A Review on Solubility Enhancement Techniques

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***Abstract*—Solubility enhancement is a critical strategy in pharmaceutical development, as a significant proportion of newly discovered drug candidates exhibit poor aqueous solubility, leading to low bioavailability and reduced therapeutic efficacy. Various techniques have been developed to overcome solubility limitations and improve drug absorption. These approaches are broadly categorized into physical, chemical, and formulation-based methods. Physical modifications include particle size reduction (micronization and nanonization), solid dispersion formation, and crystal engineering. Chemical methods involve salt formation, prodrug synthesis, and pH adjustment to improve dissolution characteristics. Formulation strategies such as the use of surfactants, co- solvents, complexation (e.g., cyclodextrin inclusion complexes), lipid-based drug delivery systems, and self-emulsifying drug delivery systems (SEDDS) further enhance solubility and dissolution rates. Advanced techniques like supercritical fluid technology and nanotechnology-based carriers also show promising results. The selection of an appropriate solubility enhancement method depends on the physicochemical properties of the drug, route of administration, and desired pharmacokinetic profile.**

***Index Terms*—solubility enhancement, bcs classification, ph adjustment, co-solvency, co-crystalization, solubilizing, formation of salt, surfactant, solvent evaporation, micro-emulsion, co-micronization, nano-emulsion, homogenization, spray drying, hydrotrophy.**

I. INTRODUCTION:

Solubility is an important phenomenon and most of the time discussed but still or not completely resolved issued. Saturation and dissolution these are the fundamental ideas in the physical and chemical sciences, as well as their applications to biopharmaceutical and pharmacokinetic aspects of drug treatment. (1) But as the synthetic approach is growing successfully to deliver many promising lead compounds for most of the pharmacological categories, they are also taking the molecules towards bulkier structures.

These properties e.g., rate and extent of absorption, rate of distribution, dose to achieve minimum effective concentration and to avoid side effects can exert a significant influence on the drug's absorption, distribution, metabolism, excretion, and toxicity. (2) The solubility of the drug, the solution, and its gastrointestinal permeability are essential factors that control the amount of absorption and absorption speed, along with the bioavailability of the drug. (3) The idea of permeability and solubility characteristics had been helpful to classify the drug under four classes prescribed by Biopharmaceutics Classification System (BCS). The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. (2) Among these are solubility, permeability, stability, safety and efficacy etc. [3] Among these challenges, poor water solubility of the newly discovered compounds has appeared as the most common challenge in the early drug development, while inefficacy was found as main reason of drug failure in later drug development phases such as phase II (4).

It is momentous to note that some operational/functional parameters like bioavailability, solubility, dissolution rate, permeability and morphology can considerably influence the physicochemical property and therefore, the therapeutic efficacy of each determined drug. Nearly 65 to 75% of prevalent APIs are recently in solid structure or consists of solid APIs formulated as solid suspensions. (5) The pharmaceutical industry includes the manufacture of compounds and medicines intended for human or veterinary use. Pharmaceutical manufacturing can be divided into primary pharmaceutical manufacturing, related to the production of chemical compounds of therapeutic value (active pharmaceutical ingredients (APIs)), and

secondary pharmaceutical manufacturing, which produces medicines by a suitable formulation of API(s) and appropriate excipient in a final product (e.g., tablets). The case studies presented here illustrate the application of chemometric techniques to primary industry processes. Nevertheless, all the techniques described in the case studies are valid for secondary [6].

Numerous formulation perspectives are currently being applied to handle challenges related to formulations of biopharmaceutical class system (BCS) drugs; this includes compound pre-dissolution in suitable solvents followed by capsule filing with this formulation, or as solid solution formulations that utilize water-soluble polymers.[7] The two features of this formulation technique are a polymer-based molecular dispersion of the medication and an enhanced glass transition temperature. Nevertheless, because the drug is poorly dissolved in solid form in the polymer, and depending on the intended dose, glass solutions may produce extremely high bulk doses in tablets or capsules, sometimes making this approach impossible.

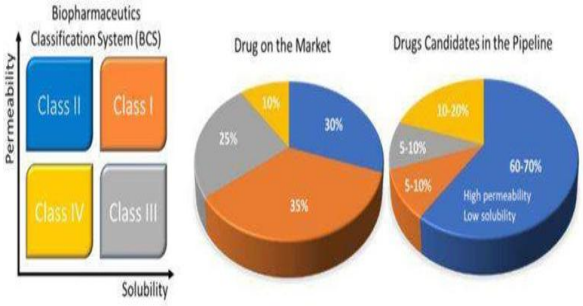

Figure (1). BCS classification chart

Table.1 Biopharmaceutics Classification System (BCS) with characteristics of drugs

Sr. No.	BCS Class	Solubility	Permeability	Example
1.	Class I	High	High	Metoprolol, Amlodipine
2.	Class II	Low	High	Ibuprofen, Naproxen
3.	Class III	High	Low	Cimetidine, Ranitidine
4.	Class IV	Low	Low	Furosemide, Nelfinavir

Currently, one of the primary challenges faced by the pharmaceutical industry is the poor water solubility and insufficient bioavailability of drugs. Current data suggest that approximately 40% of commercially available pharmaceuticals, as well as a significant majority of investigational drugs, struggle with low solubility. This issue can lead to compromised bioavailability and diminished therapeutic effectiveness, often necessitating increased dosages to achieve the desired medicinal impact [8].

