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Formulation-Driven Strategies for Overcoming Solubility Barriers in Drug Development: A Review

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Abstract: Low water solubility is one of the most critical hurdles in pharmaceutical development, as nearly 40-50% of the newly discovered drug molecules are poorly water-soluble. This low solubility often leads to inadequate dissolution, poor absorption, and reduced bioavailability, which limit the therapeutic potential of many promising drug candidates. Consequently, enhancing solubility has become a key area of focus in formulation science to improve the clinical efficacy and commercial viability of modern pharmaceuticals. This review provides a overview of the various strategies developed to improve the solubility and dissolution rate of low water-soluble drug candidates. Based on their solubility, drugs are categorized into four classes according to the Biopharmaceutics Classification System (BCS). Solubility issues are primarily encountered in Class II and Class IV drugs. Various approaches and techniques are employed to enhance the solubility and bioavailability of these poorly soluble drugs. Conventional methods such as particle size reduction, salt formation, solid dispersion, and use of co-solvents are discussed alongside novel and emerging techniques, including nanocrystals, inclusion complexation with cyclodextrin, solid lipid nanoparticles, and amorphous solid dispersions.

Keywords: *Solubility, Poorly Soluble Drugs, Nanoparticles, Hydrotropy, BCS.*

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I. INTRODUCTION

Low water solubility is a major challenge in the development of orally administered drug candidates, as it directly affects dissolution rate, absorption, and overall bioavailability. Nearly 40-50% of newly discovered chemical entities belong to Biopharmaceutics Classification System (BCS) Class II or IV, characterized by poor solubility and/or permeability, leading to inconsistent therapeutic outcomes [2,8]. Solubility can be described in both quantitative and qualitative terms [1]. In qualitative terms, solubility can be defined as the spontaneous mixing of two or more substances to create a uniform (homogeneous) dispersion. In quantitative terms, it refers to the amount of solute present in a specific volume of solvent at a given temperature to form a homogeneous solution. The solubility of a drug can be represented as a percentage, in parts, or expressed in units such as molality, molarity, mole fraction, and volume fraction [2]. The solubility of a drug in a saturated solution is a constant characteristic, while the dissolution rate of the medication is a variable characteristic. The dissolution rate is more closely linked to how quickly the drug becomes available for absorption in the body [1]. To produce a therapeutic effect, a drug needs to be sufficiently soluble in water. Understanding a drug's solubility is crucial for the manufacture of solid dosage forms like oral tablets, as well as liquid preparations such as injectables and various other formulations [10]. Solubility in a saturated solution is a fixed (static) characteristic, while the dissolution rate is a dynamic property that more directly influences the rate at which the drug becomes bioavailable [6]. Solubility is an essential pre-formulation factor that determines the achievable drug concentration in systemic circulation [1]. The solubility of a drug is characterized by several descriptive terms that reflect the quantity of the drug dissolved in the solvent, as outlined in Table No.1 [6].

Table 1 USP and BP Terminology for Describing Approximate Solubility

Descriptive terms	Amount of solvent needed to dissolve one part of solute
Very soluble	<1 part
Freely soluble	1-10 parts
Soluble	10-30 parts
Sparingly soluble	30-100 parts

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Slightly soluble	100-1000 parts
Very slightly soluble	1000-10000 parts
Practically insoluble	>10000 parts

According to USP and BP standards, solubility is categorized by the amount of solvent required to dissolve a single part of solute, independent of the solvent used. This volume-based classification provides a straightforward method for evaluating solubility in pharmaceutical applications [12].

➢ *Example:*

- Potassium chloride (USP monograph). Potassium chloride dissolves in less than 1 part of solvent per part of solute, classifying it as very soluble.
- Acetohexamide – The BP monograph states it is soluble in alkali hydroxides and pyridine.
- Acetylcysteine – Stated as slightly soluble in water and alcohol in USP monographs.

II. BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

Originating from pharmacokinetic and absorption research of the 1970s–1980s, the BCS was formally introduced in the seminal 1995 paper by Amidon and colleagues [15]. Regulatory guidance grounded in the BCS was initially released by the FDA in 2000 and later adopted by the WHO and additional authorities, solidifying its role as an international standard in regulatory science and generic drug development [17]. The BCS provides a scientific basis for categorizing drug substances according to their solubility and permeability, enabling predictions of oral absorption and in-vivo performance from in-vitro assessments [15]. The key aims are to facilitate the development of oral solid dosage forms, define appropriate dissolution specifications, and permit biowaivers for selected immediate-release products instead of in-vivo bioequivalence testing [16].

Table 2 Biopharmaceutical Classification System (BCS)

Class	Solubility	Permeability	Examples
I	High	High	Amoxicillin, Diazepam, etc.
II	Low	High	Atorvastatin, Diclofenac, etc.
III	High	Low	Metformin, Acyclovir, etc.
IV	Low	Low	Amphotericin B, Isoniazid, etc.

In BCS Class II and IV drugs, the primary rate-limiting step involves drug release and solubility in the gastric environment, not permeability. Consequently, any increase in solubility leads to improved bioavailability for these drug classes [3]. A drug is classified as having high solubility when its highest single therapeutic dose dissolves fully in 250 mL or less of aqueous media across pH 1.0–7.5 at 37 °C [18]. 'Low-solubility' drugs are those that do not satisfy this solubility-volume requirement over the specified pH range, with absorption typically constrained by dissolution or solubility [19]. A drug is considered to have high permeability when ≥85–90% of the administered dose is absorbed in humans, as evidenced by mass-balance studies or pharmacokinetic evaluations [20]. Drugs classified as having low permeability exhibit an extent of absorption below this criterion, and their absorption is chiefly restricted by epithelial transport [21].

BCS Class I compounds are characterized by high solubility and high permeability, generally achieving fast and complete absorption, as dissolution does not limit their uptake in typical gastrointestinal environments [15]. Examples: Metoprolol, Propranolol, Paracetamol, Hydrochlorothiazide, Warfarin, Ciprofloxacin, etc.

BCS Class II compounds exhibit low solubility and high permeability, with absorption primarily limited by dissolution or solubility. Consequently, formulation efforts often target improving solubility or increasing the dissolution rate [16]. Examples: Carbamazepine, Ketoconazole, Phenytoin, Danazol, Nifedipine, Piroxicam, Spironolactone, etc.

BCS Class III compounds are highly soluble yet poorly permeable, with absorption largely constrained by intestinal permeability and modulated by transporter activity or tight-junction characteristics [22]. Examples: Ranitidine, Neomycin, Captopril, Enalapril, Furosemide, Riboflavin, etc.

BCS Class IV compounds are characterized by low solubility and low permeability, leading to the lowest oral bioavailability and substantial formulation and development difficulties [21]. Examples: Etoposide, Cisplatin, Cyclosporine, Tacrolimus, Clofazimine, Dipyridamole, etc.

III. FACTORS AFFECTING THE SOLUBILITY OF THE DRUG

➢ *Nature of Solute and Solvent:*

Solubility is governed by a substance's polarity and molecular traits: polar solutes dissolve in polar solvents, while nonpolar solutes dissolve in nonpolar ones. Intermolecular forces (such as hydrogen bonding) also play a major role in how well a substance dissolves [23].

➢ *Particle Size and Surface Area:*

Reducing particle size increases the surface area, allowing more contact with the solvent and resulting in faster and enhanced solubility [5].

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➢ *pH of the Medium:*

In ionizable compounds, solubility is pH-dependent, as variations in pH alter the ionization state and consequently the compound's solubility [12].

➢ *Temperature:*

For solids and liquids, solubility typically rises as temperature increases, while gases become less soluble. This behavior reflects how temperature alters molecular kinetic energy and the nature of solute–solvent interactions [9].

➢ *Molecular Size:*

Substances with higher molecular weight and larger molecular size generally exhibit lower solubility, as their bulk makes solvation by solvent molecules more difficult. For organic compounds, increased carbon branching tends to improve solubility by decreasing the molecule's overall volume, thereby facilitating solvation [11].

➢ *Polymorphs:*

Polymorphic forms often display different melting points, and since melting point correlates with solubility, each polymorph may have a distinct solubility profile. However, these differences are usually limited to a 2–3-fold range because the variations in free energy are relatively small [24].

➢ *Importance of Solubility Enhancement:*

Oral ingestion remains the preferred drug-delivery route owing to its simplicity, patient acceptability, cost-effectiveness, minimal sterility requirements, and versatility in dosage-form design. As a result, generic drug manufacturers increasingly prioritize producing bioequivalent oral formulations [12].

- Solubility is vital for reaching the necessary drug concentration in systemic circulation, which is essential for therapeutic effectiveness across all routes of administration [25].
- Inadequate aqueous solubility causes reduced dissolution rates, which in turn produce irregular absorption, diminished bioavailability, and inconsistent therapeutic outcomes, particularly for oral medications [12].
- Over 40% of newly developed chemical entities exhibit low aqueous solubility, posing substantial formulation difficulties and necessitating the use of solubility-enhancing approaches [26].
- Enhanced solubility increases bioavailability, enabling dose reduction, minimizing adverse effects, and promoting improved patient adherence [25,26].
- Solubility enhancement facilitates broader formulation options for various dosage forms and contributes to improved drug stability and extended shelf-life [26].

IV. TECHNIQUES FOR SOLUBILITY ENHANCEMENT

When a substance shows limited solubility in aqueous media, formulation strategies must be considered early in drug discovery and remain essential throughout lead selection and commercial product development [6]. Several techniques have been employed to enhance the solubility and dissolution rates of poorly water-soluble drugs, including the following:

➢ *Physical Modifications:*

Solubility can be enhanced by modifying the drug's physical characteristics. Key techniques include:

- Reducing particle size (e.g., micronization, nanonization, nanosuspension) to increase surface area and dissolution rate.
- Altering crystal habit via polymorphic transformation.
- Forming solid dispersions, dispersing the drug in a hydrophilic matrix to enhance wettability and decrease crystallinity.
- Nanosponges
- Sonocrystallization
- Microemulsion and self-emulsifying system

➢ *Chemical Modifications:*

These strategies improve solubility by altering the drug's chemical structure or environment and include:

- Salt formation to enhance the solubility of acidic or basic drugs.
- pH adjustment to increase ionization and thereby solubility.
- Complexation, such as forming inclusion complexes with cyclodextrins.
- Co-crystallization, creating multi-component crystals with improved solubility.
- Prodrug Formation: Chemical modification of the drug molecule into a more soluble derivative that converts to the active drug in vivo.
- Cosolvency

➢ *Miscellaneous Techniques:*

- Surfactants or solubilizers to lower surface tension and improve wetting.
- Hydrotropy, using hydrotropic agents to enhance aqueous solubility.
- Nanotechnology-based methods such as nanosizing and nanoemulsions.
- Supercritical fluid techniques for particle-size reduction and solid-dispersion preparation.
- Liquisolid systems, which convert liquid drugs into free-flowing powders.
- Spray drying
- Spherical agglomeration
- Precipitation technique
- Cryogenic method

➢ *Physical Modifications:*

Physical modification techniques aim to improve the solubility and dissolution rate of poorly water-soluble drugs by altering their physical properties without changing their chemical structure.

