"BEYOND SOLUBILITY: A RESEARCH FRONTIER ON BIOAVAILABILITY ENHANCEMENT FOR IMPROVEMENT THERAPEUTICS"

Sonal Akhand[1], Mohini Rithoriya[2], Akash Yadav[3]*, Dinesh Kumar Jain[4]

Abstract

Different strategies are used to increase the bioavailability of pharmacoactive molecules because their low water solubility limits their pharmacological potential but the solubility parameter cannot be compromised. Low solubility pharmaceutically active molecules indicate a higher chance of drug development and innovation failure. One of the biggest challenges in the field of pharmaceutical formulations is improving the solubility and bioavailability of medications. The classification of biopharmaceutics states that drugs in classes II and IV (APIs) have poor solubility, lower bioavailability, and less dissolution. The complexation of active molecules, the use of cosolvents, crystal engineering techniques, drug nanocrystals, emulsion formation, micelles, microemulsions, nanomorph technology, particle size reduction technologies, pharmaceutical salts, prodrugs, the solid-state alternation technique, soft gel technology and solid dispersion methods are just a few of the technologies that are discussed in this article to improve the solubility of poorly water-soluble drugs. This review focuses on a number of other cutting-edge techniques for improving solubility and bioavailability, including drug conjugates, cyclodextrins, solid lipid nanoparticles, micronization, solid dispersions, nanosizing, and colloidal drug delivery systems. It does this by citing a number of pertinent research reports.

Keywords: Bioavailability, BCS classification, solid dispersion, self-emulsifying drug delivery systems

[1,2,3*,4]IPS Academy College of Pharmacy, Knowledge Village, Rajendra Nagar, A.B. Road, Indore-452012

***Corresponding Author:** Dr. Akash Yadav
*IPS Academy College of Pharmacy, Knowledge Village, Rajendra Nagar, A.B. Road, Indore-452012, India.
Email: akashyadav@ipsacademy.org

DOI: 10.53555/ecb/2022.11.12.305

Introduction

Bioavailability refers to the extent a substance or drug becomes completely available to its intended biological destination.[1] More accurately, bioavailability is a measure of the rate and fraction of the initial dose of a drug that successfully reaches either; the site of action or the bodily fluid domain from which the drug's intended targets have unimpeded access.[2][3] For most purposes, bioavailability is defined as the fraction of the active form of a drug that reaches systemic circulation unaltered. This definition assumes 100% of the active drug that enters systemic circulation will successfully reach the target site.[4] However, one should understand that this definition excludes drugs that do not require access to systemic circulation for function (e.g., certain topical drugs). The bioavailability of these drugs is measured by different parameters discussed elsewhere.[5]

Bioavailability is an integral part of the pharmacokinetics paradigm. Pharmacokinetics is the study of drug movement through the body and is often represented by the acronym ABCD which stands for administration, bioavailability, clearance, and distribution. Administration refers to the route and dosing of a drug. Clearance is the active form of a drug being removed from the systemic circulation. Distribution measures how widely a drug can travel to fluid compartments of the body; this definition assumes distribution follows absorption if taken orally.[6]

The route of administration (ROA) and the drug dose can significantly impact both the rate and extent of bioavailability. The dose of a drug is indirectly proportional to its bioavailability. A drug with relatively low bioavailability requires a larger dose to reach the minimum effective concentration threshold. The various routes of administration each contain a unique capability to facilitate a certain plasma drug concentration for a certain length of time. In many cases, altering the route of administration calls for an alteration of the dosage. For example, an oral drug requires passage through the gastrointestinal (GI) system, subjecting it to intestinal absorption and hepatic first-pass metabolism.[7] On the contrary, an intravenous (IV) drug is assumed to be immediately delivered to the systemic circulation because it is not subject to absorption or first-pass metabolism to determine adequate dosage.

Rheumatoid arthritis is a chronic inflammatory disorder that can affect more than just your joints. In some people, the condition can damage a wide variety of body systems, including the skin, eyes, lungs, heart and blood vessels. An autoimmune disorder, rheumatoid arthritis occurs when your immune system mistakenly attacks your own body's tissues. Unlike the wear-and-tear damage of osteoarthritis, rheumatoid arthritis affects the lining of your joints, causing a painful swelling that can eventually result in bone erosion and joint deformity. The inflammation associated with rheumatoid arthritis is what can damage other parts of the body as well. While new types of medications have improved treatment options dramatically, severe rheumatoid arthritis can still cause physical disabilities. Signs and symptoms of rheumatoid arthritis may include:

- Tender, warm, swollen joints
- Joint stiffness that is usually worse in the mornings and after inactivity
- Fatigue, fever and loss of appetite

✓ **Symptoms:** These symptoms are clues to RA:

1. Joint pain, tenderness, swelling or stiffness that lasts for six weeks or longer.
2. Morning stiffness that lasts for 30 minutes or longer.
3. More than one joint is affected.
4. Small joints (wrists, certain joints in the hands and feet) are typically affected first.

The solubilization and bioavailability of poorly water-soluble medications can be improved by a number of strategies. Medication solubilization techniques include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, and others. A frequent challenge in both formulation design and development and novel chemical entity screening studies is the solubilization of pharmaceuticals that are poorly soluble.[8] Solubility is the maximum amount of analyte that can dissolve in a volume of solvent. Therefore, solubility refers to the maximum amount of analyte that can dissolve in a given volume of solvent. It is characterized by both quantitative and qualitative factors. It can be described as the spontaneous interaction of two or more substances to form a homogenous dispersion in qualitative terms. A substance's (solute's) concentration in a specific volume of solvent at a specific temperature to create a homogenous solution is expressed quantitatively. It is possible to express a drug's solubility as a percentage, part, molality, molarity, mole fraction, or volume fraction. Solubility equilibrium is a crucial concept in pharmaceuticals. BCS classes II and IV, which

are drugs with low water solubility, exhibit issues related to dissolution.[9]