Solubility refers to the maximum amount of solute that can dissolve in a solvent, quantified by the concentration in a saturated solution. Solubilization occurs when poorly soluble solutes dissolve in aqueous surfactant solutions through interactions like dipole-dipole, ion-dipole forces, and hydrogen bonding. Factors affecting solubility include solute-related properties such as size, shape, surface area, pKa, and polymorphism; solvent-related aspects like polarity, pH, and volume; as well as environmental factors like temperature and pressure [9]. Solubility can be called the property of a substance, whether a solid, liquid, or gas which is described as a “Solute” to be dissolved in a solid, liquid or gaseous solvent to form a homogeneous one-phase system [10]. For these drug candidates, poor aqueous solubility and poor dissolution in the GI fluids is a limiting factor to the in vivo bioavailability after oral administration. Therefore, in vitro dissolution has been recognized as an important element in drug development and thus increasing the dissolution rate of poorly soluble drugs and enhancing their bioavailability is an important challenge to pharmaceutical scientists [11].

II. METHOD

SOLUBILITY ENHANCEMENT TECHNIQUES:

Figure (2). traditional solubility enhancement technique

Surfactant

Surfactant is the method which is used to reduce the void fraction from the liquid–solid, liquid– liquid, or liquid– gas. Surfactants are widely used for the purpose of improving the solubility of drugs. Surfactant is the best solubility-enhancing agents and for the dissolution purpose [1].

High HLB-value-containing surfactants are commonly used in forming EFDDS, including polysorbate 80, poloxamers, Gelucire (HLB 10), sorbitan monooleate (Span 80), cremophor EL, hexadecyltrimethylammonium bromide, sodium lauryl sulphate, and bis2-Ethylhexyl sulfosuccinate. Additionally, fatty alcohols and famous surfactants, such as cetyl and stearyl, lauryl, glyceryl, and esters of fatty acids, are also incorporated [9]. Surfactants occurring naturally are also endorsed for SEFs; the most commonly used surfactant is lecithin, with the due reason of the most significant biocompatibility. It has phosphatidylcholine as a fundamental component, having an amphiphilic structure and water-solubilizing properties. To get stable SEFs, the commonly used surfactant concentration is 30 to 60% w/w.

Co-solvency

Solute is frequently more soluble in a mixture of solvents compared to a single solvent; a phenomenon known as Co-solvency. Cosolvents are solvents that enhance the solubility of a drug in water. Commonly used water-miscible cosolvents include ethanol, propylene glycol, glycerin, and polyethylene glycols (PEG 300 and PEG 400). This concept is frequently employed in the formulation of liquid dosage forms such as syrups, elixirs, injections, creams, and lotions. Additionally, supplementary solvents such as benzyl alcohol, dimethyl sulfoxide (DMSO), dimethyl acetamide (DMA), and dimethyl formamide (DMF) are also utilized. [3].

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Table.2 *Poorly soluble drugs, co-solvent derivatives and degree of solubility enhancement*

Drug	Co-solvents	Solubility enhancement
Methyl propyl trisulfide	Ethanol and cremophur	2900 fold
Ethyl-paraben	Nicotinamide	2 fold
6-mercaptopurine	Sodium benzoate & sodium hippurate	6 fold
Phosphoramidates	Tyrosine derivative	30 fold
Enrofloxacin	Ethanol, glycerol, PEG 400, propylene glycol	1.1-3.3 fold
Ferulic acid	Isopropanol	Approx. 53 fold

Co-solvency includes altering the entire solvent environment with small amounts of water-miscible solvents.

- Feature: -Co-solvency
- Concept: -Uses water-miscible solvents to dissolve drugs.
- Mechanism: -Modifies solvent polarity to dissolve the drug. Requires small amounts of solvent. Type of Drugs Effective for lipophilic drugs. Works for a wide variety of poorly soluble drugs.
- Stability: -Less stable due to solvent evaporation.[3].

Advantage: -

Provides the optimum solubility for non-polar drugs by reducing solvent polarity. The presence of aco-solvent can provide additional solubilization for drug solutions where pH manipulation is insufficient.

Limitation: -

The use of co-solvents is limited to relatively few solvents. The risk of precipitation upon dilution. It may alter the pH and strength of the buffers that are contained in a drug formulation [4].

pH adjustment: -

Adjustment of micro-environmental pH to modify the ionization behavior is the simplest and most commonly used method to increase water solubility of ionizable compounds. As per pH-partition

hypothesis and Henderson- Hessel batch equation, ionization of a compound is dependent on the pH of media and pKa of drug. The change in the ionic milieu can also result to in situ salt formation. However, this salt formation is infeasible for unionized compounds. The formed salts may also converse to respective acid or base forms in gastrointestinal-tract 11.PH adjustment techniques they involve the solubility enhancement technique [5].

Advantage: -

The simple and powerful strategy for solubility adjustment of ionizable drugs. The level of ionization of the drug candidates enables full solvation of the target medication dose. This method works equally well with drug salts or the corresponding free basic oracid medicines.

Limitation: -

The long-term effect on the drug stability. The distortion on physiological Ph. The precipitation tendencies and incompatibility upon dilution [6].

Co-crystallization

A co-crystal is a crystalline structure wherein specific stoichiometric amounts ofnon-covalent forces hold two or more electrically neutral substances together. The co-crystallization of two active drug products, aspirin and acetaminophen, was already recorded. It is similar to salt production, especially in the case of neutral substances and can be produced via evaporation, sublimation, melt growth, and slurry preparation. In one study, the formation and characterization of three different ezetimibe crystals (utilizing methylparaben as a conformator via three different processes: solution crystallization, liquid-assisted crushing, and reaction crystallization) has been report. Differential scanning calorimetry (DSC), Fourier transform infrared (FTIR), Raman spectroscopy, and powder X-ray diffraction (PXRD) studies show that different peak melting temperatures were observed in the three co-crystals, suggesting the development of anew solid phase. The equilibrium solubility and dissolution studies of the co-crystals show that the co-crystals of ezetimibe and methylparaben could be a possible and potential alternative and effective strategy for increasing solubility [7].

