IJMPR 2023, 7(4), 66-73

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

A REVIEW ON VARIOUS TECHNIQUES OF SOLUBILITY ENHANCEMENT OF BCS CLASS-II DRUGS

Mamatha S.N.*, Snehalatha[1], Chethan Patel D.N.[1], Nagaraja T.S.[1] and Yogananda R.[1]

Department of Pharmaceutics, SJM College of Pharmacy, Chitradurga-577502 Karnataka, India.

Received on: 31/01/2023
Revised on: 21/02/2022
Accepted on: 13/03/2023

***Corresponding Author**
Mamatha S.N.
Department of Pharmaceutics, SJM College of Pharmacy, Chitradurga-577502 Karnataka, India.

ABSTRACT

Poor solubility is widely acknowledged to be one of the most frequently encountered difficulties in the field of pharmaceutics. When it comes to drug bioavailability, aqueous solubility is one of the most influential factors. Around 40% of all newly discovered chemical entities are lipophilic and fail to reach therapeutic range due to poor water solubility. When administered orally, drugs with low water solubility cause slow dissolution rates, erratic and incomplete absorption, and low bioavailability. Thus, solubility is a critical concept that plays an important role in the formulation of pharmaceuticals. The goal of this review is to discuss various solubility enhancement techniques such as chemical modification, which includes salt formation, co-crystallization, co-solvency, hydrotrophy, nanotechnology and physical modification, which includes particle size reduction, complexation, surfactants, solid dispersions, as well as pH adjustment, supercritical fluid process, liquisolid technique, and polymeric alteration.

KEYWORDS: Solubility enhancement, nanotechnology, co-crystallization, complexation, Liquisolid method.

INTRODUCTION

Solubility is defined quantitatively as the concentration of the solute in a saturated solution at a given temperature, and qualitatively as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute and solvent are in equilibrium. A drug's solubility can be expressed in terms of parts, percentage, molarity, molality, volume fraction, and mole fraction.[1]

Formulation of poorly soluble drugs for oral drug delivery is now one of the most interesting challenges for scientists in the pharmaceutical industries, and dissolutions is the rate limiting step in the process of drug absorption for formulations containing poorly soluble drugs. There are several solubilization techniques available, but there is no universal excipient or technique that is versatile enough to solubilize a wide range of drug molecules. Many potential candidates may be eliminated during the development stage due to poor solubility and bioavailability.

SOLUBILIZATION

Solubilization involves the breaking of intermolecular or inter-ionic bonds in the solute, the separation of solvent molecules to make room for the solute, and interaction between the solvent and the solute molecule or ion.[2]

Solubilization process occurs into three steps:

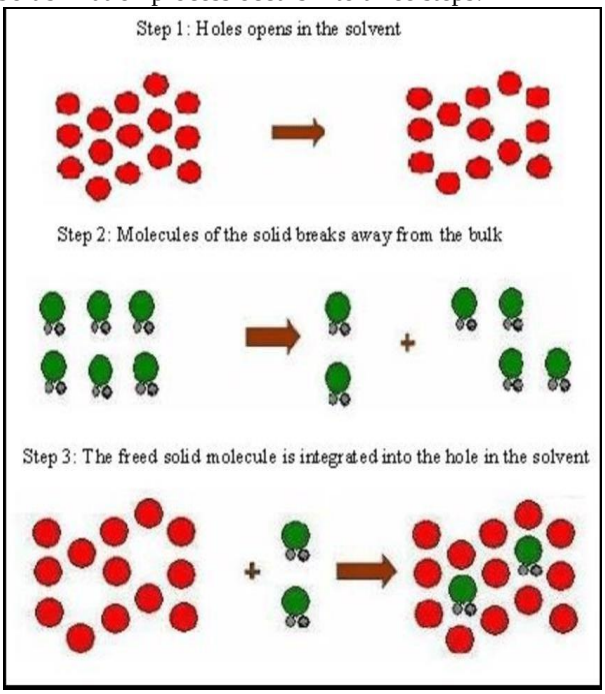

Figure 1: Mechanism of Solubilization.

