Review Article

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by IJRPS Journal

Home Page: https://ijrps.com/

A Systematic Review of Solubility Enhancement Techniques Used for BCS Class II & IV

Pavankumar Dhoble*[1], Bharat Tekade[2], Vishal Bodke[1], Mohan Kale[3]

[1]Department of Pharmaceutics, Konkan Gyanpeeth Rahul Dharkar college of pharmacy and Research institute, Karjat, Maharashtra, India

[2]Department of Pharmaceutics, H K college of pharmacy, Oshiwara, Jogeshwari, Mumbai, India

[3]Konkan Gyanpeeth Rahul Dharkar College of Pharmacy And Research Institute, Karjat, Maharashtra, India

Article History

Received on: 21 Oct 2023
Revised on: 16 Dec 2023
Accepted on: 19 Dec 2023

Keywords

BCS Class,
Solubility,
Permeability,
Absorption,
Bioavailability

Abstract

Because of their low solubility, pharmaceutical researchers encounter tremendous difficulties in creating sustainable and more soluble drugs (BCS class II). About 40% of oral dosage forms have formulation and development problems due to water insolubility. The rate of dissolving, absorption, distribution, and excretion of an active medicinal substance is determined by its solubility parameters. Based on their solubility, drugs are divided into four kinds under the BCS categorization system. BCS Class II and Class IV drugs have problems with solubility. Increasing both the bioavailability and the solubility of poorly soluble medications can be accomplished in several ways. Some techniques—like solid dispersion, solid complexation, liquisolid, hydrotropy, sonocrystallization, and self-emulsifying techniques—are commonly used for solubility augmentation. Until an orally active medication dissolves in the lining of the stomach and/or intestinal fluids, it cannot pass through the GI tract membrane and enter the bloodstream. Therefore, a medication that is insoluble in water will typically exhibit limited absorption by dissolution, and a medication that is weakly permeabilized via membranes would typically exhibit limited absorption through permeation. Consequently, improving the oral bioavailability of active substances is the focus of two areas of pharmaceutical research: (i) accelerating the process of dissolution and solubility of drugs that are poorly soluble in water, and (ii) accelerating the permeability of poorly permeable drugs.

*Corresponding Author
Name: Pavankumar Dhoble
Phone: +91 9922894339
Email: pavandhoble1@gmail.com

eISSN: 0975-7538
DOI: https://doi.org/10.26452/ijrps.v15i1.4658

Production and hosted by
IJRPS | www.ijrps.com

INTRODUCTION

Solubility is the concentration of the undissolved solid in a solution that dissolves under particular conditions. The solution is said to be saturated when the dissolved solute balances the surplus undissolved solute. [1] It is increasingly harder and harder for drugs with low water solubility to dissolve well in the gastrointestinal tract, which is necessary for maximum bioavailability. [2][3] Creating new drugs that are both

pharmacologically active and sufficiently easily soluble to dissolve rapidly at their place of administration—which is often the gastrointestinal system—is a challenge for medicinal chemists.[4]

Oral delivery of the medication form is the most effective approach. The main problem with oral delivery of the active medication is its bioavailability. Solubility is the greatest quantity of solute that can be dissolved in a given volume of solvent or volume of mixture at a specific temperature.[5][6] Solubility increases in tandem with bioavailability.

Based on its permeability and solubility, the medication is divided into four classifications by the system known as the Biopharmaceutics Classification System (BCS). [7] Class II and Class IV of the BCS system present soluble challenges; these include the newer NSAIDs such as Zaltoprofen, Aceclofenac, and Flurbiprofen, as well as their older congeners, such as Indomethacin, Ibuprofen, Ketoprofen, and Diclofenac; they also include the anti-diabetics Gliclazide and Glipizide, along with the further recently calcium channel blocking medications (CCBs) like Felodipine and Nimodipine. The BCS was first created in 1995 by Amidon et al. [8][9].