Co-crystals are high energy forms and are known to increase solubility of the included drugs due to rapid dissociation in the medium, thus creating a supersaturated drug [8].

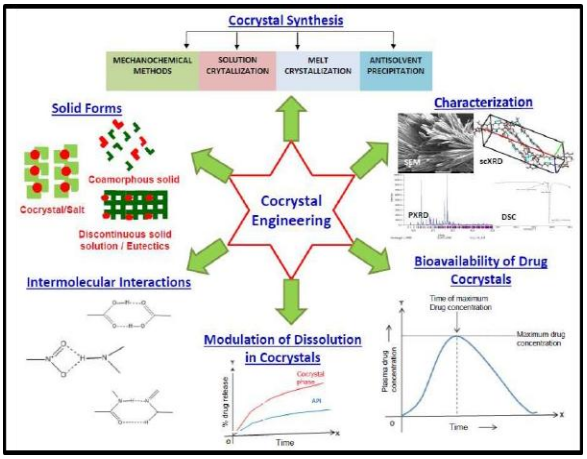

Figure. (3) co-crystal synthesis

Solubilizing agent

This is the method in which solvents are used for better solubility and dissolving of drugs to the body and for the better therapeutic effects.

The solubilizing agents like super-disintegrates such as cross-carmel lose sodium and sodium starch glycolate which is used as solubilizing compounds in different kinds of preparation which develops the solubility and dissolve of drugs. Improved gum Arabic or gum karaya, an established material was estimated as carrier for dissolution and improved the low soluble of drugs like nimtop. The water solubility of drug antimalarial agent tablet of halofantrine hydrochloride was amplified by the adding of caffeine and niacinamide [9].

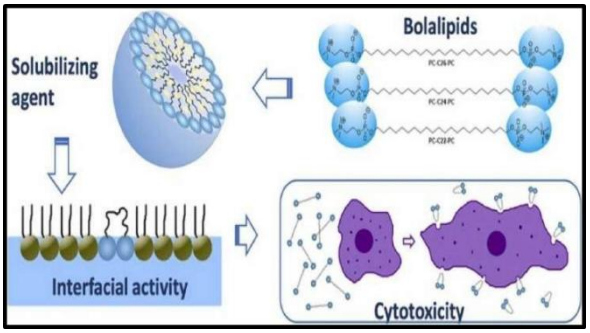

Figure. (4) Solubilizing agent

Formation of salt

Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several

decades to enhance solubility. It is an effective method in parenteral and other liquid formulations, as well as in solid dosage forms. Of approximately 300 new chemical entities approved by the FDA during the 12 years from1995 to 2006 for marketing, 120 were in salt forms. In addition, out of the 101 approved salts of basic drugs, 54 salts were prepared with hydrochloric acid, indicating the hydrochloride was the predominant salt form 12.

- There should be minimum difference of 2-3 pKa units between the drug and the counter ion.
- Counter ion should decrease crystal lattice forces.
- It should be FDA approved or should have enough toxicological data to support the selection of the counter ion.

Polymeric alteration

With the increasing world population, meeting the growing energy demand in a safe and environmentally responsible manner is a vital challenge. In 2040, oil and natural gas will still account for over 50% of the world's energy consumption, yet the contribution of renewable energy resources appears to be inadequate in meeting the rising energy demand. Due to increased energy demand, it is imperative to maximize the recovery from existing oilfields. The recovery factor of mature oilfields is nearly 30%, which means a large proportion of "original oil in place" (OOIP) is left behind in the subsurface. This increases the potential for enhanced oil recovery (EOR) methods.

The concept of polymer injection was first established by Pye and Sandiford in 1964, when they observed that water mobility was reduced and oil recovery was improved by water-soluble polymers; these included the extended family of acrylamide polymers. Several pilots and field applications were then reported in the USA during the 1970s and 1980s and, since the mid-1990s, polymer flooding has also been implemented in China with success. Recently, several researchers have focused on synthesizing water-soluble polymers with improved rheological properties high salinities and temperatures [11].

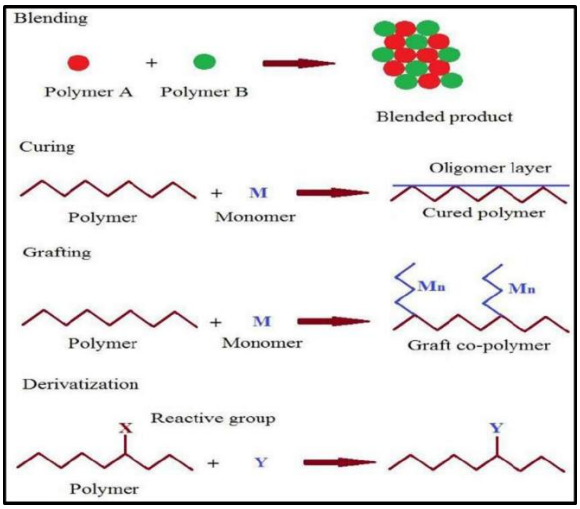

Figure (5): Polymeric alteration

Size reduction of particle

Particle size reduction is one of the oldest strategies for improving solubility of drugs since solubility of drugs is intrinsically related to drug particle size. Many strategies like polymorphism, salt formation, co–crystal formation and addition of excipient also marginally increase the solubility of the insoluble drugs but their use is mainly limited due to low success rates for increasing bioavailability and in some cases, being undesirable due to production of toxic side effects. Because of this reason, particle size reduction remains to be a safe method to increase solubility of drug substances without altering the chemical nature of the drug. It is well known that decrease in particle size and corresponding increase in the surface area of the particles, increases the dissolution rate of that substance as described by the famous Noyes–Whitney equation back in the late nine tenth century [12].