BIO PHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

The BCS is a scientific framework for categorizing drugs based on their aqueous solubility and intestinal permeability. When combined with the drug product's *in-*

vitro dissolution characteristics, the BCS considers three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from an IR solid-oral dosage form.[3] The BCS has proven to be an extremely useful guiding tool for predicting *in-vivo* performance of drug substances and developing new drug delivery systems to suit drug performance in the body, as well as for regulating drug product bioequivalence during scale up and post approval. It divides the drug into four categories as shown in figure 2.

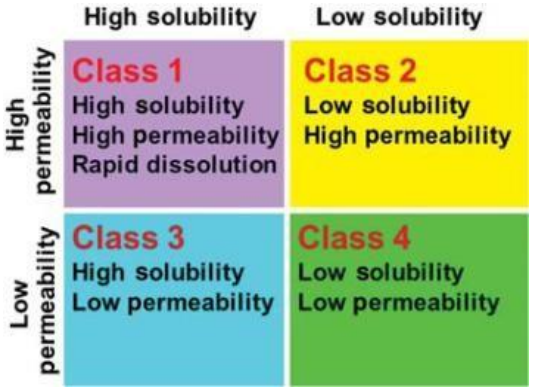

Figure 2: BCS Classification.

As a result of this major reason, solubility enhancement is one of the critical parameters that should be considered in the formulation development of orally administered drugs with low aqueous solubility.[4]

FACTOR AFFECTING SOLUBILIZATION

- **Molecular size:** A substance's solubility will decrease as its particle size or molecular weight increases. To solvate a substance, larger molecules are difficult to enclose in solvent molecules. The amount of carbon branching in organic compounds will increase their solubility since more branching will result in smaller (or lower volume) molecules, which are easier to dissolve in solvents.
- **Temperature:** If the energy is absorbed during the solution process, the temperature will rise along with the solubility. The solubility will decrease with rising temperature if the solution process releases energy. In general, a solid solute becomes more soluble as the solution's temperature rises. Solubility declines with temperature for all gases**.**
- **Pressure;** Solubility of gaseous solutes increases with the application of pressure. Pressure changes have almost no effect on the solubility of solids and liquids.
- **Particle size:** Particle size is inversely proportional to surface area, the dimension of the solid element influences solubility. The increased surface area allows for more interaction with the solvent. The effect of particle size on solubility can be describe by Eq.1

$$\log S/S_0 = 2\gamma V/2.303 RTr \quad \text{Eq. 1}$$

Where,

- S is the solubility of infinitely large particles. S_0 is the solubility of fine particles.
- V is molar volume.
- r is the radius of the fine particle.

- **Polymorphs:** Although the shape or habit of a crystal of a given substance may vary, the angles between the faces remain constant. Polymorphism refers to a substance's ability to crystallize in more than one crystalline form. All crystals have the potential to crystallize in various forms or polymorphs. Enantiotropy occurs when the transition from one polymorph to another is reversible. If the system is monotropic, a transition point exists above both polymorphs' melting points. Without undergoing a phase transition, the two polymorphs cannot be transformed from one another. Melting points can differ between polymorphs. Polymorphs will have different solubilities because the melting point of the solid is related to solubility.[5]
- **Rate of solution:** The rate of solution is determination of how fast substances dissolve in solvents.
- **Size of the particles**; Breaking a solute into smaller pieces increases its surface area, and when the total surface area of the solute particles is increased, the solute dissolves more quickly because the action occurs only at the surface of each particle, increasing its rate of solution.
- **Temperature**; Raising the temperature speeds up the process of solute dissolution for both liquid and solid solutes, increasing both the amount and rate of solute dissolution. The opposite is true for gases.
- **Amount of solute already dissolved:** When there was little solute in the solution before, dissolution happened quite quickly. Dissolution happens more slowly when the solution gets closer to the point where no solute can be dissolved.
- **Stirring:** When stirring liquid or solid solutes, new portions of the solvent come into contact with the solute, increasing the rate of solution.[6]

NEED FOR SOLUBILITY

Orally administered drugs have been identified as the primary impediment to the bioavailability of poorly soluble drugs in the systemic circulation. The drugs will be determined by two intrinsic factors, namely dissolution rate and permeability. The dissolution rate is determined by a physical property, which refers to the solvent's ability to dissolve in absolute terms. The second significant factor, the pharmacokinetics factor (pk), will apply to orally administered drugs that are highly dependent on the permeability of drug particles in an aqueous medium. Hence 90% of generic drugs are reported to be hydrophilic in nature, with these categories having low water solubility, and 40% of new chemical entities (NCE) are screened as having poor aqueous solubility in nature.

