JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

SOLUBILITY ENHANCEMENT TECHNIQUES

[1]Sanika Vijay Awchar, [2]Dr.Shivshankar Mhaske, [3]Sanjana R. Bali

[4] Om Eknath Avhale [5] Anisha Keshav Awchar.

[1]Student, [2]Principal, [3]Professor, [4]Student, [5]Student.

[1]Satyajeet Collage Of Pharmacy Mehkar, Buldhana- Maharashtra.

Abstract : Among all newly discovered chemical entities about 40% drugs are lipophillic and fail to reach market due to their poor aqueous solubility. For orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist, which can be solved by different technological approaches during the pharmaceutical product development. Solid dispersion, Micronization, Salt formation, are some of the vital approaches routinely employed to enhance the solubility of poorly soluble drugs but each approach has some limitation and advantages. Novel techniques like Nano-suspension, Supercritical processing, Cryogenic technology may allow greater opportunities in the delivery of poorly soluble drugs. The solubility behavior of drugs remains one of the most challenging aspects in formulation development. The present review is devoted to various traditional and novel techniques for enhancing drug solubility to reduce the percentage of poorly soluble drug candidates eliminated from the development.

Keywords :- Solubility, bioavailability, dissolution rate, Solid dispersion, BCS Classification.

I. INTRODUCTION

Solubility is a property of substance in a particular solvent. In quantitative terms it is the concentration of dissolved solute in a saturated solution at a specific temperature[1]. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailabilit [2]**.** The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent [3]number of methodologies can be adapted to improve solubilization of poor water solubilization of drug included micronization, chemical modification, pH adjustment,solid dispersion,complexation,co-solvency, micellar[4]. Solubility is one of the important parametersto achieve desired concentration of drug in systemic circulation for achieving required therapeutic plasma concentrations after oral administrati[5] Majority of drugs are present in second class of drug which is poorly soluble drug. BCS class of drug divided in to four categories-high solubility and high permeability, low solubility and high permeability, high solubility and low permeability, low solubility and low permeability. Solubility of drug can be increase by increasing of dissolution rate.[6] Drugs having poor water solubility classify by BCS [Biopharmacutical Classification System] class II and class IV it shows dissolution related problems. The BCS is a scientific paradigm for categorising pharmaceuticals based on their water solubility and intestinal permeability. When paired with the drug product's in vitro dissolving properties, the BCS considers three important factors: solubility, intestinal permeability, and dissolution rate, all of which influence the rate and amount of oral

drug absorption from sudden release solid oral-dosage forms. According to the US food drug administration FDA[7] 130 orally administered drugs on the WHO list 61 could be classified with certainty. 84% of these belong to class I (highly soluble, highly permeable), 17% to class II (poorly soluble, highly permeable), 24 (39%) to class III (highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble, poorly permeable). The rate and extent of absorption of class II & class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility[8] the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system[9] More than 90% of drugs approved since 1995 have poor solubility. It was estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble and not well absorbed after oral administration which can distract from the drugs inherent efficacy . Drug absorption, sufficient and reproducible bioavaiability and/or pharmacokinetic profile in human are recognized today as one of the major challenges in oral delivery of new drug substances. Orally administered drugs on the model list of essential medicines of the World Health Organization (WHO)[10] the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water soluble drug[11] . Bioavailability can determine the better solubility of drug and how it's showing the pharmacological response. Solubility is the key parameters to found out meditation of drug in complete movement to doing required pharmacological response to a particular drug. Any drug which is administered drug or to be fascinated must be existing in the aqueous solution in from of location the absorption which can easily show the response to the site of action. Liquid is the maximum common using solvent for the liquid pharmaceutical formulations or in any solubility process[12] Need of Solubility Enhancement: Drug absorption from the gastrointestinal tract can be limited by a variety of factors, most significant contributors being poor aqueous solubility and poor membrane permeability of the drug molecule. When delivering an active agent orally it must first dissolve in gastric and / or intestinal fluids before it can permeate the membranes of the GI tract to reach systemic circulation. Hence, two areas of pharmaceutic research that focus on improving the oral bioavailability of active agents[13] The most important impact of poor aqueous solubility of the compound is on dissolution rate. Low dissolution rate influenced by poor aqueous solubility might render low oral bioavailability of such compounds. This is particularly important in oral drug administration where dissolution should be completed within the intestinal transit time limit to maximize drug absorption[14]