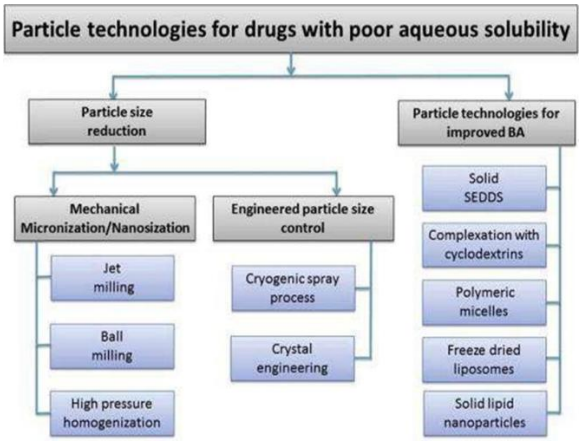

Figure. (6) size reduction particle

The drug solubility depends on its particle size. Large particles provide a low surface area, which results in less interaction of particles with the solvent.

Micronization

The process of producing drug particles in micron size by using the physical method. The methods widely used for

increasing BCS class II drugs' solubility are freeze-drying, crystallization, spray drying, and milling [13].

Ball milling

Ball milling is an organic-solvent-free method that offers opportunities to modify the formulation by controlling parameters such as milling speed, milling time, and ball-to-powder ratio. Innovations in milling techniques, including high-energy ball milling, provide avenues for optimizing particle size distribution and enhancing stability. The optimization of temperature control during milling can help to overcome challenges related to recrystallization [14].

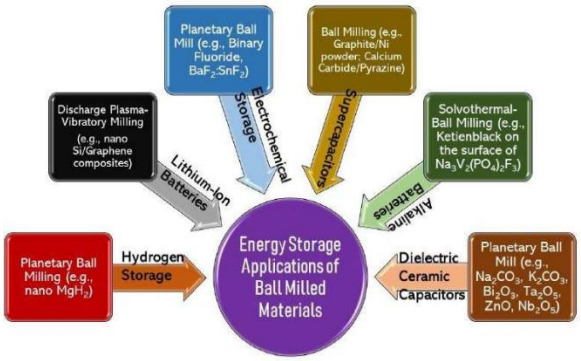

Figure. (7) ball milling

Jet milling

Jet milling is a size reduction process commonly used to produce fine powders. It uses high-pressure air or steam to accelerate particles at high speeds, causing them to collide and break down into smaller sizes. The process is highly effective for materials that are hard to grind or have a high melting point.

- Feed material
- Air jets
- Particle collision
- Separation

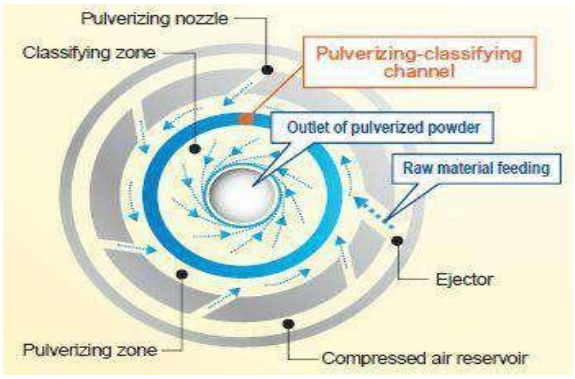

Figure (8). jet milling

Co-micronization

The concept of rapid dispersible, fast dissolving, quick dissolving, and ordispersible tablets dosage forms have acquired great importance in recent years due to their unique properties and advantages over other available dosage forms.1, 2 In the recent years, great interests in the modification of drug release by using various methods such as solid dispersion, particle size reduction, micronization, direct compaction method, melt granulation techniques, solvent deposition inclusion complexation methods were adopted in formulation.3 The basic goal behind all of such innovations include developing a suitable formulation with rapid release of poorly water-soluble drugs.4Nearly one- third of drugs in development are water insoluble and one-half fail in trials because of underprivileged pharmacokinetics.5 Tolfenamic Acid also falls in the same category, the basic challenge in formulation of Tolfenamic acid is its poor solubility.6Tolfenamic Acid is an orally and parenterally administered Nonsteroidal anti-inflammatory drug belonging to the fenamategroup.7 Since the Tolfenamic acid is poorly water soluble drug so the dissolution is the rate limiting step for the absorption of drug[15].

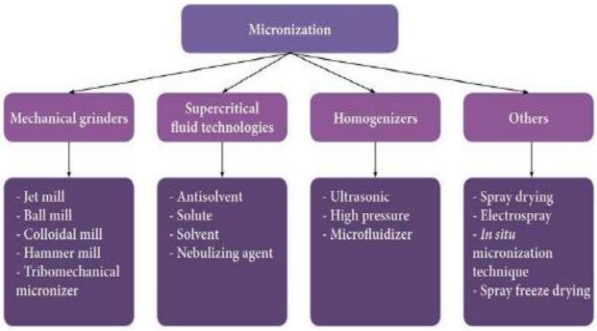

Figure. (9) micronization techniques

Micro-emulsion

Another piece of work sought to investigate excipient influences on liquid self-micro-emulsifying-drug-delivery- systems (SMEDDS) and l-tetrahydropalmatine (l-THP) containing SMEDDS laden in the pellet properties.