The pk profile in humans is also regarded as a significant barrier to oral administration. The rate of absorption and rate of solubility in classes II and IV were heavily promoted to have an impact on bioavailability andrate of dissolution.[7,8]

When taken orally, poorly water soluble medications may need high dosages to attain therapeutic plasma concentrations. The main issue in developing formulations for new chemical entities as well as generics has low water solubility. Any medicine that is to be absorbed must be present at the absorption site in the form of an aqueous solution. The preferred solvent for liquid medicine compositions is water.

Most medications have poor aqueous solubility and are either weakly basic or mildly acidic. Over 40% of the NCEs (new chemical entities) created by the pharmaceutical sector are essentially water insoluble. These poorly water soluble medications' sluggish drug absorption causes insufficient and inconsistent bioavailability as well as harmful effects on the gastrointestinal mucosa. The most crucial rate limiting factor for medications taken orally is solubility, which allows for the achievement of the desired concentration of the drug in the systemic circulation for pharmacological response. A significant hurdle for formulation scientists is the solubility issue.[9]

TECHNIQUES TO OVERCOME POOR SOLUBITY

The term "solubility enhancing" can be misleading because, while the phenomenon of super- saturation exists, the techniques used do not increase the solubility of insoluble compounds. They present the drug in a form that is optimal for absorption, given its solubility limitations. It is also important to note that water solubility requires temperature and pH specifications; many important drugs only exhibit aqueous solubility under certain physiological conditions, which must be met at the site of absorption.[10]

This article focuses on the technologies that have emerged to address the challenge posed by insoluble compounds, as well as how these technologies have made a difference. The techniques used to overcome poor drug solubility are divided into the following major categories.[11,12]

I. Chemical Modifications

1. Salt Formation
2. Co-crystallization
3. Co-solvency
4. Hydrotropic
5. Solubilizing agent
6. Nanotechnology

II. Physical Modifications

1. Particle size reductiona.
a. Micronization
b. Nanosuspension
2. Modification of the crystal habit
a. Polymorphs
b. Pseudopolymorphs.
3. Complexation.
4. Solubilization by surfactants:
a. Microemulsions.
b. Self microemulsifying drug delivery system.
5. Drug dispersion in carriers.
a. Solid dispersions.
b. Solid solutions.

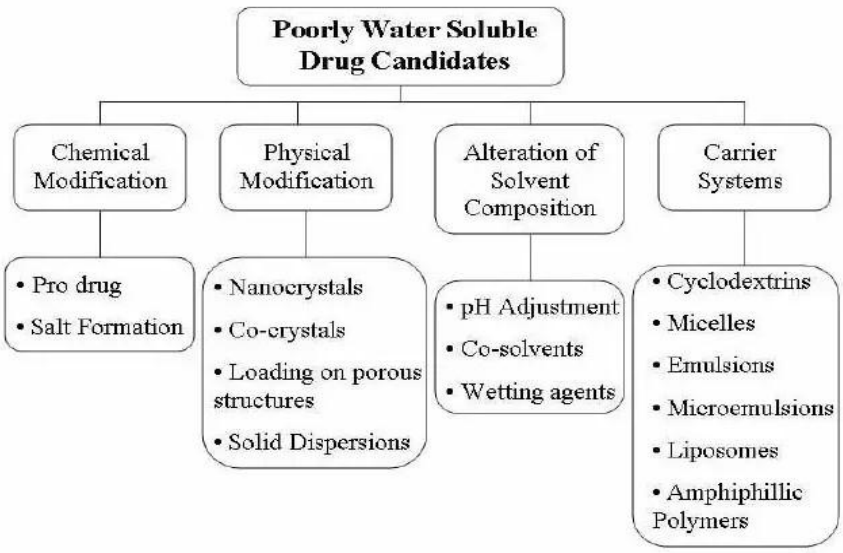

Figure 2: Approaches to Increase solubility/ Dissolution.[13]

TRADITIONAL SOLUBILITY ENCHANCEMENT TECHNIQUES

The solubility enhancement technique is listed below:[14,15]

1. Surfactant.
2. PH adjustment.

3. Co-solvency.
4. Co-crystallization.
5. Solubilizing agents.
6. Formation of salt.
7. Polymeric alteration.
8. Size reduction of particle.
9. Co-grinding and Co-micronization.
10. Micro emulsion.
11. Solvent evaporation.
12. Sonocrystalization.
13. Inclusion Complexation.