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V. PARTICLE SIZE REDUCTION

In pharmacy, size reduction techniques like milling have roots in historical practices, such as Galen's compounding around 130-200 AD. Reducing particle size is a common and efficient method for enhancing the solubility and dissolution characteristics of poorly water-soluble drugs. This reduction increases the available surface area for solvent interaction, resulting in faster dissolution in accordance with the Noyes–Whitney equation [27]. Particle size reduction can be achieved through techniques such as jet milling, ball milling, wet milling, and high-pressure homogenization. In some cases, size reduction can also induce amorphization, which further improves solubility [13]. Conventional particle-size reduction methods—such as comminution and spray drying—use mechanical energy to break down and disperse drug particles. These approaches offer an efficient, reproducible, and cost-effective way to enhance solubility. However, the mechanical forces involved in processes like milling and grinding can impose considerable physical stress on the drug, potentially leading to degradation. Likewise, the heat generated during comminution or spray drying may cause thermal stress, posing challenges for thermosensitive or chemically unstable compounds. Consequently, traditional size-reduction techniques may be insufficient for drugs that are extremely poorly soluble, where greater solubility enhancement is required. Size-reduction techniques are typically classified as:

Micronization (1–1000 μm) improves the dissolution rate without changing equilibrium solubility. It generally utilizes jet milling, Ball milling, Hammer milling. Micronization is widely used for drugs with poor solubility but adequate permeability.[12]

➢ *Advantages*:

- Reducing particle size dramatically increases the surface area available for dissolution, improving drug solubility.
- Improved dissolution can lead to quicker therapeutic response.
- Micronized particles show more uniform blending with excipients, enhancing content uniformity in tablets and capsules.
- The process is relatively inexpensive and can be easily scaled for industrial production.[15]

➢ *Disadvantages*:

- Mechanical stress during milling can cause physical or chemical degradation of the drug.
- Some micronization methods generate heat, which may affect thermosensitive or unstable drugs.
- Extremely small particles may stick together, reducing the intended increase in surface area.
- Micronized powders often exhibit poor flowability and increased cohesiveness, complicating tableting and capsule filling.[15]

Nanonization (submicron particles <1 μm) can enhance both parameters because of increased surface free energy. It generally utilizes wet milling, high-pressure homogenization, Nanoprecipitation, Microfluidization. Nanonization is particularly useful for extremely poorly soluble drugs where micronization is insufficient.[12]

➢ *Advantages*:

- Greatly improves solubility because the particles are extremely small, they dissolve much faster in body fluids.
- Since absorption improves, smaller doses may be enough to achieve the same effect.
- Drugs reach the bloodstream quicker, leading to a quicker response.
- Especially helpful for drugs that are highly permeable but poorly soluble.[29]

➢ *Disadvantages:*

- Nanoparticles tend to stick together, which can reduce the benefit of size reduction.
- The high surface energy of nanoparticles may make them more reactive, leading to degradation.
- Nanoparticles can clump, absorb moisture, or show poor flow properties, making processing difficult.[29]

➢ *Nanosuspension:*

Gary G. Liversidge discovered the nanosuspensions technique in 1990-1991 through the pioneering Dissocubes® process at RTP Pharma (now Soliqs), patenting wet media milling (pearl milling) to produce stable drug nanocrystals (10-1000 nm) for enhancing bioavailability of poorly soluble drugs like danazol. Rainer H. Müller advanced the concept in 1994, coining "nanosuspensions" and developing applications at the Free University of Berlin, building on Liversidge's patent-protected technology. [45,46].

➢ *Advantages:*

- Nanosuspensions offer significant advantages for solubility enhancement of poorly water-soluble drugs by reducing particle size to 10-1000 nm, dramatically increasing surface area and dissolution rates per the Noyes-Whitney equation.
- Enhanced bioavailability through faster dissolution, saturation solubility increase (Kelvin effect), and endocytosis uptake, reducing fed/fasted variability.
- Targeted delivery, improved stability against degradation, and reduced side effects via precise tissue distribution. [45,46]

➢ *Disadvantages:*

- Physical instability risks like Ostwald ripening, aggregation, or sedimentation requiring stabilizers (surfactants/polymers).
- Scale-up challenges, long-term storage issues (freezing/drying needed), and regulatory hurdles for nanocrystals. [45,46]

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VI. CRISTAL HABIT MODIFICATION

It stems from 19th-century crystallography where scientists like René Just Haüy (1784) first described crystal habits systematically, linking external form to internal structure. Crystal habit modification in pharmaceutics refers to altering the external shape of crystals (such as transforming them into needle-like, plate-like, or block-shaped forms) without changing their underlying crystal structure (polymorph). This approach helps improve important physical properties, including flowability, compressibility, filtration behavior, and in some cases dissolution. It is considered a physical modification technique because the crystal lattice remains unchanged, while the outer morphology is adjusted by manipulating crystallization parameters like solvent choice, degree of supersaturation, temperature, and the use of habit-modifying additives [30]. Crystal habit affects the surface area available to the medium, the wetting properties, and the packing behavior of particles, all of which can indirectly influence the dissolution rate and consequently the apparent solubility and bioavailability. In general, block- or plate-shaped crystals provide better flowability and compressibility than long needle-shaped crystals, leading to improved tabletability and more consistent content uniformity [31].

➢ *Crystal Habit Can be Modified During Crystallization by:*

- Altering the solvent or solvent mixtures to promote growth of specific crystal faces.
- Adjusting supersaturation levels and the rate of cooling or evaporation to control crystal morphology.
- Incorporating tailored crystal growth modifiers, such as pharmaceutically acceptable excipients or polymers, which selectively adsorb on fast-growing faces and slow their growth, resulting in more equant, uniform crystals.

Several studies have demonstrated that varying the crystal habit of the same polymorph can lead to differences in dissolution and overall performance. For instance, controlled crystallization of tadalafil produced needle-, plate-, and block-shaped crystals of the same polymorphic form. These different habits exhibited distinct flow properties, compressibility, and dissolution profiles, highlighting that crystal habit engineering can modulate biopharmaceutical behavior without altering the polymorph itself [30].

➢ *Advantages:*

- Changing crystal habit from needle-like to more equant shapes improves powder flow, facilitating better processing and handling during manufacturing.
- Modified crystal shapes can exhibit better packing and compressibility, leading to improved tablet formation and mechanical strength
- Improved crystal shape can decrease problems like sticking, capping, and segregation during tablet compression and granulation.[31]

➢ *Disadvantages*:

- Achieving reproducible and precise habit modification requires careful control of crystallization parameters, which may be challenging on large scale.
- Some habit modifications may result in metastable shapes that could change morphology under storage, affecting consistency.

VII. SOLID DISPERSION

In the early 1960s, Sekiguchi and Obi first introduced the concept of solid dispersions. The term "solid dispersion" describes a class of solid systems composed of at least two components, typically a hydrophobic drug dispersed within a hydrophilic matrix. This technique is widely used in pharmaceutics to enhance drug solubility, improve the rate of absorption, and increase therapeutic effectiveness [2]. In this approach, a poorly soluble drug is dispersed within a highly soluble, hydrophilic solid matrix, which enhances the drug's dissolution. Solid dispersions can be classified as eutectic mixtures, representing non-molecular level mixing, or as solid solutions, where the drug is molecularly dispersed within the carrier. Common hydrophilic carriers used in the pharmaceutical industry include polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), Plasdone, Tween 80, and sodium lauryl sulfate (SLS). Several techniques are employed to enhance the aqueous solubility of hydrophobic drugs, such as the Hot Melt (Fusion) Method, Solvent Evaporation Method, and Hot Melt Extrusion [11].

Solid dispersions are typically prepared using melting (fusion), solvent evaporation, or fusion–solvent methods. Upon contact with an aqueous environment, the hydrophilic carrier dissolves, releasing the drug either as fine particles or in an amorphous form. This greatly increases the drug's surface area and dissolution rate, thereby enhancing the bioavailability of poorly water-soluble drugs. Solid dispersions are regarded as superior to conventional solubility-enhancement techniques because they enhance dissolution through multiple synergistic mechanisms while leaving the drug's chemical structure unchanged. Advanced approaches, such as the use of supercritical fluids, allow for more precise control over particle formation and dispersion within the carrier. [32].

➢ *Advantages:*

- Reduction in particle size enhancing surface area and Reduced agglomeration of drug particles.
- Improved wettability and dispersibility due to hydrophilic carriers.
- Conversion of the drug from crystalline to amorphous state increasing dissolution.

➢ *Disadvantages:*

- Solid dispersions often face stability challenges including recrystallization of the amorphous drug into its less

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soluble crystalline form during storage and humidity exposure.

- Achieving reproducible physicochemical properties on large manufacturing scales is difficult due to complexity in controlling processing parameters.

