceutical sciences 1996; 85:85–90. https://doi.org/10.1021/js950204r

36. Laitinen R, Lobmann K, Grohganz H, Strachan C, Rades T, Amino acids as co-amorphous excipients for simvastatin and glibenclamide: physical properties and stability. Molecular pharmaceutics 2014; 11:2381–2389. https://doi.org/10.1021/mp500107s

37. Lakshmi P, Kumar GA (2010) Nanosuspension technology: A review. Int J Pharm Sci 2: 35–40.

38. Loftsson T,Drug solubilization by complexation. International journal of pharmaceutics 2017; 531:276–280. https://doi.org/10.1016/j.ijpharm.2017.08.087

39. Lu Y, Li Y, Wu W, Injected nanocrystals for targeted drug delivery. Acta Pharmaceutica Sinica B 2016; 6:106–113. https://doi.org/10.1016/j.apsb.2015.11.005

40. Dubey, A., Yadav, P., Verma, P., & Kumar, R. Investigation of Proapoptotic Potential of Ipomoea carnea Leaf Extract on Breast Cancer Cell Line. *Journal of Drug Delivery and Therapeutics*, 2022; *12*(1):51-55.

41. Mandić Z, Gabelica V. Ionization, lipophilicity and solubility properties of repaglinide. Journal of pharmaceutical and biomedical analysis 2006; 41:866–871. https://doi.org/10.1016/j.jpba.2006.01.056

42. Mata J, Majhi P, Guo C, Liu H, Bahadur P.Concentration, temperature, and salt-induced micellization of a triblock copolymer Pluronic L64 in aqueous media. Journal of colloid and interface science 2005; 292:548–556. https://doi.org/10.1016/j.jcis.2005.06.013

43. Mogal S, Gurjar P, Yamgar D, Kamod A. Solid dispersion technique for improving solubility of some poorly soluble drugs. Der Pharmacia Lettre 2012; 4:1574–1586.

44. Möschwitzer JP, Drug nanocrystals in the commercial pharmaceutical development process. International journal of pharmaceutics 2013; 453:142–156. https://doi.org/10.1016/j.ijpharm.2012.09.034