Literature Review

1. **Ayushi Sharm et al"(2023) ;**In this article solubility enhancement techniques are used to improve the dissolution rate and bioavailability of poorly water-soluble drugs. Common methods include particle size reduction (milling, micronization), which involves breaking down solid materials into smaller particles using mechanical forces.
2. **Himanshi Khatri et al"(2022) ;** Drugs with poor aqueous solubility cause slow dissolution rates, generally show low bioavailability when orally administered. The purpose of this review article is for the achievement of effective absorption and improved bioavailability.
3. **Saba Albetawi1 et al"(2021) ;** this review aims to discuss in depth the various approaches investigated in the past five years to improve the solubility and dissolution of orally administered repaglinide: namely, solid dispersion, co- amorphous technology, cyclodextrin complexation, phospholipid complexes and polymeric micelles,
nanocrystals, nanosuspensions.
4. **Abikesh P.K. Mahapatra1 et al"(2020);** The primary aim of this review was to improve the solubility and Bioavailability of BCS Class-II drugs because of their low solubility and dissolution rate. Solubility is one of the imp parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.

5. **Sakshi Minocha et al" (2019) ;** This review mentions different approaches used for the enhancement of the solubility of poorly water-soluble drugs that includes particle size reduction, pH adjustment, and solid dispersion. This describes the techniques of solubilizaton for the attainment of effective absorption and improved bioavailability.

6. **Shilpa Kumari Gupta et al"(2018) ;** This article aims is to describe the different solubility enhancement techniques to improve the solubility of the drug by different approach like Advanced and traditional methods.Micronization, Nano-suspension, and Homogenization, Salt formation, Spray Drying, Hot melt Extrusion, Solvent evaporation, and Conventional technique for solid dispersion.

7. **Rai Muhammad Sarfrazi et"(2017) ;**From this article, we clearly conclude that sol ubility is one of the most important parameters to produce desired therapeutic level of drug at the site of action. So, it is very critical for formulation development

8. **Sandeep Kumar et al"(2015) ;**The purpose of this article is to describe the techniques of solubilization for the attainment of effective absorption and improved bioavailability.

Factor Affecting Solubility:

1] Molecular structure : A small change in the molecular structure of a compound can have a marked effect on its solubility in a given liquid. For example, the introduction of a hydrophilic hydroxyl group can produce a large improvement in water solubility. In addition, the conversion of a weak acid to its sodium salt leads to a much greater degree of ionic dissociation of the compound when it dissolves in water. The overall interaction between solute and solvent is markedly increased and the solubility consequently rises. In addition, the esterification of drug will decrease the solubility.[15]

2].Polarity: Polarity of each solute and solvent molecules impacts the solubility. Generally polar solute molecules will dissolve in polar solvents and non-polar solute molecules will dissolve in non-polar solve[16]

3] Molecular size: Solubility affected by molecular size of particle. The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.[17]

4] Temperature: Solubility affected by temperature. If the solution process absorbs energy then the solubility will increase with increasing temperature. If the solution process releases energy then the solubility will decrease with increasing temperature[18]

5] Size of the particles: Breaking a solute into smaller pieces increases its surface area, when the total surface area of solute particles is increased the solute dissolves more rapidly because the action takes place only at the surface of each particle and hence increases its rate of solution[19]