1. CHEMICAL MODIFICATIONS

1. Salt formation

It is effective in parenteral and other liquid formulations, as well as solid dosage forms. Because of various instability issues, an API is frequently unable to be formulated in its purest form. As a result of this conversion, salts, co-crystals, solvates, hydrates, and polymorphs are formed. Each one imparts a distinct physiochemical property that enhances drug performance characteristics such as stability, bioavailability, purification, and manufacturability. Salt formation of poorly soluble drug candidates (weak acids and bases) has been used to improve solubility for decades. Salts are formed when a compound is ionized in solution. A salt is formed when an acidic or basic drug is converted into a salt with a higher solubility than the original drug. Between 1995 and 2006, the FDA approved approximately 300 new chemical entities for marketing, 120 of which were 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 For the salt formation drug should have ionisable groups that will assist salt formation.[16]

The following criteria were used to select counter ion:

- There should be at least a 2-3 pKa unit difference between the drug and the counter ion.
- The counter-ion should reduce crystal lattice forces.
- It should be FDA approved or have sufficient toxicological data to support the choice of the counter ion.

This method can significantly speed up dissolving, but it has drawbacks, such as the time- consuming process required for salt approval and the inapplicability of the method to neutralmolecules.

Advantages

- The best way to speed up the solubility and dissolution of all basic pharmaceuticals and acidic natural substances.

Disadvantages

- It results in the precipitation of low water soluble drugs and exhibits in epigastric stress due to alkalinity because of the high reactivity with ambient CO2 and water.

2. Co-crystallization

A more refined definition of a co-crystal can be "multicomponent crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is an acceptable ion or molecule. Co-crystals frequently contain self-assembly units based on supramolecular prodrugs derived from patterns found in crystal structures. In the case of pharmaceutical co-crystals, at least one of the components must be an API, with the remaining co-crystal former(s) being pharmaceutically acceptable entities such as commonly used food additives and excipients.[17] Co-crystals can be prepared by following methods;

- Solvent evaporation method
- Anti-solvent method
- Cooling crystallization method
- Slurry conversion method
- Sono-crystallization method
- Supercritical fluid atomization
- Dry grinding
- Liquid assisted grinding.

3. Co-solvency

A water miscible solvent can be added to a drug to make it water soluble. This procedure is simple to create and assess. Compounds with a high crystalline structure that are highly soluble in the selection solvent mixture are the best drug candidates for the co-solvent method. The aqueous solubility of a compound can be significantly increased by using co- solvents rather than the compound alone. This is accomplished by dissolving the compound in a non-aqueous but water miscible solvent, then adding water to maintain drug solubility while adjusting the dose.[18]

Advantages

- When compared to other methods, high concentrations of the compound can be dissolved.
- The co-solvent method can be combined with other solubilization techniques, such as pH adjustment, to increase solubility.

Disadvantages

- The chemical stability of the insoluble drug is worse than in the crystalline state.
- The toxicity and tolerability of the excipients must be closely monitored.
- For intravenous administration, uncontrolled amorphous or crystalline precipitation may occur upon dilution with aqueous media.[19]

4. Hydrotropic

Hydrotropy is a solubilisation process in which the addition of a large amount of a second solute increases the aqueous solubility of a third solute. The solute is made up of alkali metal salts of various organic acids. Ionic organic salts are mentioned as hydrotropic agents.

Additives or salts that increase solute solubility in a given solvent are referred to as "salt in" the solute, whereas salts that decrease solubility are referred to as "salt out" the solute.