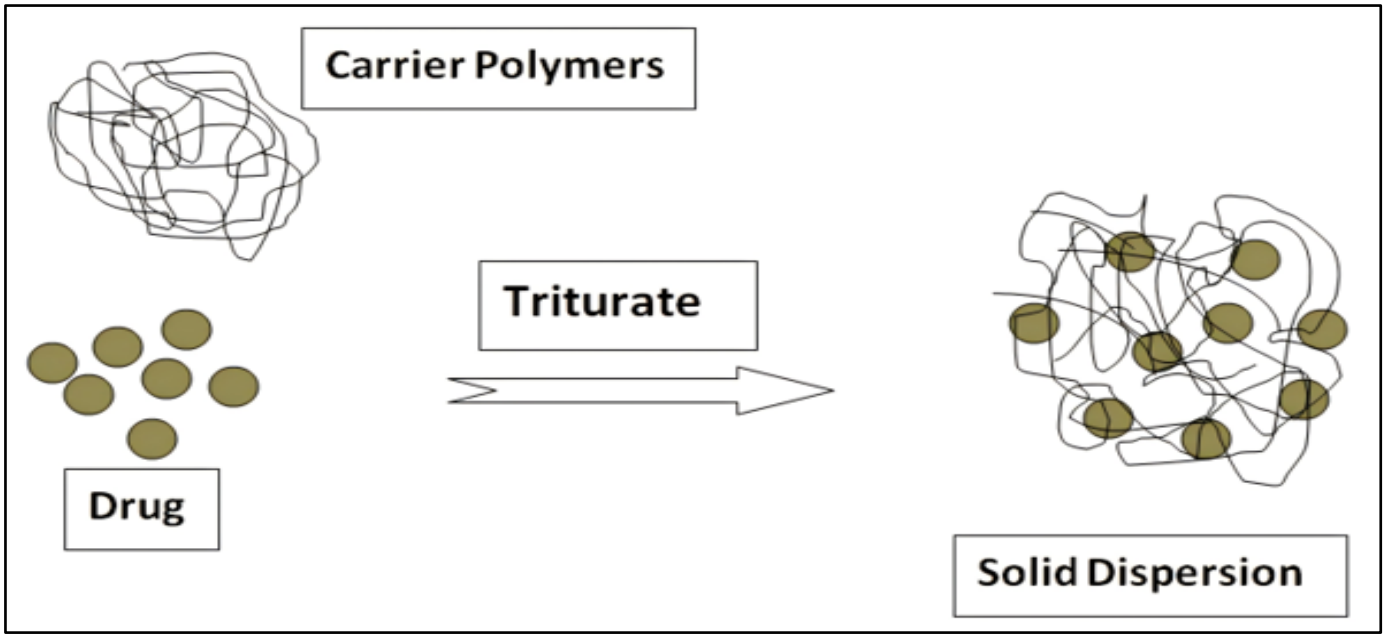

Fig 1 Solid Dispersion

➢ *Nanosponges:*

The technology was invented in 1998 by Prof. Francesco Trotta at the University of Turin, Italy, with first β-cyclodextrin nanosponge synthesis via cross-linking patented in 2001. Nanosponges enhance solubility of poorly water-soluble drugs by forming solid, three-dimensional, porous nanoparticles (100-500 nm) from cross-linked polymers like β-cyclodextrin, which entrap hydrophobic molecules in nano-cavities, increasing dissolution rates, wettability, and bioavailability via amorphization and surface area expansion.[47]

➢ *Mechanism and Preparation:*

Nanosponges trap drugs through non-covalent interactions (hydrogen bonding, van der Waals) in their sponge-like matrix, boosting solubility up to 55-fold for itraconazole or 23-fold for piroxicam by reducing crystallinity and improving release control. Methods include emulsion-solvent diffusion, ultrasound-assisted synthesis, or cross-linking with carbonyl or epichlorohydrin, enabling high drug loading (up to 90%).[47]

➢ *Advantages:*

- High drug loading capacity (up to 33-90%) for both hydrophilic and lipophilic drugs via inclusion and surface interactions, improving solubility (e.g., 50-fold for itraconazole).
- Sustained/controlled release profiles, biocompatibility, stability across pH 1-11 and up to 300°C, taste masking, and reduced side effects with self-sterilizing pores (<0.25 μm).
- Versatile for multiple routes (oral, topical, injectable) and enhanced bioavailability via amorphization and targeted delivery.[47]

➢ *Disadvantages:*

- Complex synthesis requiring precise cross-linking ratios, potentially leading to batch variability and residual cross-linker toxicity.
- High production costs, scalability challenges from organic solvents or harsh conditions, and limited long-term stability data.[47]

VIII. SONOCRYSTALLIZATION METHOD

Sonocrystallization emerged in the early 2000s as a novel particle engineering technique, building on 1990s ultrasound applications in crystallization. Melt sonocrystallization specifically for drugs emerging around 2010 through collaborative studies led by Dr. Anant R. Paradkar and his team at the University of Bradford, UK. Paradkar's group published the seminal work on melt sonocrystallization—melting poorly soluble drugs (e.g., rosiglitazone), dispersing in water, and sonicating to create porous nanocrystals, boosting solubility without solvents.[48]

➢ *Mechanism and Process:*

Ultrasound generates cavitation bubbles that collapse, promoting nucleation via shock waves, microjets, and local supersaturation, yielding irregular, porous particles (e.g., 20 min sonication at 80% amplitude on molten drug in 60°C water). This reduces induction time, alters polymorphism/lattice defects (XRPD), and boosts solubility

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(e.g., via SEM-confirmed pits) without chemical changes (FTIR).[48]

Sonocrystallization enhances solubility of poorly water-soluble drugs by applying ultrasound (20-100 kHz) to induce cavitation in molten drug dispersed in water, creating porous agglomerates with shallow pits, increased surface area, and modified crystal habits that accelerate dissolution per the Noyes-Whitney equation.[48]

➢ *Advantages:*

- Solvent- and carrier-free process, reducing toxicity risks and costs while improving environmental safety and regulatory compliance.
- Rapid nucleation, reduced induction time, and controlled particle size/morphology (porous agglomerates with pits), boosting dissolution rates via Noyes-Whitney enhancement.
- Improved micromeritics (flow, compressibility), stability, and bioavailability for BCS Class II drugs like rosiglitazone, with no chemical degradation.[48]

➢ *Disadvantages:*

- Limited to drugs with suitable melting points (<200°C) and viscosity in molten state, restricting applicability.
- Scale-up challenges due to ultrasound equipment limitations, energy intensity, and process reproducibility in large volumes.
- Potential equipment costs and need for precise control of amplitude/frequency to avoid over-processing or polymorphism issues.[48]

➢ *Microemulsion and Self-Emulsifying System:*

Microemulsions and self-emulsifying drug delivery systems (SEDDS) enhance solubility of poorly water-soluble drugs by forming thermodynamically stable nanoscale dispersions that solubilize lipophilic actives in oil phases, boosting dissolution and bioavailability. [49,50]

- Microemulsions are isotropic, pre-formed oil-in-water systems (<100 nm droplets) using oils (Labrafil), surfactants (Cremophor RH 40), and cosurfactants (Transcutol) to achieve massive solubility gains (e.g., 5785-fold for glimepiride) via pseudoternary phase diagrams, with superior diffusion and 6-month stability.[49]

➢ *Advantages:*

- Thermodynamic stability, spontaneous formation, and high solubilization (e.g., 5785-fold for glimepiride) via nanoscale droplets (<100 nm).
- Enhanced skin permeation and controlled release due to low surface tension.[49]

➢ *Disadvantages:*

- High surfactant/cosurfactant levels (20-60%) risk irritation, toxicity, or altered GI motility.
- Complex formulation requiring phase diagram optimization; limited high-melting drug solubility.[49]

- SEDDS/SMEDDS are preconcentrates that spontaneously form fine emulsions (~99 nm) on GI dilution using eucalyptus oil, Kolliphor EL, and Kollisolv, delivering 21-66-fold bioavailability increases for tenofovir through lymphatic uptake and rapid release.[50]

➢ *Advantages:*

- Spontaneous emulsification on GI dilution simplifies manufacturing.
- Thermodynamic stability, high drug loading, and reduced fed/fasted effects.[50]

Disadvantages:

- Limited to liquid fills; droplet coalescence risks upon excessive dilution.
- Surfactant-related GI irritation and potential P-gp inhibition affecting other drugs.[50]

IX. CHEMICAL MODIFICATION

Chemical modification involves altering the chemical structure or surrounding environment of a drug molecule to enhance its solubility and bioavailability. By adjusting factors such as ionization, molecular interactions, or crystalline form, this approach directly influences the drug's inherent solubility [12]. Common chemical modification techniques used in pharmaceutical solubility enhancement include:

➢ *Salt Formation:*

Pharmaceutical salt formation traces to the 1950s-1960s, when researchers like T. Higuchi systematically explored salts to improve solubility and bioavailability of weakly acidic/basic drugs, as detailed in their seminal 1965 paper establishing salt selection principles. Among chemical modification techniques, salt formation stands out as one of the most practical and successful methods for increasing the solubility and dissolution rate of drugs with poor solubility, especially those that are acidic or basic. The method works by transforming the drug into a salt through reaction with a compatible acid or base. The resulting ionic salts generally possess greater water solubility than the original drug, enhancing their dissolution in the GI tract and subsequent absorption [33]. Key aspects of salt formation for enhancing solubility include:

- Salt solubility is governed by factors such as the drug's intrinsic solubility, environmental pH, the pKa values of both the drug and counterion, and the solubility product.
- Salt forms generally dissolve more rapidly because of their increased aqueous solubility, which can enhance bioavailability.

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- Identifying the optimal salt form requires comprehensive screening for stability, solubility across physiological pH ranges, manufacturability, and safety.
- Salt formation can also modify properties like crystal habit, melting point, hygroscopicity, and chemical stability.[33]
- Salt formation has long been used as a technique to improve the solubility of drugs. Examples include aspirin, theophylline, and barbiturates [8]

➢ *Advantages*:

- It enables the development of liquid formulations intended for parenteral use due to improved solubility.
- Salt formation can also offer practical formulation benefits in terms of purity, manufacturability, stability, particle size control, and flow properties.

➢ *Disadvantages*:

- Salt formation is limited to ionizable drugs and may not be feasible for all compounds.
- Some salt forms may show stability issues including disproportionation, high hygroscopicity, and sensitivity to common ion effects, which can complicate formulation development.

➢ *pH Adjustment:*

Takeru Higuchi pioneered systematic studies on pH-solubility profiles in the 1950s, influencing modern BCS-based adjustments. pH adjustment is a widely used solubility enhancement technique that optimizes drug solubility by modifying the microenvironmental pH around the drug, particularly effective for pH-dependent poorly soluble drugs. Incorporating pH modifiers like acidifiers or alkalizers in formulations can create a favorable pH that improves the solubility and dissolution rate of ionizable drugs [8]. For example weakly basic drugs exhibit improved solubility in the presence of acidifiers, whereas weakly acidic drugs show better solubility with alkalizing agents. This strategy can also be integrated with solid dispersion techniques. A notable example is telmisartan, whose hot-melt–extruded solid dispersions showed greatly enhanced solubility and stability when pH modifiers were added—achieving up to a 13-fold increase compared to the pure drug [34]. The stomach has a pH of about 1–2, while the duodenum ranges from pH 5–7.5. Therefore, during oral administration, a drug's solubility can change significantly as it moves through different sections of the gastrointestinal tract [15].