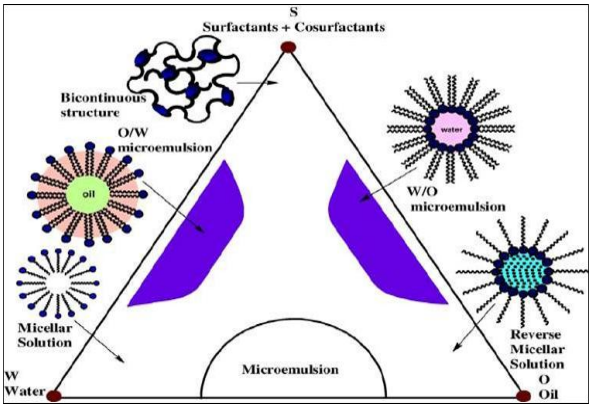

Figure (10). Micro- emulsion

In addition, the study was extended with a rabbit model to compare l-THP suspension and such SMEDDS bioavailability. Capryol90 and surfactant mis were interrogated in the SMEDDS formulation at their optimum ratio.

In pellet-SMEDDS, l-THP showed an amorphous state proved by powder X-ray diffractometry. When a pharmacokinetic study using LCMS, spectrometry was carried out in a rabbit model, the results revealed that SMEDDS enhances l-THP oral bioavailability by 198.63% compared with the l-THP suspension. The study also demonstrated that there was no noteworthy difference from the original liquid SMEDDS, the ultimate mean concentration (Cmax), and the relative mean bioavailability of pellet-SMEDDS [35]. Another potent anti- inflammatory agent, Boswellia serrate gum resin, has been vastly used in ancient medicines. However, its efficacy must be evaluated, as it has low oral bioavailability [17].

Inclusion Complexation

Inclusion complexes are formed by inserting a non-polar molecule (guest molecule) into the cavity of another molecule or group of molecules (host molecule). The inclusion complex creation approach has been used more accurately than any other solubility enhancement method to increase the aqueous solubility, dissolution rate, and bioavailability of the drugs. Here, cyclodextrins (CDs) have been used as the most common host molecule. Poorly soluble therapeutics can have their physicochemical and biological characteristics changed with CDs by having drug molecules included in the cavity of the disc. CDs can attach lipophilic compounds via a variety of intermolecular interactions because of the hollow, lipophilic core cavity [43]. The kneading method, physical mixing, the co- precipitation method, and the solvent evaporation method are widely used for the preparation of inclusion complexes [44]. Rivaroxaban (RIV), an oral anticoagulant, is a poorly soluble drughaving a solubility of 0.005 and 0.006 mg/mL in water and acetate buffer of pH 4.5, respectively [18].

Advance techniques for solubility enhancement

1. Homogenization
2. Nano suspension
3. Supercritical fluid process
4. Spray drying
5. Hydrotrophy

Homogenization

With the development of manufacturing technology, a periodic array of microstructures which is also called metamaterial can satisfy more novel mechanical properties (Kadic et al., 2019, Khakalo et al., 2018). It seems logical to learn from nature and make more widespread use of metamaterial structures, providing transformative alternatives to more traditional materials such as alloys and composites. Although the fabrication of metamaterials is extremely challenging, recent rapid advances in additive manufacturing have significantly alleviated the technical problems of fabricating metamaterials, thus suggesting that designs with carefully engineered artificial metamaterial structures may eventually be possible. While the design of nature-inspired metamaterials is not new to the scientific community and has had many successful applications, there has not been a huge advancement in the use of metamaterials within the design cycle (Bolshak & Ryvkin, 2023). The reason for this lag mainly stems from theoretical aspects, that is, an incomplete understanding of how *size-dependent surface effects* arise from the underlying microstructure and affect the intrinsic multiscale response of the material greatly limits the

ability to design and model its properties. Moreover, the metamaterial structures filled with complex microstructures often need computationally prohibitive resources if the fully-resolved microstructures are modeled using high-fidelity approaches [19].

Nano emulsions

Nano-emulsions also known as nanometricsized emulsions are fine water-in-oil (w/o) and oil-in-water (o/w) dispersions of two immiscible fluids, as opposed to the milky-white hue concomitant with coarse dispersion. These 20–200 nm droplets are stabilized by adding the appropriate amphiphilic emulsifiers or emulsifiers. Consequently, nanoemulsions are also known as mini-emulsions. Due to kinetic stability, nanoemulsions (NE) are stable on heterogeneous systems, in contrast to microemulsions (ME).. The history of nanoemulsions can be traced back to the

early 20th century when researchers first began experimenting with colloidal systems. Initial work focused on macroemulsions and microemulsions, but it laid the groundwork for the development of nanoemulsions. Nanoemulsions as a distinct category of emulsions gained significant attention in the 1990s. Researchers started to explore their unique properties, such as their extremely small droplet sizes, typically ranging from 20 to 200 nanometers. This period marked a shift toward understanding the potential applications of nanoemulsions, particularly in the pharmaceutical and food industries.