Several salts with large anions or cations that are highly soluble in water cause "salting in" of non-electrolytes known as "hydrotropic salts," a phenomenon known as "hydrotropism."[20,21]

Advantages of hydrotropic solubilization technique

- Hydrotropy is thought to be superior to other methods of solubilization, such as miscibility, micellar solubilization, cosolvency, and salting in, because the solvent character is pH independent, has high selectivity, and does not require emulsification.
- It only requires mixing the drug with the hydrotrope in water; no chemical modification of hydrophobic drugs, use of organic solvents, or preparation of an emulsion system is required.[22]

5. Nanotechnology

Several nanonization techniques have recently emerged to improve the dissolution rates and bioavailability of many drugs that are poorly soluble in water. Nanonization is the study and application of materials and structures at the nanoparticle level of 100 nm or less. Nanonization can improve drug solubility and pharmacokinetics, as well as reduce systemic side effects.[23]

Oral bioavailability enhancement by micronization is insufficient for many new chemical entities with very low solubility because micronized products tend to agglomerate, resulting in a decrease in effective surface area for dissolution; the next step is nanonization. Wet milling, homogenization, emulsification-solvent evaporation technique, pear milling, spray drying, and other techniques are used for drug nanonization. There are numerous examples ofdrug nanonization.[24]

II. PHYSICAL MODIFICATION

1. Particle size reduction

Bioavailability is intimately connected to drug particle size. Increased surface area improves dissolution properties by reducing particle size. Particle size reduction is accomplished through milling techniques such as jet mills,rotor stator colloid mills, and so on. It is not suitable for drugs with a high dosenumber because it does not change the drug's saturation solubility.[25] Particle size reduction can now be accomplished through micronisation and nanosuspension.

Micronization: Drugs are micronized using milling techniques such as jet mills, rotorstator colloid mills, and so on.

Nanosuspension is another technique that involves the sub-micron colloidal dispersion of pure drug particles stabilized by surfactants.

Advantages

- Liquid forms can be rapidly developed for pre-clinical testing and then converted into solids for later clinical development.
- Low excipient-to-drug ratios are typically required.
- Formulations are generally well tolerated as long as strong surfactants are not used tostabilize them.
- Crystal forms are generally more chemically and physically stable than amorphousparticles.
- A method to consider for difficult compounds that have resisted previous efforts toincrease solubility.

Disadvantages

- Because of the high surface charge on discrete small particles, particle agglomeration is a strong possibility.
- It may be technically difficult to develop a solid dosage form with a high pay load without encouraging agglomeration.
- Technically, developing sterile intravenous formulations is even more difficult.[26]

2. Complexation

Drugs have been complexed with cyclodextrins to improve aqueous solubility and drug stability. Pharmaceutically relevant cyclodextrins contain 6, 7, or 8 dextrose molecules (cyclodextrin) bound in a 1,4-configuration to form rings of varying diameters. The ring has a hydrophilic exterior and a lipophilic core, which allows appropriately sized organic molecules to form noncovalent inclusion complexes, increasing aqueous solubility and chemical stability.[27]

Is the formation of a non-bonded entity with a well-defined stoichiometry by the joining of two or more molecules. There are two kinds of complexes:

- Complexes that can be loaded: It is caused by the drug's non-polar area becoming associated with the complexes agent, which prevents the non-polar area from coming into contact with water. The layering can be uniform or uneven, but the end result is the same.
- Complexes of inclusion: It is created by inserting a nonpolar molecule or region of a molecule into the cavity of another molecule or group of molecules. Cyclodextrine and its derivatives are commonly used in complexation.[28]

3. PH Adjustment

For ionizable drugs, pH modification (via buffering) is a viable option. Ionizable drugs can be protonated if they contain basic groups (e.g., amine) or deprotonated if they contain acid groups (e.g., carboxylic acid). Excipients are also used to raise the pH of the environment in tablet or capsule dosage forms. pH adjustment is frequently combined with co-solvents to increase solubility even further.[29] The pH-adjusted formulations are easy to make, and development moves quickly. Tolerability and

toxicity may occur as a result of the use of non-physiological pH levels. When drug molecules in a pH-adjusted formulation are diluted in aqueous media, they may become less soluble and precipitate, and if administered intravenously, they may cause oedema. Furthermore, because the drug is less chemically stable in an aqueous environment than in crystalline form, the pH used may enhance hydrolysis or catalyse other degradation mechanisms. Commercially available products that use the pH adjustment method include phenytoin injection (Epanutin® ready mixed, Pfizer) 50 mg/ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na+ per 5 ml ampoule 22).