Class boundaries

A drug substance is considered extremely soluble if its maximum dose strength dissolves in fewer than 250 ml of water within the pH range of 1 to 7.5.[10] A pharmaceutical substance is considered very permeable whenever the degree of absorption in humans is greater than 90% of an injected dose, as determined by mass balance or in comparison with an intravenous reference dose. [11]

A medication product is considered to be swiftly dissolving when it dissolves more than 85% of its prescribed amount in thirty minutes or less employing USP apparatus I or II in the amount of lower than 900 ml containing buffer solutions. [12][13]

Factor Affecting Solubility

Nature of solute and solvent

Dependent on concentration and temperature are the properties of both the solvent and the solute. When water is at room temperature, two hundred grams of zinc chloride can dissolve in one gram of lead (II) chloride. [14]

Particle size

Solubility is affected by particle size. The ratio of surface area to volume grows when the size of an object decreases. The interaction between particle and solvent grows as its surface area grows. [15][16]

Molecular size

Particles' solubilities change as their molecular sizes change. When the molecular weight and size of a substance's molecules increase, it becomes less soluble because the solvent molecules have a harder time completely encasing the bigger molecules.[17]

Temperature

Temperature impacts solubility. If energy is being absorbed during the process of solution, then solubility should increase as temperature rises. Solubility would be expected to decrease with rising temperature if energy were released during the solution process. [18][19]

Pressure

The solubility of a solid or liquid solute does not vary with a change in pressure, whereas the solubility of a gaseous solute does rise with increasing pressure and decrease with decreasing pressure [20]

Polarity

The solute's and the solvent's respective polarity have an impact on solubility. Generally speaking, polar solute molecules will dissolve in polar solvents, while non-polar solute molecules will dissolve in non-polar solvents. [21][22].

Polymorphs

Polymorphism describes a substance's potential to crystallize in different shapes. A polymorph can take on several crystal structures depending on the conditions. The solid may crystallize into several distinct "polymorphs," or shapes.

Methods for Solubility Enhancement

1. Solid Dispersion
2. Co-solvency
3. Particle Size Reduction

Table 1: Class and Permeability

Class	Permeability	Solubility	Examples
I	High	High	Metoprolol
II	High	Low	Azithromycin
III	Low	High	Cimetidine
IV	Low	Low	Hydrochlorothiazide

Table 2: Parts of solvent required for one part of the solute

Term Known as	Parts of solvent required for one part of the solute (Range)
Very Soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly	100 – 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

4. Hydrotrophy
5. Nanonization
6. pH Adjustment
7. Inclusion Complexation
8. Sonocrystallization
9. Supercritical Fluid (SCF) Process
10. Liquisolid Methods
11. Self-Emulsifying or Self-Micro Emulsifying Systems

Nanosizing

Reducing drug particle sizes to between 100 and 200 nm, or less than the submicron threshold. This smaller particle size causes the medication to dissolve more quickly. Elans nano milling technology is utilized, functioning on two fronts: "top 5 down" (wet milling process) and "bottom-up" (precipitation, crystallization). To stabilize the nanosuspension over inter-particle forces resulting from distribution or Vander wall forces, stabilizers are employed. Repulsive forces are required to overcome the inter-particle forces. Offensive pressures or energy barriers can be applied to a colloidal system in two different ways: both electrostatic and steric stabilization. Absorption of polymers on the particle surface results in stem stabilization; adsorbing modified molecules, like charge polymeric or ionized surfactants, over the particle surface results in electrostatic stabilizing. Spray drying is a widely utilized technique for solidifying nanosuspension into a dosage form.

Micronization

The procedure entails using spray drying or air attrition techniques (fluid energy mill) to reduce the particle size of the solid particles of the drug to 1 to 10 microns. A larger surface area facilitates faster dissolution. Several steroids and sulfa medications, such as griseofulvin Table 1,Table **2**.

Co-grinding of drug with Excipients

To improve the bioavailability of medications following Micronization, poorly soluble substances are ground in a jet miller to reduce their particle size. Excipients in significant quantities that are soluble in water are employed in the co-grinding process. Markus Vogt et al. evaluated how several excipients, such as lactose monohydrate, cornflour, polyvinyl pyrrolidone, hydroxy propyl methyl cellulose, along with sodium lauryl sulfate, increased the dissolving of poorly soluble medicines, such as albendazole and felodipine.