➢ *Advantages*:

- Improves solubility and dissolution rate of ionizable drugs.
- Enhances bioavailability and absorption.
- Offers better chemical and physical stability than free acid/base forms.[33]

➢ *Disadvantages:*

- It is only applicable to ionizable drugs.
- Potential for salt instability due to environmental pH changes, which can lead to drug degradation or conversion back to free acid or base.[33]

➢ *Complexation:*

Complexation enhances drug solubility by allowing the drug molecule (guest) to form a complex with a host molecule, commonly cyclodextrins. The process relies on non-covalent interactions such as hydrogen bonds, van der Waals forces, or inclusion of the drug within the host's cavity. This encapsulation improves the drug's wettability and dispersion, thereby increasing the solubility and bioavailability of poorly water-soluble compounds [35].

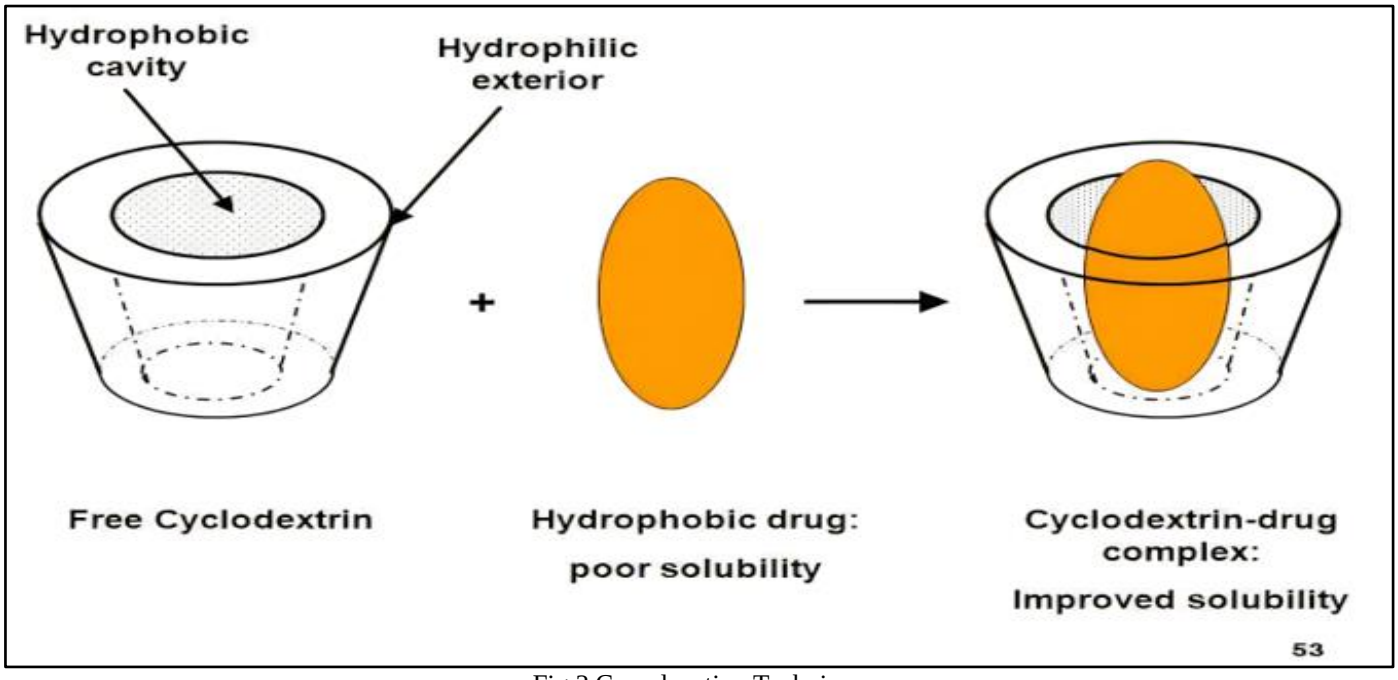

Fig 2 Complexation Technique

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Cyclodextrins—such as β-cyclodextrin and its derivatives (e.g., hydroxypropyl-β-cyclodextrin)—can markedly improve solubility and dissolution by forming stable inclusion complexes in solution. These complexes are typically evaluated using phase-solubility studies and often lead to enhanced oral bioavailability [35]. Variations in cyclodextrin structure—such as cavity diameter and functional substitutions—directly impact the strength and efficiency of complex formation, supporting targeted optimization for individual drug compounds.

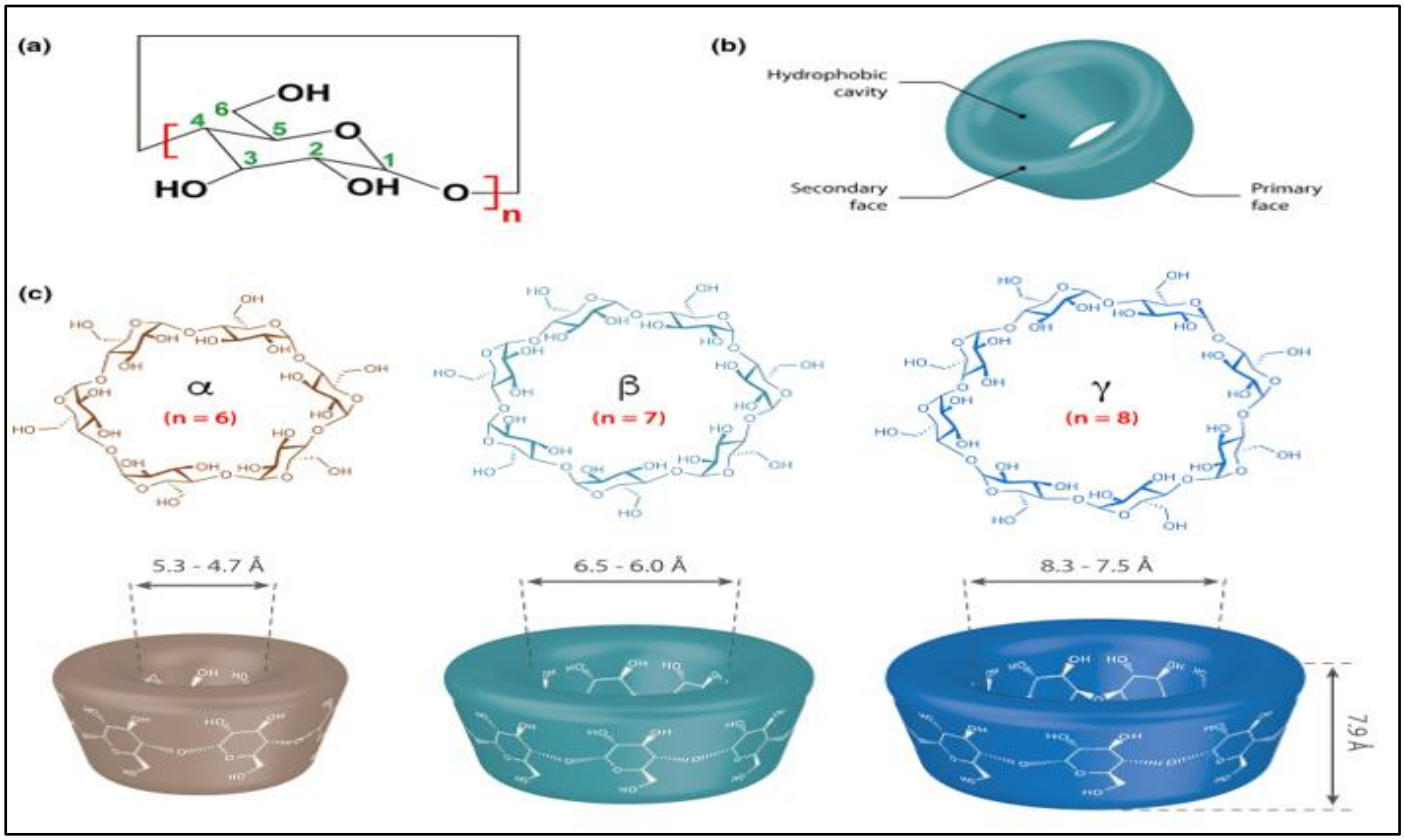

Fig 3 Cyclodextrins Structure

X. TYPES OF COMPLEXATIONS INCLUDES

➢ *Inclusion Complexation:*

In this technique, a drug molecule serves as the guest and interacts with host cyclodextrins that possess hydrophobic inner cavities capable of accommodating the drug, thereby enhancing its aqueous solubility and stability. Inclusion complexes may be produced through physical blending, kneading, spray drying, solvent evaporation, co-grinding, microwave irradiation, or freeze drying. This strategy is particularly advantageous for low-solubility drugs and improves bioavailability without requiring chemical modification [36].

➢ *Phospholipid Complexation:*

Drug–phospholipid complexes are formed through hydrophobic interactions and hydrogen bonding, leading to improved permeability and increased oral bioavailability. These complexes also decrease particle size and boost both solubility and physical stability, making the technique effective for low-solubility drugs like meloxicam [37].

- *Advantages:*

✓ A simple and economical formulation approach that preserves the drug's original chemical structure.
✓ Enhances drug stability by protecting against both physical and chemical degradation.
✓ Complexation with cyclodextrins or similar agents reduces particle size and improves absorption.
✓ Generally avoids organic solvents and high temperatures, making production safer and more efficient [2,36].

- *Disadvantages:*

✓ Complexing agents or solvents may pose risks of toxicity or intolerance.
✓ The complexed form may exhibit lower chemical stability than the crystalline drug.
✓ Complexation can unpredictably influence pharmacokinetics, necessitating detailed in vitro and in vivo sstudies [2]

➢ *Co-Crystallization:*

Friedrich Wöhler first discovered and described co-crystallization in 1844 through quinhydrone, a 1:1 co-crystal of benzoquinone and hydroquinone formed during quinone studies. Co-crystallization is a technique that enhances the solubility, dissolution rate, and bioavailability of poorly water-soluble drugs by forming co-crystals with suitable co-formers, such as malonic acid, succinic acid, acetamide, caffeine, etc. These co-crystals are composed of the API and

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a defined amount of a co-former held together by non-covalent interactions, improving physicochemical properties without changing the drug's chemical structure or activity. Co-crystallization offers notable advantages such as increased solubility, enhanced stability, improved tabletability, and greater permeability. It is regarded as a green and sustainable approach because it typically uses minimal solvents and requires fewer synthetic operations. The resulting co-crystals frequently exhibit faster dissolution and higher bioavailability, ultimately supporting improved therapeutic outcomes [38].