Advantages
- Simple to formulate and analyze.
- Simple to produce and fast track.
- Uses small quantities of compound, amenable to high through put evaluations.

Disadvantages
- Increasing the risk of precipitation by diluting with aqueous media at a pH where the compound is less soluble. This may result in intravenous oedema as well as oral variability.
- Non-physiological pH and extreme pH cause intolerance and toxicity (both local and systemic).
- A dissolved drug in an aqueous environment is frequently less chemically stable than crystalline solid formulations, as are all solubilized and dissolved systems. The pH chosen could accelerate hydrolysis or catalyse other degradation processes.[30]

4. Microemulsion

A microemulsion is an optically clear pre-concentrate containing an oil, a hydrophilic surfactant, and a hydrophilic solvent that dissolves a drug that is poorly water soluble. Microemulsions have been used to increase the solubility of many drugs that are practically insoluble in water, as well as to incorporate proteins for oral, parenteral, and percutaneous / transdermal administration.[31]

Advantages
- The pre-concentrates are relatively simple to produce.
- Well-developed microemulsion pre-concentrates are not normally dependent on digestion for drug release. As a result, without food co-administration, optimal bioavailability and reproducibility can be expected (i.e. the fasted state).

Disadvantages
- The dilution effect of the hydrophilic solvent may increase the precipitation tendencyof the drug.
- In case where long-term chronic administration is intended, the tolerability of formulations containing high levels of synthetic surfactants may be poor.
- Validating formulas with multiple components becomes more difficult.

5. Solid dispersion

There are several techniques for increasing solubility. One of the most effective methods for increasing solubility is solid dispersion. SD refers to a class of solid products that contain at least two distinct components, typically a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous, and the drug can be dispersed either way.[32]

Advantages of SD
- It is possible to improve drug bioavailability and change water solubility.
- More efficient than particle size reduction techniques, which have a particle size reduction limit of around 2-5 mm, which is frequently insufficient to significantly improve drug solubility or drug release in the small intestine.[33]
- Increased dissolution rate and absorption extent, with a decrease in pre-systemicmetabolism.
- When parameters such as carrier molecular weight and composition, drug crystallinity and particle porosity, and wettability are successfully controlled, they can produce improvements in bioavailability.[2, 21]

Disadvantages of SD
- Aging causes changes in crystallinity and a decrease in dissolution rate.
- Moisture and temperature have a worse effect on SD than on physical mixtures.
- Because of their tackiness, some SD may be difficult to handle.
- A disadvantage of SD is their poor manufacturing scale-up.[34]

6. Supercritical fluid process

Particle size reduction via supercritical fluid (SCF) processes is another novel nanosizing and solubilisation technology that has seen increased application in recent years. Supercritical fluids have temperatures and pressures that are higher than their critical temperature (Tc) and critical pressure (Tp), allowing them to have the properties of both a liquid and a gas. SCFs are highly compressible at near-critical temperatures, allowing moderate pressure changes to significantly alter the density and mass transport characteristics of a fluid, which largely determine its solvent power. Once the drug particles have been solubilized in SCF, they can be recrystallised at much smaller particle sizes.

Because of the flexibility and precision provided by SCF processes, drug particles can be micronized within narrow particle size ranges, often to sub-micron levels. Current SCF processes have demonstrated the ability to produce nanoparticulate suspensions with particle diameters ranging from 5-2,000nm.[35]

7. Liquisolid method

Liquisolid Compacts/Methods: Powdered liquid pharmaceuticals are contained in Liquid Compacts. Oily liquid pharmaceuticals and solutions or suspensions of drugs that are not soluble in water are referred to as liquidsolid medications and are transported in suitable nonvolatile solvent systems. By combining a liquid medication with particular powder excipients, such as the carrier and coating material, the liquid medication can be transformed into a dry, non-adherent, free-flowing, and compressible powder. Tweens and other surfactants are used to make poorly soluble medicines more soluble in water.[36]

Advantages of Liquisolid Methods

- Provides powdered forms of liquid medications that are easily flowing and compressible.
- The method improves the solubility and bioavailability of orally administered waterinsoluble medications and is applicable in industry.
- Beneficial in the formulation of oily/liquid drugs.
- Different carriers and additives, such as PVP, PEG 60000, Hydroxyl Propyl Methyl Cellulose, and Eudragit, can be used to modify drug release.
- A variety of drugs that are poorly soluble can be formulated into the system.
- This system is only for powdered liquid medications.
- Production costs are low when compared to soft gelatin capsule preparation.