Lyophilization

The substance that needs to be dried must first be frozen, and only the solid, dried parts of the initial fluid remain when the frozen liquid is heated to a high vacuum and sublimates. A chamber with a vacuum for the drying process, a vacuum source, a source of heat, and a vapour removal system are the four parts of a freeze-drier. The creative synthesis of lyophilized matrices 6 with gelatin, pectin, soy fibre protein, and monitor was reported by Gole et al. and Lawrence et al. Risperidone and ibuprofen, both low hydrophilic

Table 3: Recently work done on solubility enhancement by some Researchers in the last 10 years

Drug Name	BCS Class	Method of Preparation
Indomethacin (IND) and posaconazole (PCZ)	Class II	Amorphous solid dispersion
Bentonite	Class II	Amorphous solid dispersion
Itraconazole	Class II	Solid dispersion and co-crystallization technique
Clofazimine	Class II	Solid dispersion (Human milk)
Azithromycin	Class II	Solid dispersion
Ibuprofen, Cinnarizine, Griseofulvin	Class II	Automated platforms experimental method
Rivaroxaban	Class II	Binary inclusion complexation
Celecoxib	Class II	Fusion Method and Evaporation Method
Celecoxib	Class II	Solid phospholipid dispersions: Spray drying versus freeze-drying
Domperidone	Class II	Cyclodextrin-based nanosponges
Raloxifene Hydrochloride	Class II	Solid dispersion
Repaglinide	Class II	Solid dispersion
Celecoxib	Class II	Pvp amorphous dispersions: a molecular perspective
Etoricoxib	Class II	Solid dispersion technique
Buffalo milk	--	Spray-dried 'buffalo milk protein co-precipitate'

and bitter active ingredients, are particle-coated utilizing natural or synthetic polymers and organic solvents and then dried using a vapour removal technique.

Use of Surfactants

The primary mechanism by which the surface-active chemicals increase the rate of dissolution is by encouraging moisture and penetrating dissolution fluid inside the solid drug components. Since the medicine enclosed in the micelle framework fails to partition in the dissolving fluid above its critical micelle concentration (CMC) values, they are typically employed at concentrations below these values. Polysorbates, a type of nonionic surfactant, are commonly utilised. Steroids like spironolactone are among the medications whose bioavailability may have been raised by the addition of surfactants to the formulation.

Use of Salt forms

The solubility and dissolving properties of salts are better than those of the original medication. The strong acid salts of basic medications like atropine and the alkaline metal salts of medications that are acidic like penicillin are more soluble in water than the original drug Table 3.

Alteration of pH of the Drug Micro-environment

There are two ways to accomplish this: adding buffer to the formulation or forming salt in situ. For instance, sour aspirin pills Table 4.

Use of more soluble metastable polymorphs

The right medication form should be chosen with increased solubility, depending on the internal composition of the solid drug. Anhydrases are more easily soluble than hydrates, solvates are more soluble than solvates, amorphs are generally higher soluble than metastable polymorphs, and anhydrates are greater soluble than metastable polymorphs. Compared to the A and C forms, chloramphenicol palmitate's B form is more water-soluble.

Solute-solvent complexation

Pseudo polymorphs or drugs that dissolve with organic solvents, typically have more water solubility than either the actual drug or its corresponding hydrates.

Solvent deposition

Using this technique, a poorly water-soluble medication, such as nifedipine, is dissolved in an organic solvent, such as alcohol, and the solvent evaporates, depositing the drug into an inert,

Table 4: Recently work done on solubility enhancement by some Researchers in the last 10 years

Drug Name	BCS Class	Method of Preparation
Indomethacin	Class II	Complexation with protein hydrolysate
Boswellic acid	Class II	Poloxamer-based solid dispersion technique
Hydrochlorothiazide	Class II	Solid dispersions and microspheres
Atorvastatin	Class II	Solid dispersion formulation using skimmed milk
Itraconazole	Class II	Inclusion complexation method
Indomethacin and nifedipine	Class II	Adsorption by Mannitol by spray drying
Glimepiride	Class II	Solid dispersion using 'Ziziphus spina-christi - gum polymer.'
Nimodipine	Class II	Modified gum 'karaya' as a carrier solid dispersion
Spironolactone	Class II	Solid dispersion using the fusion method
Flurbiprofen	Class II	Solid dispersion using hydrophilic carriers
Hydrochlorothiazide	Class II	Solid dispersions by – 'solvent evaporation method'
Simvastatin	Class II	Solid dispersions by 'solvent evaporation method'
Loratadine	Class II	Solid dispersions by solvent evaporation method by PVP K30
Paracetamol	Class I	In Situ Micronization by Solvent Change Method.
Celecoxib	Class II	Dry Suspension Using Spray-Drying and nanoemulsion
Benexate	Class II	Salt Formation Using Artificial Sweetener
Indomethacin	Class II	Spray-Dried Co-Amorphous Formulations
Tacrolimus	Class II	Melt Extruded Amorphous Solid Dispersion of Tacrolimus
Bendroflumethiazide	Class II	Lyophilization and Physical Mixing Techniques
Famotidine	Class II	Solid Dispersion Technique

hydrophilic, solid matrix, like starch or microcrystalline cellulose.