Biopharmaceutical classification system

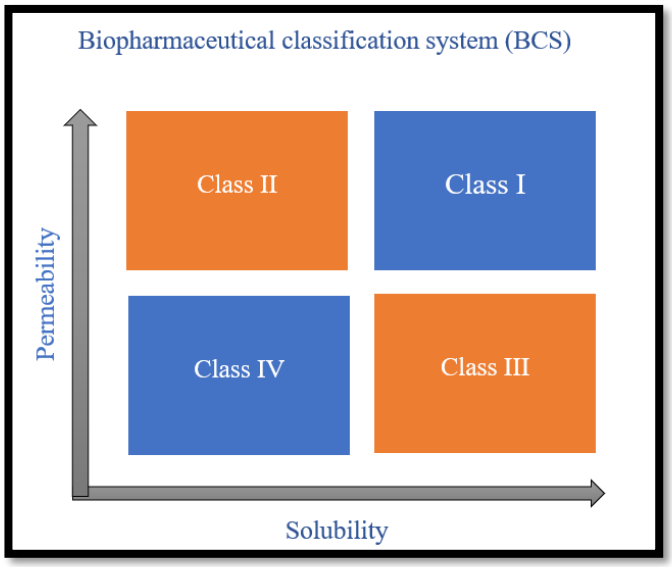

Fig. 1: BCS classification

Drugs are classified using the Biopharmaceutics classification system based on their permeability and solubility. Using the solubility and intestinal permeability parameters, this system limits the prediction. Using an aperture from the solubility classification is established by means of an aperture derived from the United States Pharmacopoeia (USP). Upon contrasting it with the intravenous shot, the intestinal permeability classification is determined. Since 85% of the most popular medications in the US and Europe are taken orally, all those factors are crucial.[10]

The Biopharmaceutical classification system (BCS) divides drug substances into four groups based on permeability and solubility.[11]

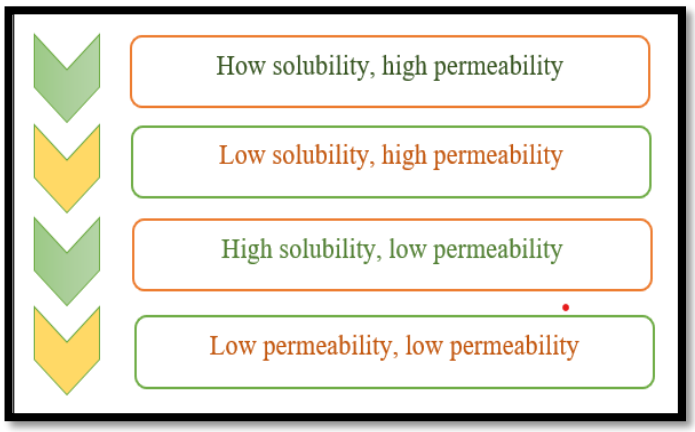

Fig. 2: Biopharmaceutical classification

✓ **Class I:** excellent solubility and permeability

For instance, metoprolol and paracetamol[12]

These substances are readily absorbed, and their rate of absorption typically exceeds that of excretion.

✓ **Class II:** low solubility and high permeability

For instance, glibenclamide, aceclofenac, bicalutamide, and ezetimibe

Their solvation rate restricts those products' bioavailability. There is a correlation between the in vitro solvation and the in vivo bioavailability.

✓ **Class III:** low solubility and high permeability

For instance, glibenclamide, aceclofenac, bicalutamide, and ezetimibe

Their solvation rate restricts those products' bioavailability. There is a correlation between the in vitro solvation and the in vivo bioavailability.

✓ **Class IV:** low solubility and permeability

Consider bifonazole.

These substances are not very bioavailable. They typically absorb poorly through the intestinal mucosa, so significant variability is to be expected.

Importance of bioavailability

Bioavailability is a critical factor in the effectiveness of medicines and drugs because it determines the proportion of the administered dose that reaches the bloodstream and is available to produce the desired therapeutic effect. Here are some key reasons why bioavailability is important in the field of pharmacology:

Efficacy: Medicines need to be absorbed and distributed in the body to be effective. Low bioavailability can lead to insufficient drug levels, reducing the therapeutic response.[14]

Dosing: Understanding bioavailability helps in determining the appropriate dosage to achieve the desired drug concentration in the body.

Consistency: It ensures consistency in drug performance, which is essential for maintaining the desired therapeutic effect over time.

Cost-effectiveness: Efficient drug delivery systems that enhance bioavailability can reduce the quantity of drug required for the same effect, potentially lowering production costs.

Safety: High bioavailability can help avoid overdosing, reducing the risk of adverse effects.

Formulation: Bioavailability considerations influence drug formulation, leading to the development of more effective delivery methods such as extended-release formulations or novel drug delivery systems.[13]

Generic Substitution: Bioequivalence studies are crucial for generic drugs to ensure they have similar bioavailability to the original branded drugs.

Food Interactions: Understanding how food affects drug absorption is important to optimize drug administration instructions.

Bioavailability enhancement techniques

There are numerous methods available to increase the solubility of medications that are poorly soluble. These methods fall into the following categories:

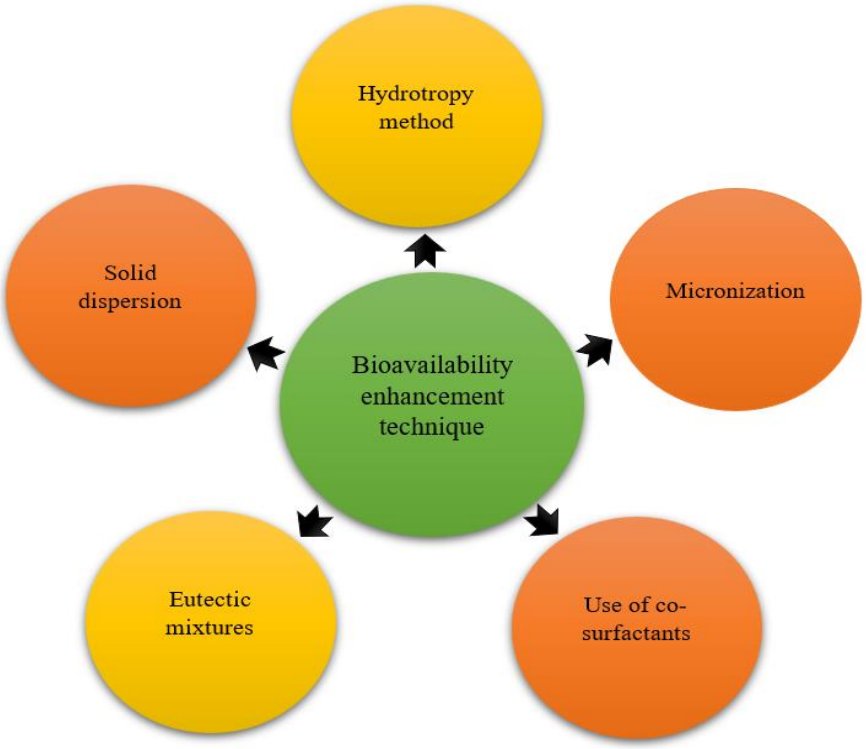

Fig. 3: Bioavailability enhancement traditional techniques

Traditional techniques

Traditional techniques include:

- Use of co-surfactants
- Hydrotropy method
- Micronization
- Use of surfactants
- Use of metastable polymorphs
- Solvent deposition
- Precipitation
- Use of prodrug
- Use of Salt forms
- Size reduction technology
- Porous Microparticle Technology
- Use of Hydrates or Solvates
- Molecular encapsulation with cyclodextrin
- Solid dispersion
- Eutectic mixtures
- Solid solutions
- Amorphous forms

Use of co-surfactants: The addition of a water-miscible or partially miscible organic solvent is a common and an effective way to increase the solubility of a nonpolar drug. This process is known as co solvency and the solvents used in combination to increase the solubility of the drugs are known as co-solvents. The hydrophobic solute and the primarily aqueous solution's interfacial tension are lessened by the co-solvent system. 4,5 Ethanol, propylene glycol, and PEG 300 are a few examples of solvents utilized in co-solvent mixtures. Oral and parenteral administration of co-solvent formulations of poorly soluble drugs is feasible.

Hydrotrophy method: A solubility technique called hydrotropy involves adding a significant amount of a second solute, increasing the solute's aqueous solubility in the process. A substance known as a hydrotropy is one that dissolves hydrophobic substances in aqueous solutions. Because hydrotropy results from the presence of a high concentration of additives, solubility in water increases. Its solubility-improving mechanism is more closely associated with complexation, which is a weak interaction between the poorly soluble drugs and hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, and urea.

Advantages

Hydrotrophy has a high selectivity and doesn't require emulsification, and its solvent

- ✓ Hydrotrophy has a high selectivity and doesn't require emulsification, and its solvent nature is independent of pH.
- ✓ It does not need the use of organic solvents, or the preparation of an emulsion system.[14]

Micronization: Because of the massive surface created, the particle size reduction technique improves the solubility and rate of dissolution of drugs that are poorly soluble in water. The process entails reducing the solid drug particle size to 1 to 10 microns, usually by spray drying or using air attrition techniques like rotor stator colloid mills, fluid energy mills, jet mills, and so on.

Use of surfactants: Surfactants possess both polar and non-polar ends, making them amphiphilic in nature. By encouraging the wetting and penetration of dissolution fluid into the solid drug particles, the surface-active agent primarily increases the rate of dissolution.

Use of metastable polymorphs: A drug's crystalline state may have an impact on its saturation solubility and, consequently, its dissolution. When a drug demonstrates polymorphism, its metastable polymorph is more soluble than its stable polymorph.[15]

Solvent deposition: This process involves dissolving the poorly aqueous soluble drug in an organic solvent, such as alcohol, and then allowing the solvent to evaporate before depositing the drug on an inert, hydrophilic, solid matrix, such as starch or microcrystalline cellulose.

Precipitation: To precipitate the drug in nanosized particles, this method involves dissolving the poorly aqueous soluble drug in an appropriate organic solvent and quickly mixing it with a non-solvent. "Hydrosol" is another name for the prepared product. For intravenous administration, hydrosols are colloidal aqueous suspensions that contain drug nanoparticles of poorly water-soluble medications.

Use of prodrug: An inert drug precursor that has undergone chemical modification to release the pharmacologically active parent compound through biotransformation is called a prodrug.

Use of salt forms: Salt formation is the preferred technique for increasing absorption in compounds with functional groups. Salts of poorly soluble substances usually dissolve in the GIT more quickly, enhancing absorption.

Size reduction technology: Among the more complicated formulations are nano formulations.

To preserve the nature and characteristics of the nanoparticles, the drug particles must not only be made nanoscale, but also carefully stabilized and prepared**.**

Porous microparticle technology: A poor water-soluble drug is embedded in microparticles with a matrix that is porous and water soluble, akin to a sponge. The matrix dissolves when combined with water, wetting the medication and leaving behind a suspension of quickly dissolving drug particles. This is HDDSTM (Hydrophobic Drug Delivery System)'s primary technology.

Use of hydrates or solvates: Both stoichiometric and non-stoichiometric adducts, such as inclusions, which involve solvent molecules trapped inside the crystal lattice, can be present in crystalline compounds. A stoichiometric adduct, also known as "Solvate," is a molecular complex that has integrated the molecules of the crystallizing solvent into particular locations inside the crystal lattice. The complex is referred to as a "Hydrate" when water is the included solvent. The term "anhydrous" refers to a compound that has no water in its crystal structure.

Molecular encapsulation with cyclodextrin: Several different molecules is molecularly encapsulated in oligosaccharides made from starch using beta-cyclodextrin. Their ability to function as a molecular container by ensnaring visiting molecules in their internal cavity is unique to them due to their molecular structure and shape. For this reason, cyclodextrin makes poorly soluble drugs more soluble in water, which enhances their bioavailability.