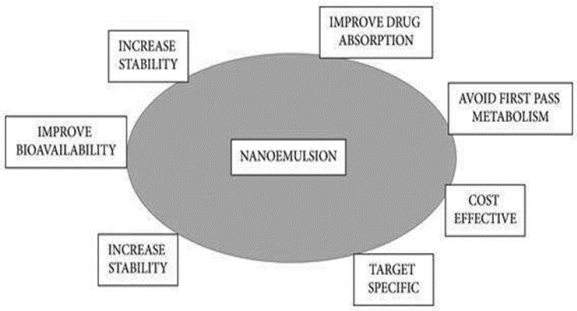

Figure (11). nano-emulsion

The following benefits explain why nanoemulsion is appealing in both the personal care and cosmetics industry and in health care.

(1) Nanoemulsion can be produced with lower concentrations of emulsifier (3–10%) than ME, which needs a high concentration (20%).

(2) Nanoemulsion helps in the effective transportation of active substances through a semipermeable membrane, and due to the large surface area, penetration increases in the emulsion system.

(3) Besides preventing droplet flocculation, nanoemulsions' small globule size additionally avoids larger droplet

flocculation. This enables the system to survive in solitude without being divided.

(4) Tiny droplets or globules in a nanoemulsion are responsible for the reduction in gravitational forces and Brownian motion. Consequently, there is no creaming or sedimentation while the product is being stored.

(5) Nanoemulsions are simple to make and do not require a lot of energy to create. Nanoemulsion formulations are said to improve the reproducibility of the plasma concentration profile and bioavailability [20].

Supercritical fluid process

Traditionally, medicinal plants and seeds are used in the production of herbal drugs owing to the preference to using allopathic medicines. The World Health Organization (WHO) has estimated that about 80% of earth's inhabitants depend on traditional medicines in the form of plant extracts and their specific molecular components. Some of these components present in oil seeds are proteins, amino acids, fatty acids, pigments, vitamins, polyphenols, etc. (Kirnak, Irik, Sipahioglu, & Unlukara, 2019). Here, development in the food and nutrition sciences has led to the use of nutraceuticals for their inherent physiological advantages. A major part of such food supplements contains oils derived from plants, or extracts as a phytochemical rich source. Plant and seed oils are not only utilized in medicinal and food industries, and are employed in cosmetic and drug products [22].

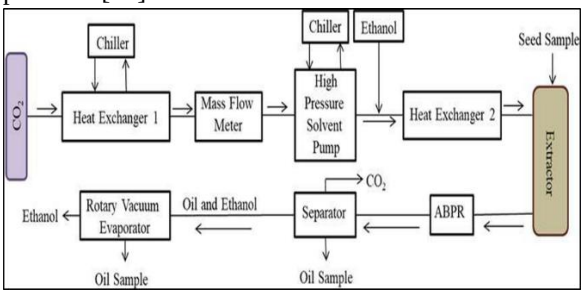

Figure (12). Super critical fluid process

Spray drying

Spray-drying parameters, including inlet temperature, feed rate, and drying gas flow rate, are critical in shaping particle characteristics.

Opportunities for modification involve optimizing these parameters for specific drug formulations, exploring novel nozzle designs for improved atomization, and integrating process analytical technologies for real-time monitoring. Innovations in spray-drying equipment could enhance overall process efficiency [23].

This approach utilizes spray-drying with enteric polymer to increase active ingredient solubility in the gastrointestinal system to achieve "super bioavailability" in comparison to traditional formulations. In this technology, API was spray-dried using a novel amorphous pH-dependent enteric polymer HPMC Phthalate. Unlike conventional Itraconazole, TOLSURA® is insoluble in the acidic environment of the stomach and soluble in the higher pH of the small intestine [76].

Hydrotrophy: - The term hydrotropy was coined by the scientist Carl A, Neuberg in 1916. Hydrotropy is a method of solubility enhancement that involves addition of large amount of a second solute to enhance the aqueous solubility of another substance. The second solute is a usually ionic organic salt which are alkali metal salts of different organic acids. If they increase the solubility in a specific solvent, these additives or salts are said to be "salt in" the solute and vice versa. They are called to "salt out" the solute. These salts have large cationic or anionic groups, are very soluble in water, and cause "salting in" non-electrolytes. They are called "hydrotropic salts," and this phenomenon is called "hydrotropism" Hydrotropic solutions do not show colloidal properties and involve a weak interactive force between the hydrotropic agent and the solute.10 There are weak van der Waal interactions like π π or attractive dipole-dipole between a hydrotropic molecule and a poorly soluble drug.11 Both hydrophobic and hydrophilic portions are found in the hydrotropes. As compared to surfactants, they contain a very small portion of hydrophobic part. The balance between the hydrophobic part and the hydrophilic part determines their efficiency.12 The more significant is the hydrophobic part, the better is the hydrotropic efficiency. The presence of charge on the hydrophilic part has no significance. Hydrotropic agents can be anionic, cationic, or neutral or can be solid or liquid and organic or inorganic [25].

III. CONCLUSIONS

Drug solubility is one of the crucial elements that control the formulation development, especially with regard to the rate and amount of medication to be absorbed. The methods covered above are able to increasing the drug's solubility. These methods in addition to or in conjunction with utilized to increase the drug's solubility and bioavailability as a result. The best way to choose the solubility enhancement technique is to guarantee the objectives of sound formulation. By increase, solubility also increases compliance with patients and also increases the less soluble drug's bioavailability. The selection of any method for improving the solubility is dependent upon the nature, and characteristics of the drug such as chemical nature, physical nature, pharmacokinetic behavior, etc. Pharmaceutical nanotechnology provides opportunities to improve materials and technology where existing technologies reaching their limits. It raiseshope to pharmaceutical industries by providing new patentable technologies in view of revenue loss caused due to off patent drugs. This provides profound tools for understanding the cells between normal and abnormal or any insights of molecular basis.