Selective adsorption on insoluble carriers

the aqueous media's hydration and swelling of the clay, as well as the adsorbate and adsorbent's feeble physical bond. By keeping its concentration gradient through its maximum, bentonite can accelerate the pace at which weakly water-soluble medications such as griseofulvin, the results obtained within and prednisolone dissolve.

Molecular encapsulation and cyclodextrins

The capacity of both beta and gamma cyclodextrins, as well as some of their derivatives, to generate molecular inclusion complexes alongside hydrophobic medicines that have low aqueous solubility makes them special. These cyclodextrin compounds are adaptable because their hydrophobic cavity is big enough to hold lipophilic medications as guests while the host molecule's outside is comparatively hydrophilic. Barbiturates, benzodiazepines, and thiazide diuretics Figure 1.

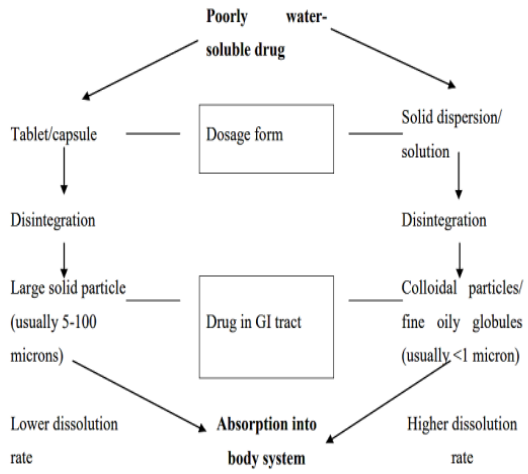

Figure 1 Process of solid dispersion

Solid Dispersions

These are often made by the solvent or co-precipitation method, which involves dissolving the solid carrier solvent and the guest solute in a typical volatile liquid solvent like alcohol. By using freeze-drying or reduced pressure evaporation, which causes the guest to precipitate amorphously in a crystalline carrier, the liquid

solvent is eliminated. The drug precipitates into an amorphous state in solid dispersion, whereas it does so in its crystalline form in solid solution. This is the fundamental distinction between the two Figure 2.

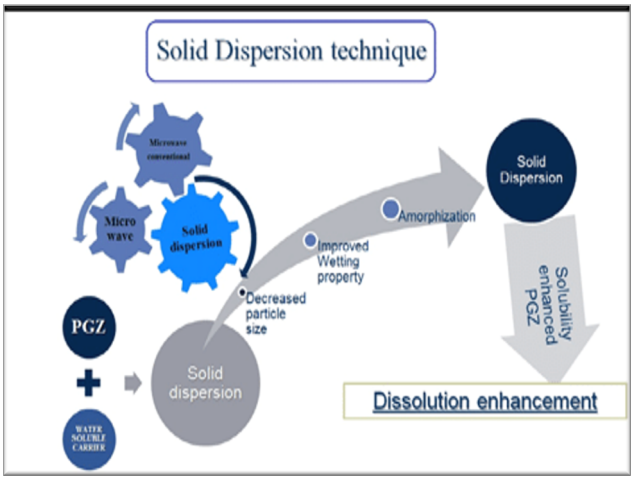

Figure 2 Solid Dispersion Technique

A drug in a matrix that is physiologically inert is called a solid dispersion. Because the drug remains in an amorphous state and is soluble in hydrophilic carriers, it increases wettability and, potentially, bioavailability for medications that are poorly soluble in water. It also speeds up the pace of dissolution by reducing particle size and increasing porosity. Polymers of lower molecular weight materials, such as sugars, are utilized, namely polyethene glycol & polyvinyl pyrrolidone. It was unclear how to improve disintegration at the time. Surfactants have recently been added to formulations to stabilize them, preventing medication recrystallization and enhancing solubility.