Solid dispersion: A solid dispersion is a collection of solid products made up of two or more distinct components, usually a hydrophilic drug and a hydrophobic matrix (carrier). It is possible for the matrix to be crystalline or amorphous.

One of the following mechanisms explains how oily dispersions speed up the rate at which drugs that are not very water-soluble dissolve:

- Reduction in particle size
- Improvement in wettability and dispersibility
- Changing crystalline form of drug to amorphous form
- Reduction in aggregation and agglomeration drug

Therefore, the primary distinction between solid dispersion and solid solution/eutectics is that the drug precipitates out in an amorphous form in the former as opposed to a crystalline form in the latter, such as amorphous sulfathiazole found in crystalline urea. Co-evaporates or co-precipitates are common terms used to describe these dispersions. Although the method works well for thermolabile substances, it has several drawbacks, including high processing costs, the need for large amounts of solvent, and challenges with solvent removal. The carriers utilized are the same as those for glassy materials in eutectics or solid solutions, as well as for glass suspensions and dispersions. The comparative griseofulvin dissolution rate from PVP dispersion is shown in the following figure.

Eutectic mixtures: Additionally, fusion method is used to prepare the systems. Essentially, eutectics melts are a physically mixed mixture of two crystalline components that are intimately blended, in contrast to solid solutions, where the fused melt of the solute solvent exhibits complete but negligible miscibility. In Figure 11, a two-component system's phase diagram is displayed. The eutectic mixture solubilizes quickly because the soluble carrier dissolves when it comes into contact with water, leaving the drug in a microcrystalline state. These are two examples of eutectic formation in pharmaceuticals. The first involves a combination of acetaminophen and aspirin, two widely used antipyretic analgesics. There has always been a certain "magic" to eutectic formation; in fact, because this type of binary composition melts at a lower temperature than other combinations, it is likely to have fewer binding forces, if any, and dissolves more quickly due to its extremely fine grain size.

Aspirin-acetaminophen (APAP) eutectic (37 percent APAP by weight) dissolves more quickly than a simple mixture of the two of the same composition. It is known that many drug compounds form eutectics. The formation of a eutectic occurs under the equilibrium condition of intimate mixing, as previously mentioned. This means that the two compounds come into much closer contact than would be possible with a simple dry powder. The increased dissolution rate that eutectics provide may also accelerate physiological absorption.

The other example involves urea and acetaminophen forming a eutectic that melted in the 1100–1150 range and contained roughly 46% urea and 54% acetaminophen. 1150 intervals.

Reduction in aggregation and agglomeration of drug Reduction in aggregation and agglomeration of drug particles.

Solid solutions: A solid solution is a binary system made up of a solid solvent and a solid solute that are dispersed molecularly. Molecular dispersion or mixed crystals are other names for solid solutions since the two components crystallize together in a homogenous one phase system. Solid solutions exhibit higher aqueous solubility and faster dissolution than eutectics and solid dispersion due to the molecular-level reduction of particle size.
They are typically made using the fusion method, which involves physically mixing the solute and solvent and then quickly solidifying the mixture. Systems made this way, like griseofulvin-succinic acid, are frequently referred to as melts. Compared to pure griseofulvin, the griseofulvin from such a solid solution dissolves six to seven times faster. The solute molecule can fit within the intermolecular gaps of solvent molecules, such as in the digitoxin-PEG 6000 solid solution, if its diameter is less than 60% of solvent molecules or its volume is less than 20% of solvent molecule volume. Such a system dissolve more quickly.

Glass solution is the term used to describe the resulting solid solution, which is homogenous, transparent, and brittle. Two methods that have been proposed to improve the solubility and speed of molecular dispersions' dissolution are:

- The soluble carrier quickly dissolves in the binary mixture when it comes into contact with water, leaving the insoluble drug in a state of microcrystalline dispersion of extremely fine particles and
- In the solid state, which is made up of randomly arranged solvent and solute molecules in the crystal lattice, the insoluble drug remains stranded at nearly the molecular level while the soluble carrier dissolves quickly upon exposure to the dissolution fluid.

Amorphous forms: Atoms or molecules are arranged randomly and have a higher thermodynamic energy in amorphous forms than in corresponding crystalline forms. Both solubility and rate of dissolution are typically higher.

Newer and novel techniques

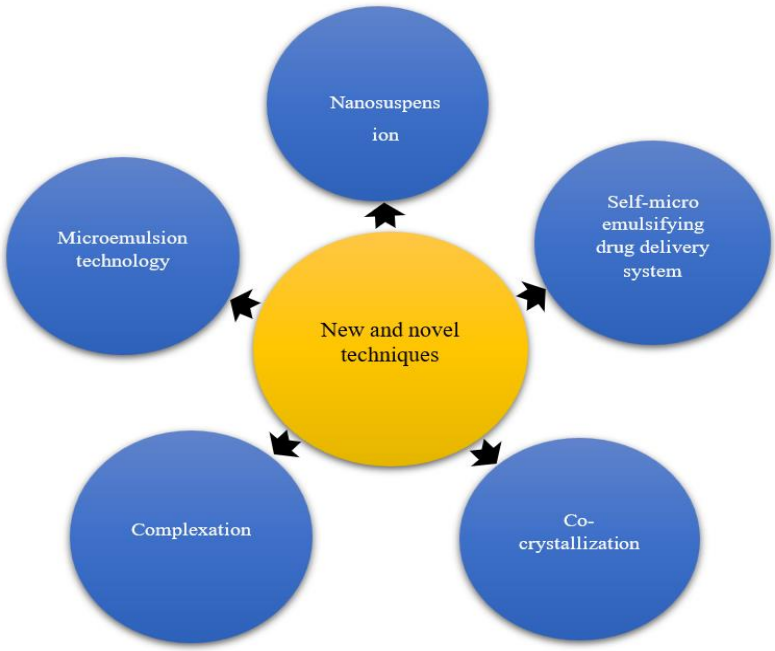

Fig. 4: New and novel techniques of bioavailability enhancement

Newer and novel drug delivery technologies developed in recent years for solubility enhancement of insoluble drugs are