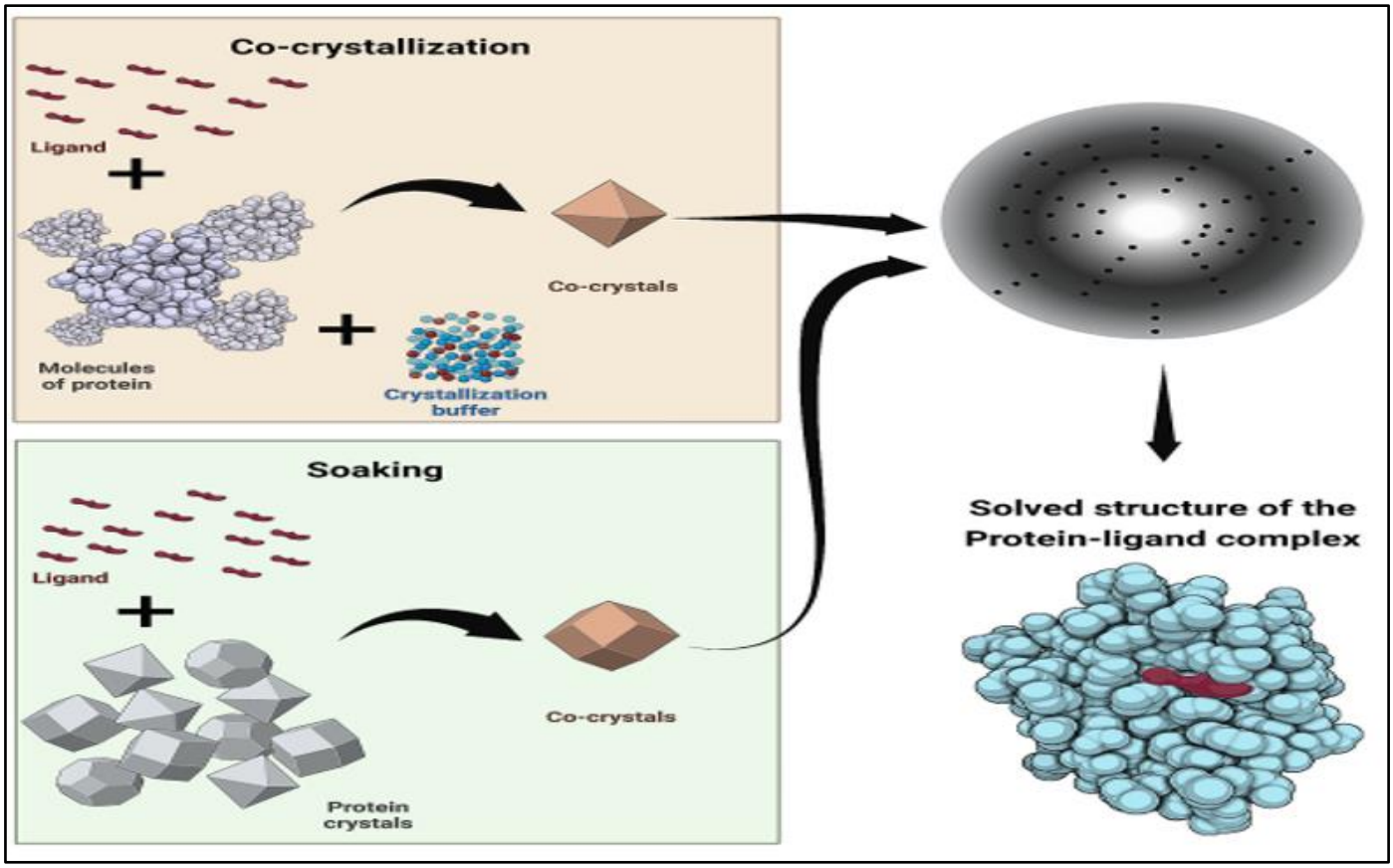

Fig 4 Co-Crystallization and Soaking

Co-crystallization involves crystallizing an API and a co-former together to form a new, well-defined crystalline phase with improved physicochemical properties, while soaking involves immersing an already formed crystal in a solution containing another molecule so that it diffuses into the crystal without creating a new crystal form. Co-crystallization results in a distinct solid form with a specific stoichiometric ratio, whereas soaking simply introduces guest molecules into an existing lattice, typically for structural or analytical purposes rather than modifying drug properties [38].

- *Advantages*:

✓ Provides enhanced stability under a range of environmental conditions, thereby extending shelf life and ensuring consistent drug performance.
✓ Enables modulation of drug release characteristics, supporting controlled and sustained delivery systems.
✓ Preserves the active compound's pharmacological activity and potency, minimizing the potential for adverse effects.
✓ Avoids the use of hazardous reagents typically required for chemical modification, contributing to safer and more environmentally responsible processing.

- *Disadvantages*:

- Selecting a suitable co-former can be challenging and often demands extensive screening and compatibility studies.
- Intellectual property and patenting can be more complex than with conventional formulations.

➢ *Prodrug Formation:*

Adrian Albert first coined and described the term "prodrug" in 1958 in a Nature paper, formalizing the concept of inactive compounds converted in vivo to active drugs. Prodrug formation is a pharmaceutical approach in which an active drug is chemically transformed into an inactive or less active derivative known as a prodrug. Once administered, the prodrug is enzymatically or chemically converted in vivo to release the active compound at the target site. This strategy is primarily employed to overcome limitations of the parent drug, including poor solubility, suboptimal bioavailability, rapid metabolic degradation, toxicity, or insufficient targeted delivery. Prodrugs can be categorized as carrier-linked prodrugs, in which the drug is attached to a removable carrier, or bioprecursor prodrugs, which require metabolic

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conversion to release the active agent. Their activation is triggered by enzymes, pH changes, redox reactions, or other biochemical factors. Choosing appropriate promoieties is essential for controlling pharmacokinetics, stability, and site-specific activation [39].

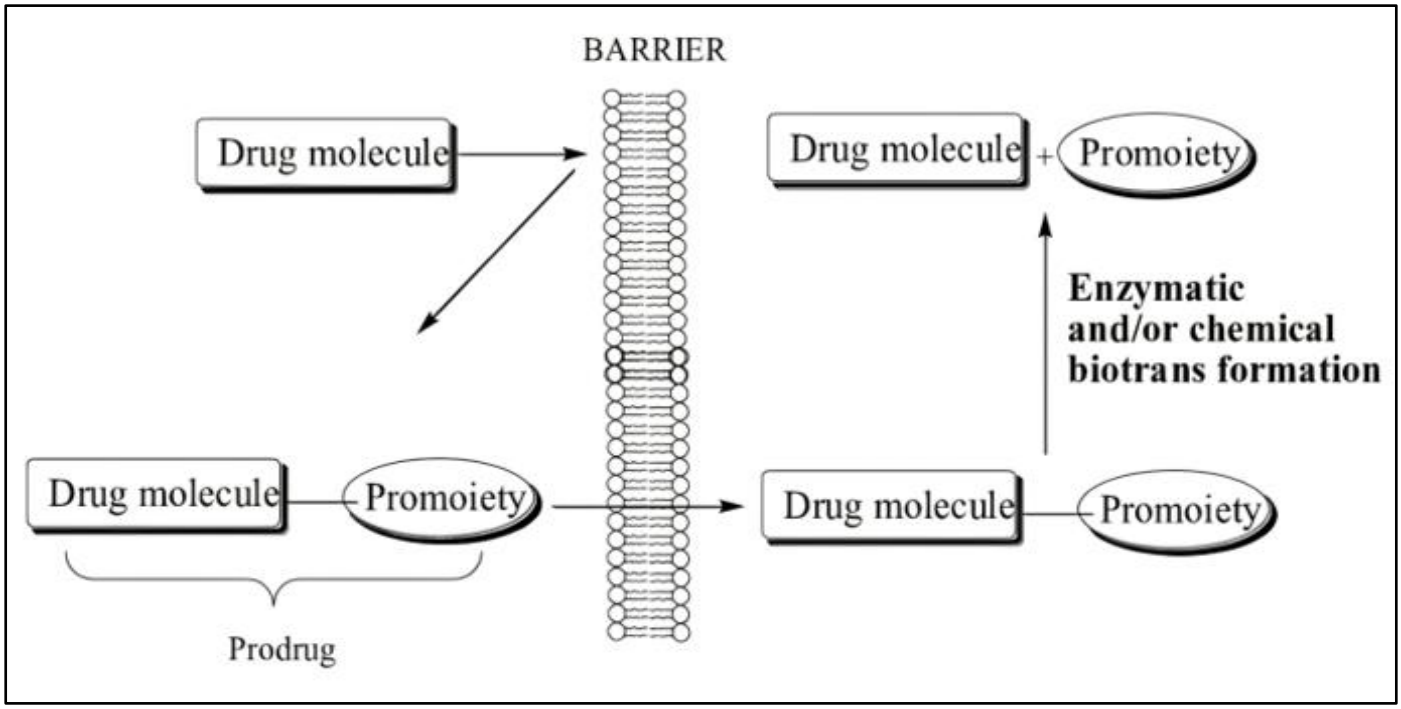

Fig 5 Prodrug Formation

- *Advantages*:

✓ Prodrug strategies provide an effective way to improve solubility without major chemical modification, enabling faster formulation development and potentially lowering costs.
✓ Incorporating ionizable or polar promoieties in prodrugs increases drug polarity, thereby enhancing solubility and bioavailability.
✓ Prodrugs improve oral absorption and undergo enzymatic conversion to the active drug post-absorption, preserving both permeability and therapeutic effect.[39]

- *Disadvantages*:

✓ Careful design of promoieties is essential to enhance solubility while maintaining stability and controlling bioconversion.
✓ Prodrugs can complicate regulatory approval, as safety and efficacy must be demonstrated for both the modified drug and its metabolites.[39]

➢ *Cosolvency:*

Cosolvency emerged in the 1960s for parenteral formulations and analytical method development, with systematic mathematical modeling in the 1970s-1980s led by Samuel H. Yalkowsky at the University of Arizona. Cosolvency enhances solubility of poorly water-soluble drugs by adding water-miscible organic solvents to aqueous media, reducing solution polarity and interfacial tension to promote hydrophobic solute dissolution.[51]

➢ *Mechanism*:

Cosolvents like ethanol, propylene glycol (PG), polyethylene glycol (PEG 400), or glycerol create mixed solvent systems where solubility increases exponentially with cosolvent fraction per log-linear models (Yalkowsky equation: $\log Xm = f \cdot \sigma + (1-f) \cdot \log Xw$, where f is cosolvent fraction, σ is solubilization capacity). This favors non-polar drugs via dielectric constant reduction and hydrogen bonding disruption.[51]

- *Common Co-Solvents*:

✓ Ethanol (up to 50% v/v): Broad use but volatile.
✓ PG/PEG 400: Less toxic, higher viscosity.
✓ Glycerol: Safe for oral use.[51]

- *Advantages:*

✓ Cost-effective compared to complex techniques like nanosuspensions .
✓ Predictable solubility enhancement via log-linear Yalkowsky models.
✓ High solubilization capacity (up to 100-fold increase with PEG 400).[51]

- *Disadvantages:*

✓ Altered drug stability and potential degradation in mixed solvents.
✓ Regulatory limits on cosolvent concentrations (e.g., ethanol <10% oral).