Suitable Carriers for Solid Dispersion

Polyvinyl alcohol and polyvinyl acetate (PVA)/PVP copolymer, Crospovidone cellulose derivatives, HPMC, Polyacrylates and Polymethacrylates, Polyethylene glycol (PEG), Polyvinylpyrrolidone (PVP), Carboxymethyl Ethyl Cellulose (CMEC), Urea

Methods of preparing solid dispersions

1. Fusion Process
2. Solvent Method
3. Fusion-Solvent Method
4. Spray Drying
5. Lyophilization
6. Dropping Method
7. Inclusion Complexation

Solid Dispersion

Sekiguchi and Obi, who studied the formation and dissolving behaviour of eutectic melts of a sulfonamide medication along with a water-soluble carrier at the beginning of the 1960s, are credited with originating the idea of solid dispersion. This method improves the drug's solubility by dispersing a weakly soluble medication in an extremely soluble solid hydrophilic matrix. Solid solutions or eutectic (non-Molecular Lebel mixture) can be produced using the solid dispersion technique. Products of (Molecular-Lebel Mixing). Drugs that are crystalline or amorphous can be uniformly dispersed in crystallized or amorphous carriers using eutectic dispersions. The solid dispersion approach has not gained popularity despite the promising element of improvement in dissolution and the concept's simplicity due to Manufacturing, Scale, and Stability Problems. One helpful pharmaceutical method for improving the solubility of medications in dose form is solid dispersion. The pharmaceutical business uses a variety of hydrophilic carriers, including polyvinyl pyrrolidone, PEG, Tween 80, SLS, Plasdone, and others. Hydrophobic medications can be made more soluble in water by using a variety of methods, including the Hot Melt Extrusion, Solvent Evaporation, and Holt Melt Methods (Fusion).

Hot Melt Method (Fusion Method)

Using this technique, the drug and water-soluble carrier physical combination was heated until it melted. After that, the melted fluid was quickly cooled and hardened while being vigorously stirred in an ice bath. Following that, the remaining solid mass was ground, powdered, and sieved so that it could be compacted into tablets using a tablet excipient.

Solvent Evaporation Method

Using this method, a common solvent was used to dissolve the medication and carrier, and the solvent was then evaporated under a vacuum to create a solid solution. Using this method, numerous researchers looked at the solid dispersion of Naproxen, Nimuselide, and Meloxicam 15.

Hot Melt Extrusion

This is much the same as the fusion method, with the extruder causing the components to mix intensely. The insoluble state of the drug and matrix may cause challenges, just like in the conventional fusion process.

High shear forces also result in a high temperature locally in the extruder for heat-sensitive materials.

Solid Dispersion Technology Definition

A collection of solid products made up of two or more distinct components, usually composed of a hydrophilic matrix along with a hydrophobic medicament, are referred to as solid dispersions. There are two types of matrix: crystalline and amorphous. The medication may be distributed as crystalline, amorphous, or molecular particles (clusters).

Improving the oral bioavailability of medications that are poorly soluble in water is still one of the most difficult elements of drug research. While increasing the rate of dissolution and bioavailability has frequently been achieved through salt production, solubilization, as well as particle size reduction. These methods have certain practical drawbacks. Neutral, moderately acidic, or moderately basic substances can't create salts. Surfactants and co-solvents are used to solubilize medicines in organic solvents or aqueous media, resulting in liquid formulations that are typically unsatisfactory from the perspectives regarding patient acceptability and commercialization. Sekiguchi and Obi19 created a workable technique in 1961 that allows for the improvement of poorly water-soluble drug bioavailability while overcoming many of its limitations. This technique was dubbed "Solid Dispersion."

Advantages:

1. By increasing the drug's solubility, solid dispersions are utilised to increase the bioavailability of weakly water-soluble medications.
2. To increase solubility, solid dispersions are preferable to other methods of particle size reduction because the latter only manage to reduce the size to a range of roughly 2–5 microns, which is insufficient to increase the solubility of the drug or allow it to diffuse in the small intestine or to increase its bioavailability.
3. Reduce pre-systemic metabolism; this may be caused by the drug's biotransformation enzyme being inhibited by the carrier.
4. The medication can be changed from its liquid to solid state.
5. Solid dispersions can be used to solve the issues with solid powder, such as smaller particle sizes that exhibit poor mechanical properties (such as strong adhesion and poor flow characteristics).
6. Extended-release dosage forms can be created using solid dispersions.