6] Pressure: For solids and liquid solutes, changes in pressure have practically no effect on solubility but for gaseous solutes, an increase in pressure, increases solubility and a decrease in Pressure, decrease the solubility.[20]

Technique For Solubility Enhancent A]

Physical Modification

1] Partical Size Reduction:

a] Nanosuspension:

Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system consisting of nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600nm.Various methods utilized for preparation of nanosuspensions

include precipitation technique, media milling, highpressure homogenization in water, high pressure homogenization in nonaqueous media, and combination of Precipitation and high- Pressure homogenization.[21]

b] Micronization:

Micronization is a specialized form of milling that targets reducing particle size to the micrometer or sub-micrometer range. It is particularly relevant in the pharmaceutical industry, where the bioavailability of poorly soluble drugs can be significantly improved by reducing their particle size to the micron level. Micronization is often achieved using technologies like air jet milling, spiral jet milling, or bead milling. In air jet milling, compressed air or gas is used to create a high-velocity stream that impacts and fractures the particles, reducing them to the desired size. Spiral jet mills employ a similar principle but with the addition of a classifier to separate particles of different sizes. Bead milling involves the use of small beads as grinding media in a dispersion medium to achieve particle size reduction.[22]

2] Crystal Engineering:

a] Polymorphs:

The ability of a solid material to exist in two or more different crystalline forms with different crystal lattice arrangements is known as polymorphism. Different crystalline forms are called polymorphs. Phenomenon in which solvent molecules gets incorporated into crystal lattice of solid are known as solvates. This solvates exist in different crystal form called pseudopolymorphs and the phenomenon is called as pseudo polymorphism. Drugs that exist in crystalline form are chemically identical, but they differ physiochemically in terms of melting point, texture, density, solubility and stability. Similarly, an amorphous form of a drug is more suitable than a crystalline form due to its larger surface area and higher associated energy.Order of different solid form of drugs is Amorphous > Metastable polymorphs > Stable polymorphs.[23]

b] Co-crystallization:

. Co-crystals basically consists of two components that are the API and the former. Now, the former can be any other excipient or API which when given in combination reduces the dose and also the side effects. Hence even if the API is the same changing the former will also change the pharmaceutical properties (chemical stability, bioavailability, solubility, melting point,[24]

Co-crystals are structurally homogeneous crystalline materialscontaining two or more active electrically neutral species clenched together by noncovalent forces, present in definite stoichiometric amounts.60 Co-crystals have neutral molecular reactants that are solid at ambient temperature., the co-crystal technique is the most favourable method in the pharmaceutical industry. Co-crystals prepared by evaporation of a heteromeric solution or by grinding the components together or by sublimation enhances its solubility, dissolution rate, bioavailability, and physical stability, also improving other essential properties like flow, chemical stability, and compressibility.61 Co-crystallization is an alternative technique for salt formation and is used for neutral compound[25]

B] Chemical Modification

1] Salt Formation:

Salt formation techniques are is used to improvement of the solubility and dissolution of drug. This method is for the purpose to see any reaction of different drug or chemical reaction. Salt forms when the drug is ionised formed. It's having different method like physiochemical property and affects characteristics stability, bioavailability, purification and manufacturability of the drug. Salt formation of low soluble drug candidates has been an approach for numerous periods to enhance solubility[12] for salt formation should have ionizable groups that will assist salt formation. For the selection of count er ion the following criteria are used

1 The drug and the counter ion should have mini mum difference of 2-3 pKa units.

2. Counter ion should decrease crystal lattice forces.

3. It should be FDA approved[26]

2] Prodrug :

Hydrophilic or water soluble drugs are desired where solubility is the rate limiting step in the dissolution and absorption of poorly aqueous soluble agents or when parenteral or ophthalmic formulation of such agents are desired. Drugs with hydroxyl function can be converted into their hydrophilic forms by use of half-esters such as hemisuccinates, hemiglutarates or hemiphthalates; the other half of these acidic carriers can form sodium, potassium or amine salts and render the moiety water soluble. Although prodrug formation method can result in high increase in solubility, they require synthesis of essentially new drug entities as well as additional animal studies to confirm their efficacy and safety.Example : Acetyl Salicylic Acid is a prodrug form of Salicylic Acid.[27]