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✓ Unsuitable for high-dose drugs due to volume constraints.[51]

➢ *Miscellaneous Techniques*

It involves following methods or techniques which contribute to enhance solubility of poorly soluble drugs:-

➢ *Use of Surfactants or Solubilizers:*

Surfactants and solubilizing agents are crucial for improving the aqueous solubility and bioavailability of drugs with poor water solubility. These amphiphilic compounds decrease surface tension, facilitating drug wetting and dispersion. Once the concentration surpasses the critical micelle concentration (CMC), micelles form, encapsulating hydrophobic drugs within their cores and markedly enhancing apparent solubility and dissolution.[40]

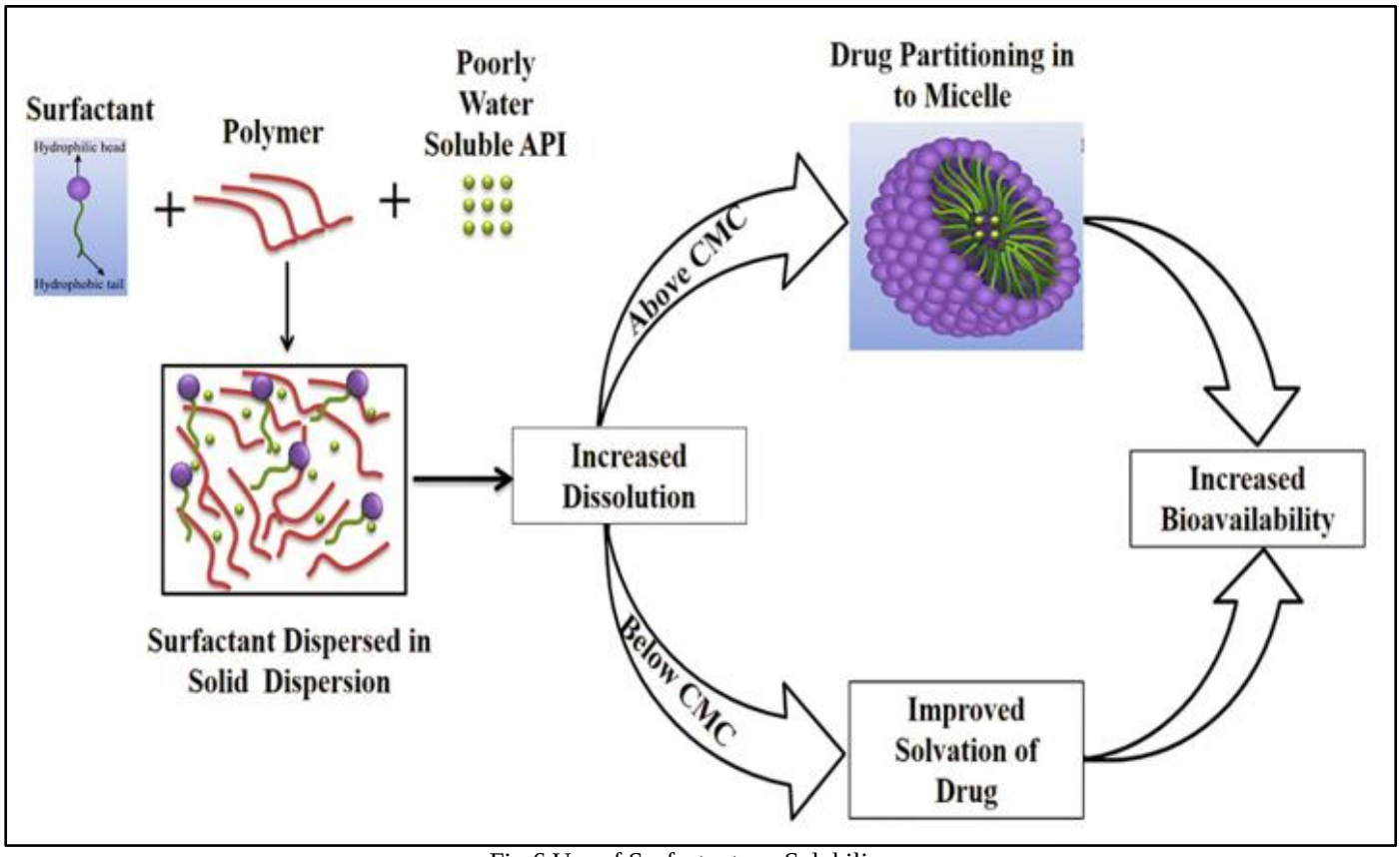

Fig 6 Use of Surfactants or Solubilizers

Surfactants contribute to formulation stability by inhibiting particle aggregation and crystallization, thereby maintaining drug potency. They also promote drug absorption by interacting with lipid bilayers and modulating tight junctions between epithelial cells. Frequently used pharmaceutical surfactants include non-ionic agents like Tween 80 and poloxamers, as well as ionic surfactants such as sodium lauryl sulfate. Incorporation of surfactants enhances homogeneity and uniformity of dosage forms, leading to reliable drug delivery.[40]

- *Advantages*:

✓ Surfactants lower surface tension and enhance the wetting of hydrophobic drug particles, improving dispersion and dissolution rates.
✓ Above the critical micelle concentration (CMC), surfactants form micelles that solubilize hydrophobic drugs in their cores, significantly increasing apparent solubility and bioavailability.
✓ They stabilize formulations by preventing drug particle aggregation and crystallization, enhancing physical and chemical stability.
✓ Surfactants can interact with biological membranes, increasing permeability and promoting improved drug absorption.[40]

- *Disadvantages*:

✓ Certain surfactants can cause toxicity or irritation at elevated concentrations, requiring careful selection and dosing.
✓ Formulations containing surfactants may exhibit lower chemical stability compared to crystalline drug forms.
✓ High surfactant levels can adversely affect the taste and palatability of oral dosage forms.
✓ Surfactant formulations can face challenges in long-term physical stability due to potential micelle disruption or phase separation.[40]

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➢ *Hydrotropy:*

Carl Neuberg first discovered and described hydrotropy in 1916, coining the term to explain how large amounts of second solutes (hydrotropic agents like sodium benzoate or nicotinamide) dramatically increase the aqueous solubility of poorly soluble organic compounds without forming complexes or micelles. Hydrotropy is a pharmaceutical technique for improving the solubility of poorly water-soluble drugs through the addition of high concentrations of a hydrotropic agent. This method differs from micellar solubilization, as it depends on specific molecular interactions between the drug and hydrotrope. Typical hydrotropes, such as sodium benzoate, sodium citrate, and urea, increase solubility by perturbing water structure and establishing weak interactions with drug molecules. Hydrotropic solubilization can markedly increase the solubility and bioavailability of drugs, with studies showing synergistic effects when using mixed hydrotropic agents. This method is safe, cost-effective, and environmentally sustainable due to the avoidance of organic solvents. Hydrotropic agents are versatile, compatible with various drug delivery systems, and suitable for the preparation of solid dispersions and tablets with enhanced dissolution profiles.[41]

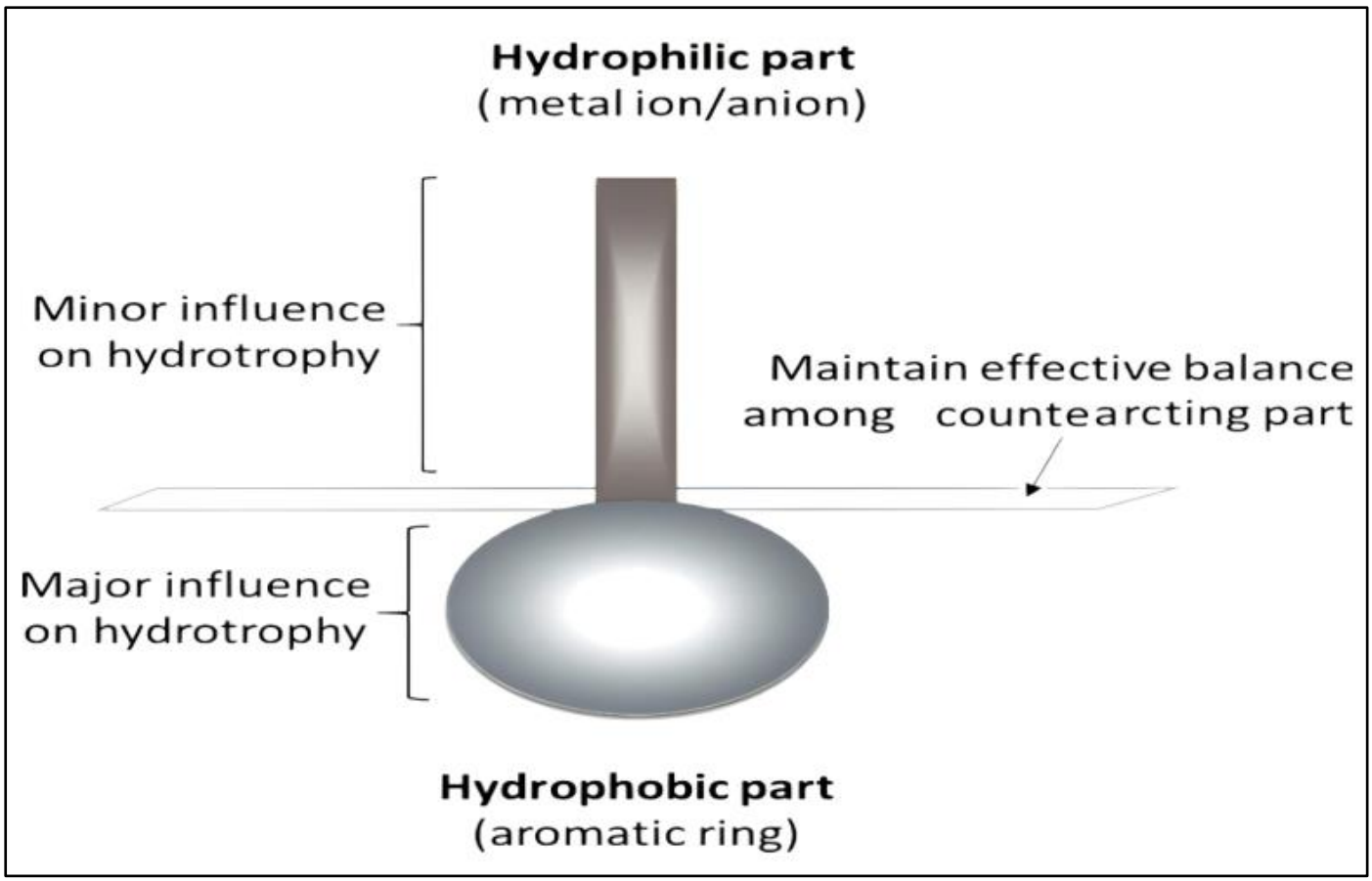

Fig 7 Hydrotropy

- *Advantages:*

✓ Hydrotropy improves the aqueous solubility of poorly soluble drugs without chemically modifying the drug.
✓ It employs hydrotropic agents that are cost-effective, environmentally friendly, and often non-toxic, eliminating the need for harmful organic solvents.
✓ The solubility enhancement is generally pH-independent, allowing broad applicability.
✓ Mixed hydrotropy, which uses combinations of hydrotropic agents, can lower the required concentration of each agent and reduce potential toxicity.[41]