- Size reduction technologies
- Nanoparticle technology
- Nanocrystal technology
- Nanosuspension
- Cryogenic technology
- Supercritical technology
- Lipid based delivery system
- Microemulsion technology
- Self-dispersing lipid formulation (SDLF)
- Micellar technologies
- Mixed micelle
- Polymeric micelle
- Porous microparticle technology
- Self-emulsifying drug delivery system
- Cryogenic techniques

- Co-crystallization
- Supercritical nanotechnology
- Solid-lipid nanoparticles
- Complexation

Size reduction technology: Among the more intricate formulations are nanoformulations. The medication particles not only need to be made nanoscale, but they additionally need to be prepared and stabilized strictly to preserve the qualities and nature between the nanoparticles.

Microemulsion technology: Interfacial films of surface-active molecules stabilize microemulsions, which are isotropically clear, thermodynamically stable dispersions of two immiscible liquids. Oil, water, surfactant, and co-surfactant are simply agitated to create the microemulsions. Interfacial tension is lowered to extremely low and sometimes even momentary negative values when the co-surfactant and surfactant are combined.

Self-dispersing liquid formulation: The drug is mixed with an oil and a surfactant mixture to create the SDLFs. When combined with an aqueous environment, they emulsify.

Micellar technologies:

- **Mixed micelles**

Molecules that have the ability to lower a solvent's surface tension, such as those that are amphiphilic, ionic, anionic, or ampholytic, typically form micelles above a critical concentration. Only above a specific solute concentration, known as the critical micellar concentration (CMC), and at solution temperatures higher than the critical micellar temperature (CMT), can micellar formation take place.

- **Polymeric micelles**

Polymeric micelles are tiny supramolecular core-shell structures made of amphiphilic polymers. The block copolymers Pluronics, poly (ethylene glycol) (PEG)-phospholipid conjugates, PEG-b-poly (ester), and PEG-b-poly (L-amino acids) are utilized to form polymeric micelles. The micelles that are polymeric and nonpolymeric.

Porous microparticle technology: The medication, which is not very water soluble, is enclosed in microparticles with a matrix that is porous and water soluble. The matrix dissolves when combined with water, wetting the medication and producing a suspension of quickly dissolving drug particles. This is HDDSTM (Hydrophobic Drug Delivery System)'s primary technology.

Solid dispersion system: "A dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures" is how Chiou and Riegelman defined "solid dispersion." A collection of solid products with at least two distinct components typically a hydrophilic matrix and a hydrophobic drug—are referred to as solid dispersions. There are two types of matrix: crystalline and amorphous. The medication may be distributed crystalline, amorphous, or molecularly in the form of particles or clusters.

Types of solid dispersion system

Based on their molecular arrangement, six different types of solid dispersions can be distinguished

Simple eutectic mixtures: In contrast to other compositions where one component starts to crystallize out before the other, when a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously. In order to create a physical mixture of extremely fine crystals of the two components, solid eutectic mixtures are typically made by quickly cooling a co-melt of the two compounds. The carrier will dissolve quickly in an aqueous medium when a mixture with composition E—a slightly soluble drug and an inert, highly water soluble carrier—is dissolved, releasing very fine crystals of the drug. The resultant suspension's large surface area should boost the rate of dissolution and, in turn, boost bioavailability. The eutectic system's phase diagram.

Solid solution

- **Continuous solid solution**

All ratios of the components in a continuous solid solution are miscible. This indicates, in theory, that there is a stronger bond between the two components than there is between the molecules of each individual component.

- **Discontinuous solid solution**

The solubility of each component in the other component is restricted in discontinuous solid solutions. The mutual solubilities of the two components begin to diminish below a certain temperature. As per Goldberg's suggestion, the term "solid solution" ought to be utilized exclusively in situations where the two components' mutual solubility surpasses 5% (35). The dose of the drug component as well as the mutual solubility of the two components will determine whether or not a particular solid solution

can be used as a dosage form strategy. A tablet or capsule's mass cannot exceed approximately 1g.

Substitutional crystalline solid solution
In crystalline solid solutions, the solute molecules can either fill the spaces between the solvent molecules or act as a stand-in for the solvent molecules in the crystal lattice. Only in cases where there is a size difference between the solute and solvent molecules of less than 15% is substitution feasible.

Interstitial crystalline solid solution
The dissolved molecules in interstitial solid solutions fill the voids created by the solvent molecules in the crystal lattice. To occupy interstitial space, solute molecules must have a molecular diameter no greater than 0.59 of the solvent molecules' molecular diameter. Furthermore, no more than 20% of the solvent should be contained in the volume of the solute molecules.

Amorphous solid solution
The solute molecules in an amorphous solid solution are distributed irregularly but molecularly throughout the amorphous solvent. It was the first attempt to report the formation of an amorphous solid solution to improve the dissolution properties of a drug using griseofulvin in citric acid. In the early research, urea and sugars like sucrose, dextrose, and galactose were also employed as carriers. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose.

Glass solution and glass suspension
A glassy solvent dissolve a solute in a homogenous, glassy system known as a glass solution. Usually, an abrupt quench of the melt produces the glassy or vitreous state. Transparency and brittleness are its defining characteristics below the glass transition temperature (Tg). It softens gradually and continuously when heated, not melting completely at once.