REFERENCE

[1] M. Patidar and B. Chouhan, "Recent advancement of solubility enhancement," [PDF]. Available: https://share.google/2idd5ta8rnhcvrab3

[2] Y. S. Thorat, I. D. Gonjari, and A. H. Hosmani, "Solubility enhancement techniques: A review on conventional and novel approaches," International Journal of Pharmaceutical Sciences and Research (IJPSR). Available: http://www.ijpsr.com

[3] D. V. Bhalani, N. Bhingaradiya, A. Kumar, and A. K. S. Chandel, "Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics," Biomedicines, vol. 10, no. 9, p. 2055, 2022. Available: https://doi.org/10.3390/biomedicines10092055

[4] M. Alshamrani, M. K. Khan, B. A. Khan, A. Salawi, and Y. Almoshari, "Technologies for

solubility, dissolution and permeation enhancement of natural compounds," Pharmaceuticals, vol. 15, no. 6, p. 653, 2022. Available: https://doi.org/10.3390/ph15060653

[5] M. J. Ansari, "An overview of techniques for multifold enhancement in solubility of poorly soluble drugs," Current Issues in Pharmacy and Medical Sciences. Available: http://www.curipms.umlub.pl/

[6] J. A. Alamode, "Recent advancements toward the increment of drug solubility using environmentally-friendly supercritical CO_2: A mainlining prospective," Frontiers in Medicine, 2024. doi: 10.3389/fmed.2024.1467289.

[7] A. Shoaib, B. Mangla, S. Javed, M. H. Sultan, S. S. Alqahtani, and F. Shakeel, "Vicissitudes of liquid crystals for solubility enhancement of poorly soluble drugs," Journal of Molecular Liquids, 2020. doi: 10.1016/j.molliq.2020.11492.

[8] R. K. Mehta, K. Soni, and A. Bhattarai, "Recent advances in improving the bioavailability of hydrophobic/lipophilic drugs and their delivery via self-emulsifying formulations," Colloids, vol. 7, no. 1, p. 16, 2023. doi: 10.3390/colloids7010016.

[9] R. Shelke, V. Velagacherla, and U. Y. Nayak, "Recent advances in dual-drug co-amorphous systems," Drug Discovery Today, 2023. doi: 10.1016/j.drudis.2023.103863.

[10] P. Khadka et al., "Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability," Asian Journal of Pharmaceutical Sciences, vol. 9, no. 6, pp. 304–316, 2014. doi: 10.1016/j.ajps.2014.05.005.

[11] D. V. Bhalani, N. Bhingaradiya, A. Kumar, and A. K. S. Chandel, "Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics," Biomedicines, vol. 10, no. 9, p. 2055, 2022. Available: https://www.mdpi.com/2227-9059/10/9/2055

[12] S. Tambe, D. Jain, S. K. Meruva, G. Rongala, A. Juluri, G. Nihalani, H. K. Mamidi, P. K. Nukala, and P. K. Bolla, "Recent advances in amorphous solid dispersions: Preformulation, formulation strategies, technological advancements and characterization," Pharmaceutics, vol. 14, no. 10, p. 2203, 2022. doi: 10.3390/pharmaceutics14102203.

[13] Y. Liu, Y. Liang, J. Yuhong, P. Xin, J. L. Han, Y. Du, X. Yu, R. Zhu, M. Zhang, W. Chen, and Y. Ma, "Advances in nanotechnology for enhancing the solubility and bioavailability of poorly soluble drugs," Drug Design, Development and Therapy, 2024. doi: 10.2147/DDDT.S447496.

[14] M. A. El Hamd, R. H. Obaydo, D. Nashed, M. El-Maghrabey, and H. M. Lotfy, "Hydrotropy and co-solvency: Sustainable strategies for enhancing solubility of poorly soluble pharmaceutical active ingredient," Talanta Open, 2024. doi: 10.1016/j.talo.2024.100391.

[15] A. D. Khan, M. Tabish, R. Kaushik, V. Saxena, P. Kesharwani, and S. Gupta, "Hydrotropy: Recent advancements in enhancement of drug solubility and formulation development," [Journal details not provided].

[16] P. Khadka et al., "Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability," Asian Journal of Pharmaceutical Sciences, vol. 9, no. 6, pp. 304–316, 2014. doi: 10.1016/j.ajps.2014.05.005.

[17] M. Patidar and B. Chouhan, "Recent advancement of solubility enhancement," [PDF]. Available: https://share.google/2idd5ta8rnhcvrab3

[18] R. K. Ameta, K. Soni, and A. Bhattarai, "Recent advances in improving the bioavailability of hydrophobic/lipophilic drugs and their delivery via self-emulsifying formulations," Colloids, vol. 7, no. 1, p. 16, 2023. doi: 10.3390/colloids7010016.

[19] D. V. Bhalani, N. Bhingaradiya, A. Kumar, and A. K. S. Chandel, "Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics," Biomedicines, vol. 10, no. 9, p. 2055, 2022. Available: https://www.mdpi.com/2227-9059/10/9/2055

[20] M. A. El Hamd, R. H. Obaydo, D. Nashed, M. El-Maghrabey, and H. M. Lotfy, "Hydrotropy and co-solvency: Sustainable strategies for enhancing solubility of poorly soluble pharmaceutical active ingredient," Talanta Open, 2024. doi: 10.1016/j.talo.2024.100391.