- *Disadvantages:*

✓ Complete removal of water after formulation can be challenging since hydrotropy relies on aqueous solutions.
✓ Hydrotropy may not be equally effective for all drugs, requiring optimization of agents and concentrations.[41]

➢ *Nanotechnology-Based Methods:*

Nanotechnology has emerged as a key strategy for improving the solubility of poorly water-soluble drugs. By decreasing drug particle size to the nanometer range, these methods increase surface area, enhance dissolution rates, and consequently improve bioavailability. Common nanotechnology approaches include nanocrystals, nanosuspensions, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), liposomes, nanoemulsions, and polymeric nanoparticles.[42]

- Nanocrystals consist of pure drug particles at the nanometer scale, which increase saturation solubility and

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dissolution rates as a result of their elevated surface-to-volume ratio.

- Nanosuspensions maintain the stability of drug nanoparticles in an aqueous medium, enhancing solubility and allowing flexible formulation into oral, intravenous, or topical dosage forms.
- Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) employ solid or semi-solid lipid matrices to encapsulate drugs, improving solubility, providing controlled release, and enhancing stability. [42]

Nanocarriers enhance drug permeability and targeted delivery through interactions with biological membranes. Polymer functionalization allows controlled release and lowers toxicity, while maintaining drugs in amorphous forms to improve solubility and absorption.[42]

- *Advantages*:

✓ These technologies enable precise, controlled, and targeted drug release, minimizing adverse effects and improving therapeutic outcomes.
✓ Nanoparticles enhance drug permeability and absorption through biological membranes, leading to increased bioavailability.
✓ Nanotechnology supports the delivery of challenging drugs, such as those in BCS Class II and IV, while reducing pill burden and promoting patient adherence.
✓ Advances in formulation design and process optimization have improved the scalability and reproducibility of nanoparticle-based drug delivery platforms.[42]

- *Disadvantages*:

✓ Producing nanotechnology-based formulations is complex and expensive, demanding specialized equipment and technical expertise.
✓ Ensuring consistent particle size distribution, stability, and reproducibility between batches is challenging.
✓ Potential nanomaterial toxicity necessitates thorough safety assessments, adding regulatory complexity.[42]

➢ *Supercritical Fluid Technique:*

Charles Cagniard de la Tour first discovered supercritical fluids in 1822 through cannon barrel experiments observing the critical point where liquid and gas phases merge above a substance's critical temperature. Supercritical fluid (SCF) techniques enhance drug solubility by using fluids above their critical temperature and pressure, combining gas-like diffusivity with liquid-like density. Supercritical CO2 is commonly employed due to its low toxicity, non-flammability, and adjustable solvent properties. Methods such as RESS, SAS, and SFEE enable efficient particle size reduction, micronization, and uniform particle formation. Supercritical fluid methods significantly improve drug solubility and dissolution rates by generating micro- and nanoparticles, frequently in amorphous forms, thereby enhancing bioavailability. The rapid extraction of organic solvents and inhibition of particle agglomeration enable precise control of particle size distribution and morphology. SCF processes are environmentally sustainable and allow fine adjustment of formulation properties by varying temperature and pressure conditions.[43]

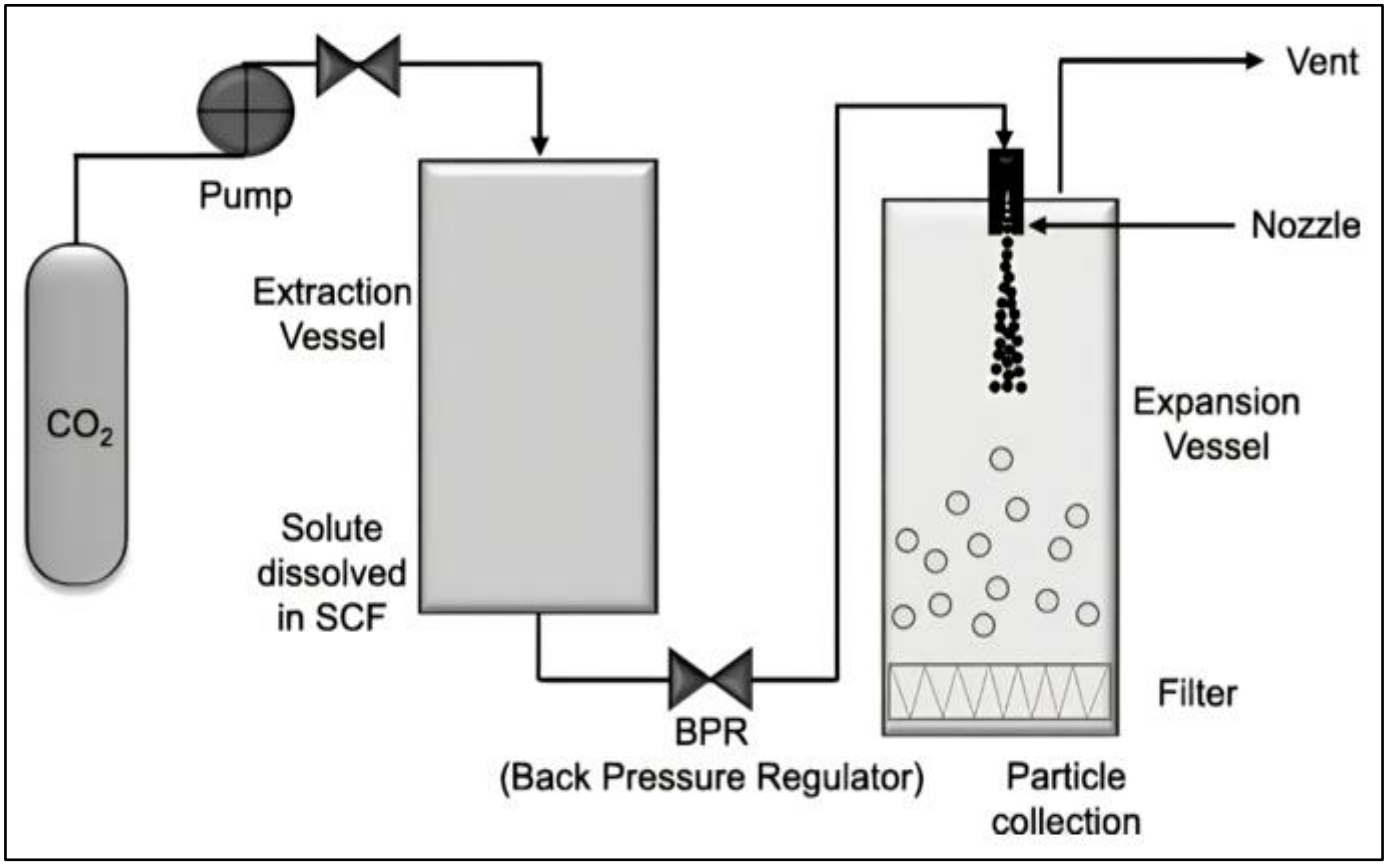

Fig 8 Supercritical Fluid Technique

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- *Advantages:*

✓ SCF techniques generate uniform, narrowly sized particles with controlled morphology, enhancing drug bioavailability.
✓ These methods enable solvent-free or minimal-solvent processing, making them environmentally friendly and minimizing residual solvent issues.
✓ Supercritical fluids, such as CO2, offer tunable solvent properties through temperature and pressure adjustments, allowing precise control over particle formation.
✓ SCF processes can improve solubility by producing amorphous drug forms or solid dispersions.[43]

- *Disadvantages*:

✓ SCF technology involves specialized high-pressure equipment, making it costly and technically complex.
✓ Limited solubility of certain drugs and polymers in supercritical fluids can restrict the applicability of the method.
✓ High pressures and temperatures used in SCF processes may cause degradation of heat-sensitive drugs.[43]

➢ *Liquisolid Method:*

Spireas and colleagues first discovered and described the liquisolid technique in the mid-1990s as a method to convert liquid drug formulations into free-flowing, compressible powders for enhanced dissolution of poorly water-soluble drugs. The liquisolid technique is an innovative strategy to improve the solubility and bioavailability of poorly water-soluble drugs. It involves transforming liquid drugs or solutions in non-volatile solvents into dry, non-adherent, free-flowing, and compressible powders by blending with suitable carriers and coating agents. The resulting liquisolid systems exhibit enhanced wetting, decreased particle size and crystallinity, and increased surface area, thereby improving dissolution rates. The liquisolid technique can provide superior dissolution enhancement compared to solid dispersion methods. It is versatile, suitable for both immediate- and sustained-release formulations, and helps reduce the influence of pH variations on drug release. Additionally, it can improve the photostability of drugs and is regarded as a cost-effective, scalable, and industrially feasible approach for large-scale manufacturing. [44]