Self-emulsifying drug delivery systems (SEDDS)
This tactic is applied to poorly soluble, highly porous drug molecules in order to address low bioavailability problems. It is possible to liquefy hydrophobic drug molecules in this system. Because the SEDDS components are introduced into the gastrointestinal tract lumen, where they come into contact with the gastrointestinal fluid and induce the formation of a fine micro/ nanoemulsion, this mixture is referred to as a self-emulsification in situ emulsion. The ability of lipid preparations to improve bioavailability has been linked to a number of their in vivo properties. The bioavailability-improving property of the lipid preparations has been linked to several in vivo properties.[31]

- Self-nano emulsifying drug delivery system (SNEDDS)
- Self-micro emulsifying drug delivery system (SMEDDS)

Ingredients for a self-emulsifying medication delivery system:
Active pharmaceutical ingredients (APIs): For the purpose of improving the solubility of medications with low aqueous solubility, self-emulsifying drug delivery systems are typically utilized; BCS class II medications, such as itraconazole, naproxen, vitamin E, mefenamic acid, danazol, nifedipine, simvastatin, etc., are generally preferred.

Excipients used in SEDDS

- Oils
- Surfactants
- Co-surfactants
- Enhancers
- Polymers
- Antioxidant agents

Table 1: Parenteral microemulsion products were marketed

Drug	Therapeutic area	Product name
Cyclosporine A	Immunomodulation	Restasis
Diazepam	Sedation	Diazemuls
Dexamethasone palmitate	Corticosteroid	Limethason
Etomidate	Anaesthesia	Etomidat
Flurbiprofine	Analgesia	Lipofen
Perflurodecalimp perflurotripropylamine	Analgesia	Fluosol-DA
Propofol	Anaesthesia	Propofol diprivan
Prostaglandin E-1	Visodilator	Liple
Vitamin A, D, E, K	Nutrition	Vitalipid

Cryogenic techniques: By using cryogenic techniques, which produce an amorphous drug with a high porosity level at low temperatures, drugs can be made to dissolve more quickly. After the powder has been cryopreserved, it can be dried by vacuum, spray, or lyophilization. Figure 3 mentions a number of cryogenic techniques.[32][33][34]

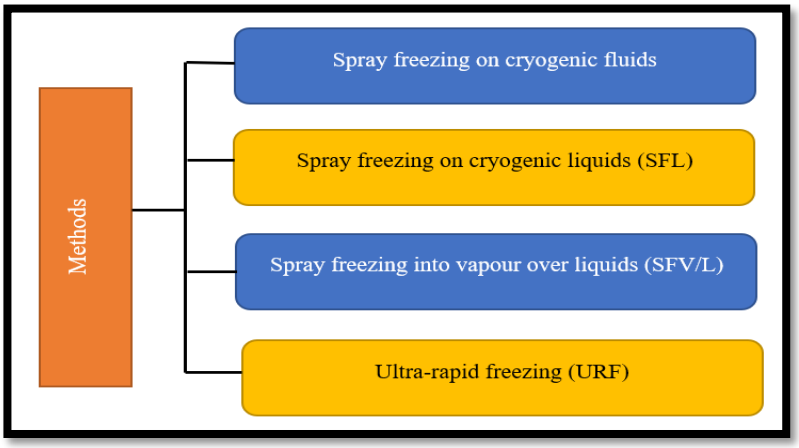

Fig. 5: Various cryogenic methods

Co-crystallization: Co-crystals are supramolecular materials in complex form that are not ionic. Drug solubility, bioavailability, stability, and other physical property issues can be resolved with APIs without modifying their chemical structure. When two or more distinct molecular units are used to create co-crystals, intermolecular interactions like hydrogen bond interactions and π–π stacking act as weak forces. Co-crystallization alters the molecular interactions and composition of pharmaceutical compounds and is recognized as a useful strategy to maximize the therapeutic properties. Co-crystals will provide a variety of pathways for the crystallization of any API, regardless of whether it is an ionizable, basic, or acidic group. Because of their nonionizable functional groups, compounds with low pharmaceutical profiles may benefit from this.[35]

Supercritical fluid technology: The pharmaceutical industry was the first to use supercritical fluid technology on a large scale in the early 1980s. During that time, pharmaceutical companies used SCF technology to develop pharmaceutical materials by precipitating and crystallizing them.[23] The SCF method is economical, safe, and environmentally beneficial. SCFs are appealing for pharmaceutical research because of their low operating parameters (temperature and pressure). Above its critical temperature (Tc) and pressure (Pc), a SCF persists as a single phase.[24]

Solid-lipid nanoparticles

Drug delivery uses solid-lipid nanoparticles for targeted and organized delivery. They have an average particle size of 50 –1000 nm and are biocompatible and biodegradable. They consist of a hydrophobic phospholipid coating that is solid. In order to create this coating, a solid, room-temperature lipid matrix must be dissolved into an aqueous surfactant solution or water. [16][17][18] The drug-containing solid cores are distributed throughout the lipid matrix. They are probably going to carry both hydrophilic and hydrophobic medications. Table 8 lists several examples of medications created with the use of SLN technology. A selection of commonly used lipid excipients in lipid-based nanocarriers is provided in Table 2.[19][20][21][22]

Table 2: Examples of different medications created using SLN technology.

Drug	Lipid utilized
Apomorphine	Glycerylmonostearate
Calcitonine	Trimyristin
Clozapine	Trimyristin, tristearin and tripalmitine
5- Fluro uracil	Dynasan 114, Dynasan 118
Gonodropine	Monostearin
Idarubicine	Emulsifying wax
Nimesulide	Glycerylbehanate, Glycerylmonostearate
Repaglinide	Glycerylmonostearate and tristearin

Complexation

The complex consists of two or more molecules connected by a bond that forms an entity independent of a specific balancing. This is dependent upon relatively weak forces, such as London forces, hydrophobic interactions, and hydrogen bonds.[24]

- **Stanching complexation:** Stanching complexes are typically formed when aromatic compounds' overlapping planar domains come together. Strong hydrogen bonding connections between the nonpolar groups cause the H2O to be removed. The following particular particles have been shown to produce stanching complexes: anthracene, benzoic acid, pyrene, salicylic acid, methylene blue, nicotinamide, ferulic acid, theobromine, gentisic acid, naphthalene, purine, and caffeine.