Disadvantages:

1. An amorphous medicine has the potential to crystallize.
2. Crystallinity changes and the rate of disintegration may be slowed down by aging.
3. Solid dispersions are susceptible to degradation when exposed to high temperatures and dampness. Moisture affects the drug's crystallinity, therefore stability problems can be challenging. Due to their hygroscopic nature, certain polymers employed in solid dispersion have the potential to absorb moisture and crystallize. Drugs can occasionally be converted from their metastable to stable forms. As a result, both solubility and rate of dissolution might decrease.
4. Understanding the relationship between a drug's structure and its release through solid dispersion is similarly challenging.
5. Difficulty identifying the physical structure of solid dispersions.
6. The issue with solvent residue.
7. It is difficult to forecast how long amorphous materials will last.

Applications:

1. To ensure that a tiny quantity of medication is distributed uniformly.
2. To make the erratic medication stable.
3. To administer gaseous or liquid substances in a solid dosage (up to 10%).
4. to combine a fast-release primary dose with a sustained-release dosage form.

5. To use insoluble or weakly soluble carriers to develop a sustained release plan for soluble drugs.
6. To decrease the pre-systemic breakdown of drugs like morphine and progesterone.
7. Polymorphs can be converted into isomorphous, solid-state solutions, eutectic, and even molecular addition compounds in a given system.
8. Increase exposure (lower dose, faster onset, bioavailability)
9. Diminish volatility (lessening of the Fed/Fasted impact).

Successful Formulation Development Techniques for Active Pharmaceutical Ingredients That Are Not Well-soluble

The solubility of the API is a critical factor in the creation of topical medications. Unfortunately, the majority of APIs have low solubility, which calls for adjustments to the excipient composition and formulation technique. Moreover, 80% of newly discovered chemical substances (BCS classes II and IV) have limited solubility. Insufficient solubility of an active ingredient in the dose form mostly results in decreased drug loading, low skin penetration, and stability issues.

Many kinds of formulators are experimenting with different formulation strategies to make less water-soluble drugs more soluble. Among these include complexation, surfactant usage, salt creation, crystal engineering, and particle size reduction. One such strategy is the addition of active chemicals to very hydrophilic nanoparticle surfaces. By providing an immense surface when they come into a relationship with water molecules, they might grow more soluble in water. This increases their hydrophilicity and facilitates their dissolution. The three most widely used solvent systems are glycols/polyols, surfactants/surface active agents, and polymers for the rapid and efficient solubilization of non-water soluble APIs. The following are efficient methods for developing formulations including poorly soluble active pharmaceutical ingredients (APIs):

Designing an appropriate solvent/co-solvent/solubilizer system

Poor-soluble APIs are exceedingly challenging to formulate because of their poor solubility, especially in the topical market. Therefore, selecting the right kind choice solvent, co-solvent, any solubilizer system used in a formulation is crucial for improving an API's water-solubility requiring the need for complicated formulation or physicochemical adjustments.

To enhance the skin penetration and other pharmacological qualities of weakly water-soluble active ingredients (APIs), adequate formulation and solubilization are required. This solubility attribute is crucial for the effective creation of pharmaceuticals and will influence the excipient selection and formulation parameters.

Particle size reduction strategies and crystal engineering

Both Micronization and nanosizing are size-reduction procedures that can be used to increase a drug's effective surface area (S). Additionally, there is a need for improvement in the formulations' usage of polymeric stabilizers. A medicine needs to be soluble to become absorbed and dissolved. It is possible to look into a variety of methods, such as crystal engineering, particle size reduction, and drug structure modification.

For a BCS Class II medication featuring minimal solubility as well as elevated permeability that corresponds to the dissolving profile, an extremely fine PSD of the API is required. Formulators can meet this requirement by offering a micronized API having a range of particle sizes. Formulating aims to formulate a drug regimen that satisfies the specified needs, such as the drug's physical/chemical delivery being compatible with it and its other desirable features holding when taken orally or systemically. Taking active components at therapeutic dosages does not present a major risk because of sub-potent systemic exposure. Systemic bioavailability is acceptable. a favourable excipient profile.

Salt formation strategies

Salt production is the most effective way to hasten the dissolution and solubility of acidic as well as basic drugs. The salt form may have an impact on wettability, which could result in a hundred-fold boost in solubility and a significant shift affecting the rate of dissolution.