Disadvantages of liquisolid method

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

CONCLUSION

We conclude from this article solubility is the most important physical property of a drug for its oral bioavailability, formulation, development of different dosage forms of different drugs, therapeutic efficacy of the drug, and quantitative analysis. Proper solubility enhancement method selection is critical for achieving the goals of a good formulation such as good oral bioavailability, reduced frequency of dosing, and improved patient compliance while maintaining a low production cost. The various techniques described above, either alone or in combination, can be used to improve drug solubility. Many techniques can be used to improve solubility and the number of folds increase in solubility. Many drugs bioavailability is compromised due to solubility issues, and thus solubility enhancement is required. It is now possible to increase the solubility of poorly soluble drugs using the techniques described above.

REFERENCES

1. Kumar S, Singh P. Various techniques for solubility enhancement: An overview. The Pharma Innovation, 2016; 5(1, Part A): 23.
2. Godse SZ, Mohini S, Patil SM, Saudagar RB. Techniques for solubility enhancement of Hydrophobic drugs: A Review. Journal of Advanced Pharmacy Education & Research, Oct-Dec, 2013; 3(4).
3. Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, Shah VP, Lesko LJ, Chen ML, Lee VH, Hussain AS. Biopharmaceutics classification system: the scientific basis for biowaiver extensions. Pharmaceutical research, Jul, 2002; 19(7): 921-5.
4. Lindenberg M, Koop S and Dressman J: Classification of orally administered drugs on the WHO model list of essential medicines according to biopharmaceutical classification system. European Journal of Pharmaceutical and Biopharmaceutical, 2004; 58(2): 265-278.
5. Reddy N, Reddy A, Srinivasan S, Kavitha K, Kumar R, Singh J. Review on: better solubility enhancement of poorly water soluble drugs. International Journal of Inventions in Pharmaceutical Sciences, 2013; 1(4): 67.
6. Chaudhary A, Nagaich U, Gulati N, Sharma VK, Khosa RL, Partapur MU. Enhancement of solubilization and bioavailability of poorly soluble drugs by physical and chemical modifications: A recent review. J Adv Pharm Educ Res., 2012; 2(1): 32-67.
7. Mello GD, Cardoso AD, Oliveira EW, Siqueira AB. Tryptophan. Journal of Thermal Analysis and Calorimetry, 2015; 3(122): 1395-401.
8. Kadam SV, Shinkar DM, Saudagar RB. Review on solubility enhancement techniques. IJPBS, 2013; 3(3): 462-75.
9. Sharma D, Soni M, Kumar S, Gupta GD. Solubility enhancement—eminent role in poorly soluble drugs. Research Journal of Pharmacy and Technology, Apr, 2009; 2(2): 220-4.
10. Madhavi C, Sowmya N, Keerthi B, Sathwika S. Enhancement Of Dissolution And Bioavailability Of Bcs-Class Ii Drug By Solid Dispersion Method. Ininternational Conference On Innovative Research In, 2019; (5). RFI.
11. Shinde A. Solubilization of poorly water soluble drugs. Pharminfo. Net., 2007; 5(6): 44-52.
12. Perrett S, Venkatesh G. Enhancing the bioavailability of insoluble drug compounds. Innov Pharm Technol, 2006; 19: 80-5.
13. Kumar K. Solid dispersion: solubility enhancement technique of poorly water soluble drug. Journal of Drug Delivery and Therapeutics, Mar 14, 2020; 10(1): 173-7.
14. Beig A, Miller JM, Lindley D, Carr RA, Zocharski P, Agbaria R, Dahan A. Head-to- head comparison of different solubility-enabling formulations of etoposide and their consequent solubility–permeability interplay. Journal of pharmaceutical sciences, Sep 1, 2015; 104(9): 2941-7.
15. Loh ZH, Samanta AK, Heng PW. Overview of