[21] D. V. Bhalani, N. Bhingaradiya, A. Kumar, and A. K. S. Chandel, "Bioavailability enhancement techniques for poorly aqueous soluble drugs and

therapeutics," Biomedicines, vol. 10, no. 9, p. 2055, 2022. Available: https://www.mdpi.com/2227-9059/10/9/2055

[22] D. V. Bhalani, N. Bhingaradiya, A. Kumar, and A. K. S. Chandel, "Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics," Biomedicines, vol. 10, no. 9, p. 2055, 2022. Available: https://www.mdpi.com/2227-9059/10/9/2055

[23] M. A. El Hamd, R. H. Obaydo, D. Nashed, M. El-Maghrabey, and H. M. Lotfy, "Hydrotropy and co-solvency: Sustainable strategies for enhancing solubility of poorly soluble pharmaceutical active ingredient," Talanta Open, 2024. doi: 10.1016/j.talo.2024.100391.

[24] L. Kumar, Y. Choudhari, P. Patel, G. D. Gupta, D. Singh, J. M. Rosenholm, K. K. Bansal, and B. D. Kurmi, "Advancement in solubilization approaches: A step towards bioavailability enhancement of poorly soluble drugs," Life, 2023. Available: https://www.mdpi.com/journal/life

[25] M. J. Ansari, "An overview of techniques for multifold enhancement in solubility of poorly soluble drugs," Current Issues in Pharmacy and Medical Sciences. Available: http://www.curipms.umlub.pl/

[26] D. V. Bhalani, N. Bhingaradiya, A. Kumar, and A. K. S. Chandel, "Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics," Biomedicines, vol. 10, no. 9, p. 2055, 2022. Available: https://www.mdpi.com/2227-9059/10/9/2055

[27] Y. S. Thorat, I. D. Gonjari, and A. H. Hosmani, "Solubility enhancement techniques: A review on conventional and novel approaches," International Journal of Pharmaceutical Sciences and Research (IJPSR). Available: http://www.ijpsr.com

[28] M. Mirzaie Yegane, P. E. Boukany, and P. Zitha, "Fundamentals and recent progress in the flow of water-soluble polymers in porous media for enhanced oil recovery," Energies, 2020. Available: https://www.mdpi.com/journal/energies

[29] D. V. Bhalani, N. Bhingaradiya, A. Kumar, and A. K. S. Chandel, "Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics," Biomedicines, vol. 10, no. 9, p. 2055, 2022. Available: https://www.mdpi.com/2227-9059/10/9/2055

[30] C. Anand, G. Vidyasagar, M. Rajmane, V. Agrawal, and S. Sawan, "Approach of co-micronization in solubility enhancement and release profile of rapid dispersible tablets of tolfenamic acid," Journal of Drug Delivery and Therapeutics. Available: http://jddtonline.info

[31] R. Shelke, V. Velagacherla, and U. Y. Nayak, "Recent advances in dual-drug co-amorphous systems," Drug Discovery Today, 2023. doi: 10.1016/j.drudis.2023.103863.

[32] M. A. El Hamd, R. H. Obaydo, D. Nashed, M. El-Maghrabey, and H. M. Lotfy, "Hydrotropy and co-solvency: Sustainable strategies for enhancing solubility of poorly soluble pharmaceutical active ingredient," Talanta Open, 2024. doi: 10.1016/j.talo.2024.100391.

[33] R. K. Ameta, K. Soni, and A. Bhattarai, "Recent advances in improving the bioavailability of hydrophobic/lipophilic drugs and their delivery via self-emulsifying formulations," Colloids, vol. 7, no. 1, p. 16, 2023. doi: 10.3390/colloids7010016.

[34] L. Kumar, Y. Choudhari, P. Patel, G. D. Gupta, D. Singh, J. M. Rosenholm, K. K. Bansal, and B. D. Kurmi, "Advancement in solubilization approaches: A step towards bioavailability enhancement of poorly soluble drugs," Life, 2023. Available: https://www.mdpi.com/journal/life

[35] S. Li and L. Li, "A homogenization method incorporating surface effect for thin metamaterial structure," International Journal of Engineering Science, 2024. doi: 10.1016/j.ijengsci.2024.104093.

[36] Preeti, S. Sambhakar, R. Malik, S. Bhatia, A. Al Harrasi, C. Rani, R. Saharan, S. Kumar, Geeta, and R. Sehrawat, "Nanoemulsion: An emerging novel technology for improving the bioavailability of drug," Journal of Nanomaterials, 2023. doi: 10.1155/2023/6640103.

[37] R. K. Ameta, K. Soni, and A. Bhattarai, "Recent advances in improving the bioavailability of hydrophobic/lipophilic drugs and their delivery via self-emulsifying formulations," Colloids, vol. 7, no. 1, p. 16, 2023. doi: 10.3390/colloids7010016.

[38] P. H. Ahangari, J. W. King, A. Ehsani, and M. Yousefi, "Supercritical fluid extraction of seed oils – A short review of current trends," Trends in Food Science & Technology, 2021. doi: 10.1016/j.tifs.2021.02.066.

[39] R. Shelke, V. Velagacherla, and U. Y. Nayak, "Recent advances in dual-drug co-amorphous systems," Drug Discovery Today, 2023. doi: 10.1016/j.drudis.2023.103863.

[40] S. Tambe et al., "Recent advances in amorphous solid dispersions: Preformulation, formulation strategies, technological advancements and characterization," Pharmaceutics, vol. 14, no. 10, p. 2203, 2022. doi: 10.3390/pharmaceutics14102203.

[41] A. D. Khan, M. Tabish, R. Kaushik, V. Saxena, P. Kesharwani, and S. Gupta, "Hydrotropy: Recent advancements in enhancement of drug solubility and formulation development," [Journal details not provided].