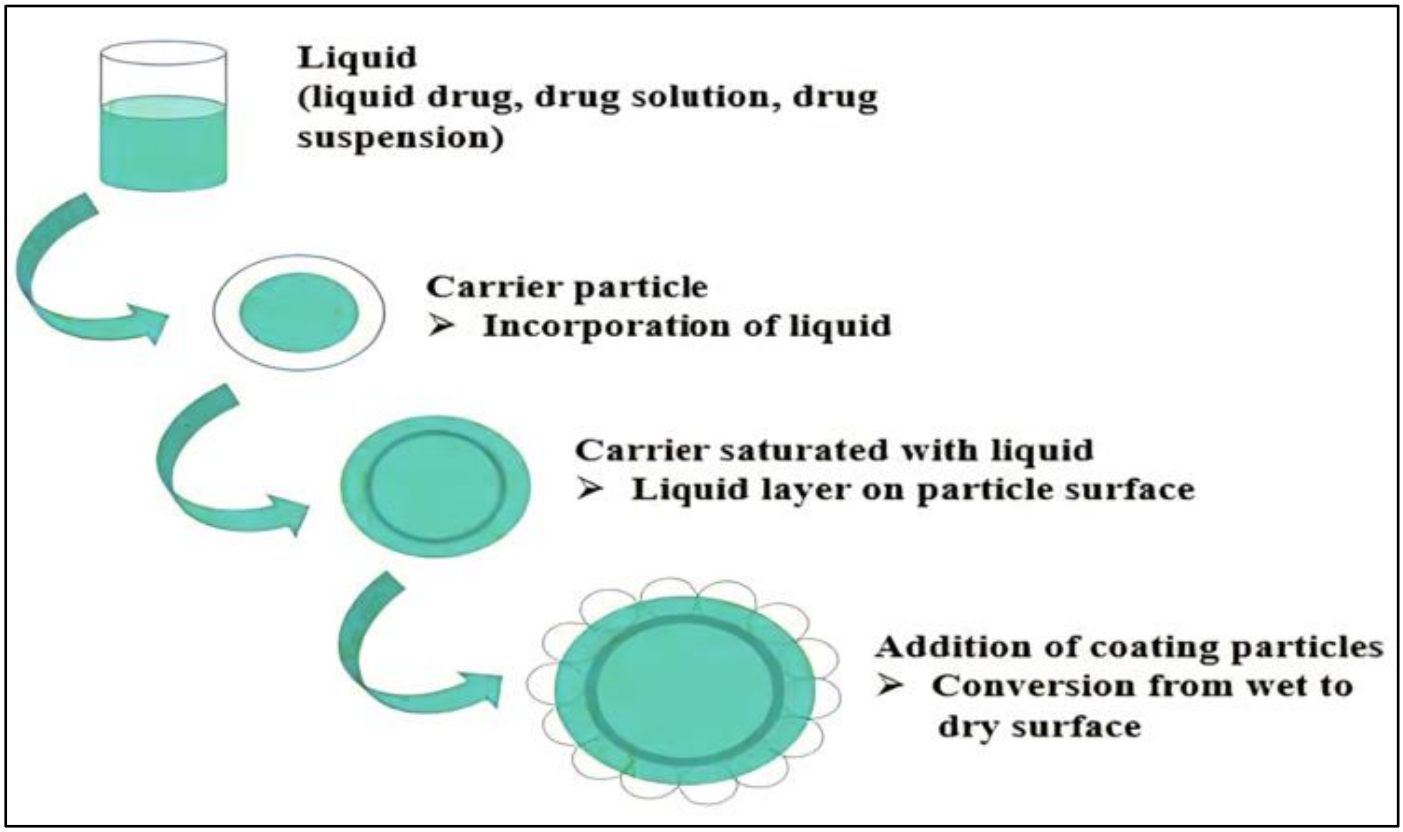

Fig 8 Liquisolid Method

- *Advantages:*

✓ It offers substantial improvement in the dissolution rate and bioavailability of poorly water-soluble drugs, including those that are only slightly or practically insoluble in water.
✓ The technique produces liquisolid systems with superior wetting properties and a larger effective surface area, promoting faster drug dissolution.
✓ It is adaptable for both immediate-release and sustained-release formulations, with the potential to achieve zero-order release in controlled-release systems.[44]

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- ✓ The method reduces the impact of pH variations on drug release and can enhance the photostability of sensitive drugs.
- ✓ Liquisolid formulations typically exhibit good flowability and compressibility, making them suitable for industrial-scale production.
- ✓ Compared with solid dispersions and conventional tablets, liquisolid tablets generally provide markedly improved dissolution performance.[44]

- *Disadvantages:*

- ✓ Tablets may become larger and heavier, which can make swallowing difficult, particularly for sustained-release liquisolid formulations.
- ✓ Careful formulation optimization is needed to balance drug load, excipient ratios, flow characteristics, and dissolution performance.
- ✓ Some liquid drug may be lost during processing, potentially impacting dose uniformity and consistency.[44]

➢ *Spray Drying:*

Samuel Percy first discovered and patented spray drying in 1872 with U.S. Patent No. 125,777 titled "Improvement in Drying and Concentrating Liquids by Atomizing and Desiccation," describing atomization of liquids into hot air for rapid drying to prevent chemical changes.[52]

Spray drying atomizes liquid feed (drug dissolved in organic solvents with polymers like PVP or HPMCAS) into hot gas, evaporating solvent in seconds to yield fine, porous powders (1-100 μm) ideal for BCS Class II/IV compounds, preventing recrystallization via polymer stabilization.[53]

- *Mechanism and Process:*

Drug-polymer solution sprayed via nozzle into drying chamber (inlet 100-200°C); rapid drying “locks” API in amorphous form, increasing solubility 10-1000x while polymers inhibit nucleation. Key parameters: inlet temperature, atomization pressure, feed rate.[53]

- *Advantages:*

- ✓ Rapid, continuous, scalable process producing uniform particles (1-100 μm) with controlled morphology for tablets/capsules.
- ✓ Aseptic manufacturing capability, taste masking, and improved bioavailability for BCS Class II drugs without thermal degradation.[53]

- *Disadvantages*:

- ✓ High equipment/maintenance costs and nozzle clogging requiring skilled operation.
- ✓ Heat sensitivity risks for thermolabile drugs despite short exposure (milliseconds).[53]

➢ *Spherical Agglomeration:*

Dr. Yukihiro Kawashima from Gifu Pharmaceutical University, Japan, discovered and introduced spherical agglomeration (SA) in 1986 for pharmaceutical applications, patenting the technique to enhance flowability and dissolution of poorly water-soluble drugs through controlled crystallization. Kawashima's seminal work demonstrated SA using tolbutamide in solvent-antisolvent-bridging liquid systems, achieving spherical crystals with enhanced micromeritics and solubility, establishing it as a novel particle engineering method.[54]

Spherical agglomeration enhances solubility of poorly water-soluble drugs by inducing controlled crystal aggregation during crystallization, forming uniform spherical particles with improved wettability, surface area, and dissolution rates while enhancing flow properties for direct compression.[54]

➢ *Mechanism and Process:*

Drug solution in good solvent (e.g., methanol) added to anti-solvent mixture (water/chloroform) with bridging liquid and polymer (PVP K-30), creating spherical agglomerates (100-300 μm) via interfacial tension reduction and partial amorphization, yielding 10-15x solubility increase for cilostazol or simvastatin.[54]

- *Advantages*:

- ✓ Simultaneous improvement in solubility, dissolution, and micromeritics (flow, compressibility) for tableting.
- ✓ Simple, one-step, solvent-based process without high energy input.[54]

- *Disadvantages:*

- ✓ Filtration and drying processes challenging for large batches.
- ✓ Restricted to water-insoluble drugs; hydrophilic excipients incompatible. [54]

➢ *Precipitation Technique:*

Precipitation for nanosuspensions emerged in the mid-1990s as a bottom-up approach, with early pharmaceutical applications building on 1980s antisolvent crystallization. Liversidge et al. (1990s RTP Pharma) combined it with homogenization (Nanocrystals® process), while Müller advanced it academically. Precipitation technique enhances solubility of low water-soluble drugs by dissolving the drug in a good solvent and rapidly adding it to a miscible antisolvent, inducing supersaturation and controlled nucleation to form nanocrystals or amorphous precipitates with increased surface area and dissolution rates.[12]

➢ *Mechanism and Process:*

Drug dissolved in organic solvent (e.g., acetone) injected into aqueous antisolvent with stabilizers (PVA, Tween 80); rapid desolvation forms nanoparticles (100-500 nm). Often combined with high-pressure homogenization to arrest growth and stabilize amorphous forms. [12,5]

- *Advantages*:

- ✓ Simple, low-cost equipment and rapid process.

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- ✓ Solvent evaporation leaves pure drug nanocrystals.
- ✓ Suitable for thermolabile drugs (room temperature).[12,8]

- *Disadvantages*:

- ✓ Particle growth to microparticles without immediate homogenization.
- ✓ Limited to drugs soluble in solvent but insoluble in antisolvent.
- ✓ Stability issues (Ostwald ripening, aggregation).[12]

➢ *Cryogenic Method:*

Briggs and Maxvell first introduced spray freezing onto cryogenic fluids in the early 1990s, atomizing drug solutions above boiling fluorocarbon refrigerants. Spray freezing into liquid (SFL) was commercialized by Dow Chemical Company in the late 1990s, with ultra-rapid freezing (URF) emerging around 2000 using solid cryogen substrates. These evolved from 1980s cryopreservation techniques. [12,4]

Cryogenic methods enhance solubility of poorly water-soluble drugs by ultra-rapid freezing of drug solutions using liquid cryogens (liquid nitrogen, argon), creating nanostructured amorphous particles with high porosity and surface area that improve dissolution rates upon lyophilization. [12,13]

- *Key Processes:*

- ✓ SFD/SFL: Drug solution sprayed into liquid N_2, frozen, then lyophilized to porous powders (10-100x solubility boost).
- ✓ URF: Solution applied to cryogenic solid surface for instant freezing and amorphization. [12,9]

- *Advantages:*

- ✓ Produces highly porous amorphous nanostructures without thermal degradation.
- ✓ Excellent for thermolabile biologics and high bioavailability gains.
- ✓ Controlled particle morphology and superior stability post-lyophilization.[12]

- *Disadvantages:*

- ✓ Requires cryogenic liquids and lyophilization (high cost, complexity).
- ✓ Scale-up challenges and equipment investment.
- ✓ Limited to freeze-dryable formulations.[12]

XI. CONCLUSION

A review of " Formulation-Driven Strategies for Overcoming Solubility Barriers in Drug Development" emphasizes that improving aqueous solubility is essential for increasing drug dissolution, absorption, and overall bioavailability, all of which are crucial for achieving optimal therapeutic outcomes. Numerous conventional and advanced techniques (such as particle size reduction, solid dispersions, inclusion complexes, micronization, nanotechnology-based systems, supercritical fluid processing, hydrotropy, co-crystallization, prodrug design, liquisolid technology, etc.) offer diverse mechanisms to enhance solubility and performance. Each approach provides specific benefits, including improved dissolution efficiency, enhanced stability, targeted delivery potential, and better patient compliance. The review underscores the need to carefully choose a suitable technique by considering the physicochemical characteristics of the drug and the intended formulation objectives. Despite the significant progress made in overcoming solubility challenges, issues related to scalability, long-term stability, regulatory requirements, and manufacturing complexity continue to pose constraints.

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