- **Inclusion complex:** For the development of inclusion complexation, a nonpolar particle or a portion of the guest particle added to the cavity of different particles or an assembly of molecules (referred to as the host) has been used. Perfect adaptation of the guest molecules within the host cavity is the primary physical prerequisite for complexing the inclusion. The host particle's cavity should be sufficiently large to hold the guest molecule and sufficiently small to eliminate H2O as the interaction between H2O and the nonpolar domains of the host and guest molecules weakens. Naturally occurring CDs come in three different forms: α, β, and γ-cyclodextrin.[25]

- **Inclusion complex:** In complexation, cyclodextrin is used to improve solubility. The molecular phenomenon that is cyclodextrin's embodiment. Through a cavity in cyclodextrin, one guest particle can come together to form a stable association. The hydroxyl group configuration within a particle gives rise to an internal hydrophobic activity and an external shallow hydrophilic activity in the cyclodextrin molecule. Positions are examined to determine whether cyclodextrin inclusion complexation is a one-step or two-step reaction that involves structural transformation and proceeds sequentially. Through inclusion complexation, cyclodextrins improve the solubility of drug molecules in water. When cyclodextrin is combined with clofibrate, rofecoxib, melarsoprol, celecoxib, cyclosporin A, taxol, etc., the medication's solubility will be enhanced.[26][27]

Manufacturing techniques for complexation /inclusion complexation:

- Kneading method
- Microwave irradiation method
- Co-precipitate method
- Lyophilization/freeze-drying technique
- Spray drying

Peptide complexation: There are numerous benefits to using protein nanoparticles for the delivery of substances like growth factors, peptide hormones, poorly water-soluble medications, genetic materials, and DNA and RNA. The stability and ease of production of protein nanoparticles give them an advantage over other colloidal carriers. A simple, cost-effective, and environmentally benign synthesis method can be used to create nanoparticles from proteins derived from various sources. It is predicted that these nanoparticles will have a great potential for in vivo use and require less chemicals than nanoparticles made of other materials.[28]

Chang and colleagues discovered that encasing the investigated compound in egg white protein nanoparticles and improving the hydrophobic encapsulation of curcumin within these particles effectively reduced the degradation ratio and maintained the antioxidant activity of the encapsulated curcumin.[29]

Curcumin nanoassembly conjugated with lysozyme produced a nanoconjugate with enhanced antibacterial, antioxidant, and anticancer activity, according to a different study. The water solubility of indomethacin, a nonsteroidal anti-inflammatory medication that is poorly soluble in water, was enhanced by complexing it with the casein hydrolysate (Figure 4). Likewise, peptide complexation has the ability to improve the solubility of medications that are not very soluble in water.[30]

Conclusion

This review provides a critical overview of some of the currently under development and previously published technologies, along with a few relevant research reports and recent advancements. These technologies include formulation design, solid particle techniques, prodrug strategies, crystal engineering, micronization, solid dispersions, particle size reduction technologies, nanosizing, cyclodextrins, solid lipid nanoparticles, drug conjugates, colloidal drug delivery systems, complexation of drugs, use of micelle formation, microemulsions, cosolvents, polymeric micelles, pharmaceutical salts, prodrugs, solid state alternation, soft gel technology, drug nanocrystals,

and nanomorph theory. The solubility improvement technique of poorly water-soluble drugs is crucial when creating a formulation to fulfil the therapeutic action and drug bioavailability of the pharmaceutically active ingredient (drug) at the target site. Screening programs for the pharmaceutical industry found that about 40% of new chemical.

Thus, there are a number of trends in solubility enhancement concerning novel procedures, such as the use of novel excipients to aid poorly soluble molecules. One area of particular research that is receiving a lot of attention is the modelling and comprehension of the poorly soluble molecules and the optimal formulations for them. This does not yet exist, but we are moving in the direction of modelling molecules and using their characteristics to determine which polymer will be most effective in completing the process swiftly.

Acknowledgements

We would like to express our sincere gratitude to IPS Academy College of Pharmacy, Indore for providing access to resources and facilities that facilitated our above article.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Kumar, M., Clinical evaluation of patients suffering from rheumatoid arthritis with respect to iron deficiency. International Journal of Medical and Biomedical Studies, 2019, pp no.178-2.
2. Majithia, V. and Geraci, S.A., Rheumatoid arthritis: diagnosis and management. The American Journal of Medicine, 2007, pp no. 936-939.
3. Hasan, A.A., Khudhur, H.R. and Hameed, A.K., Rheumatic autoimmune diseases: prevalence, types, causes and diagnosis. Karbala Journal of Pharmaceutical Sciences, 2022, pp no.109.
4. Osthoff, A.K.R., Juhl, C.B., Knittle, K., Dagfinrud, H., Hurkmans, E., Braun, J., Schoones, J., Vlieland, T.P.V. and Niedermann, K., 2018. Effects of exercise and physical activity promotion: meta-analysis informing the eular recommendations for physical activity in people with rheumatoid arthritis, spondyloarthritis and hip/knee osteoarthritis. Rheumatoid and Musculoskeletal Diseases, 2018, pp no .713.
5. Penman, L.D. and Lees, C.W., 2014. Alimentary tract and pancreatic disease. U: Walker BR, College NR, Halston SR, Penman ID. Davidson's Principles and Practice of Medicine, 22nd edition, 2014, pp no. 389.
6. Vemula, V.R., Lagishetty, V. and Lingala, S., Solubility enhancement techniques. International Journal of Pharmaceutical Sciences Reviews and Research, 2010, pp no.41-51.
7. Kshirsagar, S., Choudhari, M., Sathyan, R. and Dhore, S., Solubility enhancement by various techniques based on pharmaceutical and medicinal chemistry approach: an overview. Asian Journal of Pharmacy and Technology, 2019, pp no.141-146.
8. Papich, M.G.; Martinez, M.N. Applying Biopharmaceutical Classification System (BCS) Criteria to Predict Oral Absorption of Drugs in Dogs: Challenges and Pitfalls. American Association of Pharmaceutical Scientists, 2015, pp no. 948–964.
9. Cornelissen J, Orphan medicines and patent law Department: Tilburg Law School Program: Law & Technology Master, 2019, pp no. 12.
10. Mehta, M. "Biopharmaceutics Classification System (BCS): development, implementation, and growth.", 2016, pp no. 978-991.
11. Savjani, K.T.; Gajjar, A.K.; Savjani, J.K. Drug solubility: Importance and enhancement techniques. International Scholarly Research Notices**,** 2012, pp no. 42.
12. Varandal, A.B.; Magar, D.; Saudagar, R. Different approaches toward the enhancement of drug solubility: A review. Pharmaceutical Education & Research**.** 2013, pp no. 415–426.
13. Reddy, A.; Parthiban, S.; Vikneswari, A.; Senthilkumar, G. A modern review on solid lipid nanoparticles as novel controlled drug delivery system**.** The International Journal of Research in Pharmaceutical and Na no Sciences, 2014, pp no. 313–325.
14. Severino, P.; Pinho, S.C.; Souto, E.B.; Santana, M.H. Polymorphism, crystallinity and hydrophilic–lipophilic balance of stearic acid and stearic acid–capric/caprylic triglyceride matrices for production of stable nanoparticles. Colloids Surf. B Biointerfaces. 2011, pp no. 125–130.
15. Garud, A.; Singh, D.; Garud, N. Solid lipid nanoparticles (SLN): Method, characterization and applications. International Journal of Current Pharmaceutical Research. 2012, 1, pp no. 384–393.