milling techniques for improving the solubility of poorly water-soluble drugs. Asian journal of pharmaceutical sciences, Jul 1, 2015; 10(4): 255-74.
16. Serajuddin AT. Salt formation to improve drug solubility. Advanced drug delivery reviews, Jul 30, 2007; 59(7): 603-16.
17. Patole T, Deshpande A. Co-crystallization-a technique for solubility enhancement. International journal of pharmaceutical sciences and research, Sep 1, 2014; 5(9): 3566.
18. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. International journal of pharmaceutical sciences review and research, Nov, 2010; 5(1): 41-51.
19. Hart ML, Do DP, Ansari RA, Rizvi SA. Brief overview of various approaches to enhance drug solubility. J. Dev. Drugs, 2013; 2(03).
20. Badwan AA, El-Khordagui LK, Saleh AM, Khalil SA. The solubility of benzodiazepines in sodium salicylate solution and a proposed mechanism for hydrotropic solubilization. International journal of Pharmaceutics, Dec 1, 1982; 13(1): 67-74.
21. Jain AK. Solubilization of indomethacin using hydrotropes for aqueous injection. European Journal of Pharmaceutics and Biopharmaceutics, Mar 1, 2008; 68(3): 701-14.
22. Jain P, Goel A, Sharma S, Parmar M. Solubility enhancement techniques with special emphasis on hydrotrophy. International Journal of Pharma Professional's Research, Jul, 2010; 1(1): 34-45.
23. Riehemann K, Schneider SW, Luger TA, Godin B, Ferrari M, Fuchs H. Nanomedicine—challenge and perspectives. Angewandte Chemie International Edition, Jan 19, 2009; 48(5): 872-97.
24. Zaheer A, Naveen M, Santosh MK, Imran K. Solubility enhancement of poorly water soluble drugs: A review. IJPT, 2011; 3(1): 807-2.
25. Chaumeil JC. Micronization: a method of improving the bioavailability of poorly soluble drugs. Methods and findings in experimental and clinical pharmacology, Apr 1, 1998; 20(3): 211-6.
26. Müller RH, Peters K, Becker R, Kruss B. Nanosuspensions for the iv administration of poorly soluble drugs-stability during sterilization and long-term storage. InProceedings of the 22nd International Symposium on Controlled Release of Bioactive Materials, Jul 30, 1995; (574-575).
27. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. Journal of pharmaceutical sciences, Oct, 1996; 85(10): 1017-25.
28. JS P, Kadam D, Marapur S, Kamalapur M. Inclusion complex system; a novel technique to improve the solubility and bioavailability of poorly soluble drugs: A review. Int. J. Pharm. Sci. Rev. Res., 2010; 2: 29-34.
29. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. International journal of pharmaceutics, Nov 25, 2011; 420(1): 1-0.
30. Allen L, Ansel HC. Ansel's pharmaceutical dosage forms and drug delivery systems. Lippincott Williams & Wilkins, 2013 Dec 23.
31. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Advanced drug delivery reviews, Dec 6, 2000; 45(1): 89-121.
32. Bhatnagar P, Dhote V, Chandra Mahajan S, Kumar Mishra P, Kumar Mishra D. Solid dispersion in pharmaceutical drug development: from basics to clinical applications. Current drug delivery, Apr 1, 2014; 11(2): 155-71.
33. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug discovery today, Dec. 1, 2007; 12(23-24): 1068-75.
34. Kurmi R, Mishra DK, Jain DK. Solid dispersion: a novel means of solubility enhancement. J Crit Rev., 2016; 3(1): 1-8.
35. Martin TM, Bandi N, Shulz R, Roberts CB, Kompella UB. Preparation of budesonide and budesonide-PLA microparticles using supercritical fluid precipitation technology. AAPS PharmSciTech., Sep. 2002; 3(3): 16-26.
36. Karmarkar A, Gonjari I, Hosman A, Dhabal P, Bhis S. Liquisolid tablets: a novel approach for drug delivery. International Journal of Health Research, 2009; 2(1).