Use of Surfactants

A thorough evaluation of the surfactant solubilization mechanisms has been conducted. As a result, these methods are appealing since they are highly economical, readily scalable, and compatible with conventional tabletting procedures. Additionally, surfactants can carry out a wide range of functional tasks, including improving the solubility, wettability, and dissolution of APIs. Minimizing precipitation of API in vivo.

Use of Cyclodextrins

Cyclodextrins, which are cyclical oligosaccharides, are utilized to improve the water solubility and bioavailability of medications. In solutions containing APIs, these functional excipients create dynamic inclusion complexes. The formulation usually employs the substituted β-cyclodextrins. The hydrophilic cyclic oligosaccharides on the outside give the complex molecules extremely high aqueous solubility and usually solubilize APIs as a function of concentration. This is where the hydrophobic API usually resides.

Hydrophilic and Lipidic Solvents

Lipid-based formulations have been shown to decrease side food effects and enhance oral lipophilic drug absorption. Furthermore, since lipidic solvents solubilize the compounds before their accumulation in the body (higher Cs), this approach enables the effective administration of drugs with high Log P.

The various parts of self-emulsifying systems, as well as their selection criteria, are critically reviewed, along with the various scientific endeavors to solidify liquid self-emulsifying systems for drug delivery (SEDDS) using the lyophilization adsorption, spray drying, along melt granulation. PEGs, poloxamers, and other kinds of hydrophilic vehicles are miscible with water and possess high solvating properties, rendering them superior solvents.

Amorphous Stabilized Approaches

Amorphous stabilized methods can produce thermodynamically metastable APIs and improve solubility by overcoming crystal lattice energy. These methods have the potential to greatly increase solubility and bioavailability.

CONCLUSION

Solubility is a challenging problem for scientists and pharmaceutical experts who are researching the preparation and development of various dosage forms. When used separately or in combination, the aforementioned techniques may help make poorly soluble drugs more soluble. Using the right method is essential to improving solubility, dissolution, and bioavailability while simultaneously preventing the rejection of new chemical entities due to low solubility. The biopharmaceutical grouping structure indicates that class II and IV pharmaceuticals (APIs) have limited water solubility, poor dissolution, and low bioavailability. While the solutions to the previously listed problems rely on specific molecular properties, solid dispersions and lipid distributions are considered to be the most desirable approaches for doing so for practical compounds. Increasing the drug's bioavailability and solubility presents several difficulties for pharmaceutical formulations, particularly for NCEs. Researchers are now developing a variety of tactics, such as the introduction of innovative excipients, to improve the solubility of poorly soluble chemicals. Scientists have been closely examining the chemical characteristics of weakly soluble compounds to optimise these procedures, with their eventual objective being the provision of 100% dissolution-effective methods to accomplish these for reasonable drugs.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Funding Support

The authors declare that they have no funding for this study.

Authors Contributions

All the authors own contributed equally.

REFERENCES

[1] Sareen S, Mathew G, Joseph L. Improvement in solubility of poorly water-soluble drugs by solid dispersion. Int J Pharm Investig. 2012 Jan;2(1):12-7. doi: 10.4103/2230-973X.96921. PMID: 23071955; PMCID: PMC3465159.

[2] Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm.

2012;2012:195727. doi: 10.5402/2012/195727. Epub 2012 Jul 5. PMID: 22830056; PMCID: PMC3399483.

[3] Khatri, Himanshi & Hussain, Md Sadique & Tyagi, Swati. (2022). Solubility Enhancement Techniques: An Overview. World Journal of Pharmaceutical Research. 11. 468-482. 10.20959/wjpr20225-23812.

[4] Bhalani, D.V.; Nutan, B.; Kumar, A.; Singh Chandel, A.K. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. *Biomedicines* 2022, *10*, 2055.

[5] Narmada I. Contemporary Review on Solubility Enhancement Techniques. JDDT [Internet]. 15Feb.2023 13(2):110-2.

[6] Albetawi S, Abdalhafez A, Abu-Zaid A, Matrouk A, Alhourani N. Recent solubility and dissolution enhancement techniques for repaglinide a BCS class II drug: a review. Pharmacia 68(3): 573-583.

[7] Sopyan I, Gozali D, Megantara S, Wahyuningrum R, Sunan Ks I. Review: An Efforts To Increase The Solubility And Dissolution Of Active Pharmaceutical Ingredients. Int J App Pharm [Internet]. 2022 Jan. 7 [cited 2023 Dec. 22];14(1):22-7.