16. Kadam, S.V., Shinkar, D.M. and Saudagar, R.B., Review on solubility enhancement techniques. The International Journal of Pharmacy and Biological Sciences, 2013 pp no. 462-75.
17. Ekambaram, P.; Abdul Hasan Sathali, A.; Priyanka, K. Solid lipid nanoparticles: A review. Scientific Reviews & Chemical Communications Scientific Reviews & Chemical Communications, 2012, pp no. 80–102.
18. Westesen, K.; Bunjes, H.; Koch, M.H.J. Physicochemical characterization of lipid nanoparticles and evaluation of their drug loading capacity and sustained release potential. The Journal of Controlled Release, 1997, pp no. 223–236.
19. Westesen, K.; Siekmann, B.; Koch, M.H.J. Investigations on the physical state of lipid nanoparticles by synchrotron radiation X-ray diffraction. International Journal Pharmacy, 1993, pp no. 189–199.
20. Mukherjee, S.; Ray, S.; Thakur, R.S. Solid lipid nanoparticles: A modern formulation approach in drug delivery system. Indian Journal Pharmacy Science. 2009, pp no. 349–358.
21. Lenhardt, T.; Vergnault, G.; Grenier, P.; Scherer, D.; Langguth, P. Evaluation of nanosuspensions for absorption enhancement of poorly soluble drugs: In vitro transport studies across intestinal epithelial monolayers. Journal of the American Association of Pharmaceutical Scientists 2008, pp no. 435–438.
22. Lipinski, C. Poor aqueous solubility—An industry wide problem in drug discovery. American Journal of Pharmacy. 2002, pp no. 82–85.
23. Loftsson, T.; Brewster, M.E. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. Journal of Pharmaceutical Science, 1996, pp no. 1017–1025.
24. Kumar, S.K.; Sushma, M.; Raju, P.Y. Dissolution enhancement of poorly soluble drugs by using complexation technique-a review. Journal of Pharmaceutical Science, 2013, 5, pp no.120.
25. Vimalson, D.C. Techniques to enhance solubility of hydrophobic drugs: An overview. Asian J. Pharm. Asian Journal of Pharmaceutics, 2016, pp no 5-10.
26. Hong, S.; Choi, D.W.; Kim, H.N.; Park, C.G.; Lee, W.; Park, H.H. Protein-Based Nanoparticles as Drug Delivery Systems. Pharmaceutics, 2020, pp no. 604.
27. Chang, C.; Meikle, T.G.; Su, Y.; Wang, X.; Dekiwadia, C.; Drummond, C.J.; Conn, C.E.; Yang, Y. Encapsulation in egg white protein nanoparticles protects anti-oxidant activity of curcumin. Food Chemicals, 2019, pp no. 65–72.
28. Somu, P.; Paul, S. Surface conjugation of curcumin with self-assembled lysozyme nanoparticle enhanced its bioavailability and therapeutic efficacy in multiple cancer cells. The Journal of Molecular Liquids, 2021, pp no. 338.
29. Inada, A.; Oshima, T.; Takahashi, H.; Baba, Y. Enhancement of water solubility of indomethacin by complexation with protein hydrolysate. International Journal of Pharmaceutical. 2013, pp no. 587–593.
30. Vemula, V.R., Lagishetty, V. and Lingala, S., Solubility enhancement techniques. International Journal of Pharmaceutical Sciences Reviews and Research, 2010, pp no.41-51.
31. Mumenthaler M, Leuenberger H. Atmospheric spray-freeze drying: a suitable alternative in freeze-drying technology. International Journal of Pharmaceutics. 1991, pp no. 97-110.
32. Leuenberger H. Spray freeze-drying–the process of choice for low water-soluble drugs? Journal of Nanoparticle Research. 2002, pp no. 9-111.
33. Williams III RO, Johnston KP, Young TJ, Rogers TL, Barron MK, Yu Z, Hu J, inventors; University of Texas System, assignee. Process for production of nanoparticles and microparticles by spray freezing into liquid. United States patent. 2005, pp no. 14-35.
34. Papich MG, Martinez MN. Applying biopharmaceutical classification system (BCS) criteria to predict oral absorption of drugs in dogs: challenges and pitfalls. the American Association of Pharmaceutical Scientists. 2015, pp no. 64-948.
35. Patole T, Deshpande A. Co-crystallization-a technique for solubility, enhancement. International Journal of Pharmaceutical Sciences and Research. 2014 pp no. 35-66.