[8] Dn Cp, A S. A Solubility Enhancement Of Aceclofenac By New Crystallization Technique. Asian J Pharm Clin Res [Internet]. 2022 Feb. 7 [cited 2023 Dec. 22];15(2):113-8.

[9] Sarkar P, Das S, Majee Sb. Solid Dispersion Tablets In Improving Oral Bioavailability Of Poorly Soluble Drugs. Int J Curr Pharm Sci [Internet]. 2022 Mar. 15 [cited 2023 Dec. 22];14(2):15-20.

[10] Deshmukh AS, Tiwari KJ, Mahajan VR. Solubility Enhancement Techniques for Poorly Water-Soluble Drugs. Scopus Indexed [Internet]. 2017 May 31 [cited 2023 Oct. 20];10(3):3701-8.

[11] Abdullah Ali H, Kamal Omer H. Solubility Enhancement of a Poorly Water-Soluble Drug Using Hydrotropy and Mixed Hydrotropy-Based Solid Dispersion Techniques. Adv Pharmacol Pharm Sci. 2022 Nov 28;2022:7161660. doi: 10.1155/2022/7161660. PMID: 36479276; PMCID: PMC9722314.

[12] Charalabidis A, Sfouni M, Bergström C, Macheras P. The Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS): Beyond guidelines. Int J Pharm. 2019 Jul 20;566:264-281. doi: 10.1016/j.ijpharm.2019.05.041.

[13] Rahman, Asim, and Md. Faheem Haider. "Solubility of Drugs, Their Enhancement, Factors Affecting and Their Limitations: A Review." International Journal of Pharmaceutical Sciences Review and Research, vol. 79, no. 2, Apr. 2023.

[14] Agustina R, Setyaningsih D. Solid Dispersion As A Potential Approach To Improve Dissolution And Bioavailability Of Curcumin From Turmeric (Curcuma Longa L.). Int J App Pharm [Internet]. 2023 Sep. 7 [cited 2023 Dec. 22];15(5):37-4.

[15] B.A. Bhairav, J.K. Bachhav, R.B. Saudagar. Review on Solubility Enhancement Techniques. Asian J. Pharm. Res. 2016; 6(3): 147-152.

[16] Attia, Mohamed Salah. "Solid Dispersion as a Technical Solution to Boost the Dissolution Rate and Bioavailability of Poorly Water-Soluble Drugs." Indian Journal of Pharmaceutical Education and Research, vol. 55, no. 2s, 2021, pp. s327–39.

[17] Purwa Jain, Achhrish Goel, Shweta Sharma, & Meghal Parmar. (2022). Solubility Enhancement Techniques With Special Emphasis On Hydrotrophy. International Journal Of Pharma Professional's Research (Ijppr), *1*(1), 34-45.

[18] Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability Enhancement Techniques for Poorly Aqueous Soluble Drugs and Therapeutics. Biomedicines. 2022 Aug 23;10(9):2055. doi: 10.3390/biomedicines10092055. PMID: 36140156; PMCID: PMC9495787.

[19] Williams HD, Trevaskis NL, Charman SA, Shanker RM, Charman WN, Pouton CW, Porter CJ. Strategies to address low drug solubility in discovery and development. Pharmacol Rev. 2013 Jan;65(1):315-499. doi: 10.1124/pr.112.005660. PMID: 23383426.

[20] Strategies for Low Drug Solubility Hywel D. Williams, Natalie L. Trevaskis, Susan A. Charman, Ravi M. Shanker, William N.

Charman, Colin W. Pouton and Christopher J. H. Porter.

[21] Zhang X, Xing H, Zhao Y, Ma Z. Pharmaceutical Dispersion Techniques for Dissolution and Bioavailability Enhancement of Poorly Water-Soluble Drugs. Pharmaceutics. 2018 Jun 23;10(3):74. doi: 10.3390/pharmaceutics10030074. PMID: 29937483; PMCID: PMC6161168.

[22] Mahmood T, Sarfraz RM, Ismail A, Ali M, Khan AR. Pharmaceutical Methods for Enhancing the Dissolution of Poorly Water-Soluble Drugs. Assay Drug Dev Technol. 2023 Feb-Mar;21(2):65-79. doi: 10.1089/adt.2022.119. PMID: 36917562.