3] Complexation :

Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1,4 configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non covalent inclusion complexes resulting in increased aqueous solubility and chemical stability.[28]

4] Inclusion complexes:

It is formed by inserting the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. There are no forces involved between them and therefore there are no bonds. Hence, these are also called as no-bond complexes. Cyclodextrins (CD) are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α, ß and γ-CD are composed of six, seven, and eight D-(+) glucopyranose units. Cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. Cyclodextrins and their derivatives are commonly used in complexation. They form complex with drug and improve the solubility and bioavailability of poorly soluble drug. Derivatives of R cyclodextrin with increased water solubility (e.g. hydroxypropyl-R-cyclodextrin HP-R-CD) are most commonly used in pharmaceutical formulation[29]

C] Solublization Technique

1] PH Adjustment:

pH adjustment is Poor water soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs[30]ph adjustment is simple to formulate and analyze. pH adjustment can in principle be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with Ph between 7.2 7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines[31]

2] Hydrotrophy:

Agents that are employed to enhance solubility of solutes which are poorly soluble in solvents are termed as hydrotropes or hydrotropic agents.We can easily correlate hydrotropy as a solubilization process which enhances aqueous solubility of a solute which is dependent over the addition of another solute (hydrotropic agents)[32]

Hydrotrophy it is a solubilization phenomenon where addition of a large amount of second solute results in an increase in the aqueous solubility of existing solute. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs. Hydrotropic agents are ionic organic salts. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute.[33]

3] Use of co-solvent:

Cosolvent addition is a highly effective technique for enhancement of solubility of poorly soluble drugs. It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. This can be achieved by addition of another solvent. This process is known as cosolvency. Solvent used to increase solubility is known as cosolvent. Cosolvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxyethylene glycols, dimethylsulfoxide, ethanol and N, N dimethyl formamide can be used[34]

4] Surfactant:

Permeability and dissolution rate could be improved with surfactant. Absorption rate likewise be boost due to enhancing of particle size. Mechanism includes initially wettability and then permeation of solvent in the particles of drug. Solubility of ample poorly water soluble anti-microbial drugs can be improved by use of surfactant. Surfactant are of three types; anionic, cationic and non-ionic. Anionic and cationic are choice over the non-ionic surfactant. It deeds as good solubilizing agent[35]

D] Nanotechnology Based Approches

Nanotechnology will be used to improve drugs that currently have poor solubility7. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers (nm) or less. For many new chemical entities of very low solubil ity, oral bioavailability enhancement by micronisation is not sufficient because micronised product has very low effective surface area for dissolution and next step taken was nanonisation[36]

1] Polymeric micelles: Polymeric micelles (PMs) are carriers composed of one or more polymers and amphiphilic copolymers that self-assemble in aqueous medium forming a hydrophobic core and a hydrophilic outer shell, the corona, with size between 20– 200 nm. This process is thermodynamically conducted and occurs above the critical micellar concentration (CMC) of the polymer[37]

2] Nanosuspensions:

A pharmaceutical Nano-suspension is a biphasic system which consist of nano sized drug Particles which is stabilized by using the surfactants for either oral or topical use or parenteral and for pulmonary administration. This technology has been developed as a promising candidate for the efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. The particle size distribution of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm[38] Techniques for the production of nanosuspensions include Homogenization and wet milling Active drug in the presence of surfactant is defragmented by milling. Other technique involves the spraying of a drug solution in a volatile organic solvent into a heated aqueous solution. Rapid solvent evaporation produces drug precipitation in the presence of surfactants.[39]

3] Liposomes:

Liposomes are vesicles formed by either synthetic or nature phospholipids. These phospholipid molecules arrange themselves spontaneously into bilayer structures in water, so that the hydrophobic tails are shielded from water by hydrophilic heads. Vesicles can consist of one or more phospholipid bilayers with hydrophilic and hydrophobic compartments. The hydrophobic

compartments can carry or fill with hydrophobic or water-insoluble drugs while the hydrophilic compartments can load hydrophilic or water-soluble drugs.[40]

E] Other Technique

1] Supercritical Fluid Technology (SCF):

The Process Particle size decrease utilizing supercritical liquid (SCF) procedures is another progressive nanosizing and solubilisation technique whose utilization has filled as of late because of the headway of SCF innovation. At the point when the temperature and tension of a liquid are higher than the basic temperature (Tc) and the basic strain (Tp), the liquid might accept the attributes of both a fluid and a gas, which is alluded to as supercritical liquids[41]

The flexibility and precision offered by SCF processes allows micronisation of drug particles

within narrow ranges of particle size, often to submicron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5–2,000nm in diameter[42] SCF techniques can be applied to the preparation of solvent- free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Tradi tional methods suffer from the use of mechanical forces and excess organic solvents. A solid dispersion of Carbamazepine in polyethylene glycol 4000 (PEG- 4000) increased the rate and extent of dissolution of carbamazepine. In this method, a precipitation vessel was loaded with solution of Carbamazepine and PEG-4000 in acetone, which was expanded with supercritical CO2 from the bottom of the vessel to obtain solvent-free particles[44] Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle size reduction and solubility enhancement.[43] This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, superconductors and catalyst precursors dyes and biomolecules such as proteins and peptides[46]

2] Solid Dispersion:

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug andawater-soluble carrier in the early 1960s Solid disp[44]ersions represent a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic effi cacy of drugs in dosage forms[47] Solid dispersion refers to a group of solid products consisting at least two When a mixture of A & B with composition E is cooled, A and B crystallize out simultaneously, whereas when other composition are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a component of the two compound in order to obtain a physical mixture of very fine crystals of the two component[48]

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, de-mixing (partially or complete) and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted[49] The drug can be dispersed molecularly, in amorphous particles or in crystalline particles .Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Solid dispersions should preferably be designated according to their molecular arrangement.[50] solid dispersion surfactants are used as carrier. If carrier has surface active or self emulsifying properties, the dissolution profile of poorly soluble drug can be improved and hence eventually result in increased bioavailability. Typically used surfactants as solid dispersion carriers are polaxamer 40725 , gelucire 44/1426 , compritol 888 ATO27 inulin[51] solid dispersion can be prepared through different approaches approaches, including kneading, co-milling, fusion, solvent evaporation and solvent melting techniques. These methods are classified according to their scalability into lab and large-scale techniques[52]

Emerging and Advanced Techniques 1]

Hot Melt Extrusion

It is a very common method used in the polymer industry. But Speiser and Huttenrach were the first persons who use this technology for pharmaceutical purpose. A melt extrusion consists of the following sections: An opening to feed raw materials, a heated barrel that consists of extruder screws to convey and mix the fed materials, and an exit port, which consists of an optional die to shape the extruding mass[53] In this method, the physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed pulverized, and sieved, which can be compressed into tablets with the help of tabletting agents. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system[54] Hot-melt extrusion is a process of applying heat and pressure to melt a polymer or mixture and force it through an orifice in a continuous process, which was introduced into the pharmaceutical field for SDs manufacturing in 1980s. drug/carrier mixture is simultaneously melted, homogenized and then extruded with a twin-screw extruder. The resulting intermediates can be further processed into conventional dosage forms, such as the tablets and capsules. The prominent advantage of hot-melt extrusion lies in the shorter subjection to high temperature, approximately for 1~2 min, which secures APIs that are somewhat heat-labile.[55]

2] Microemulsions:

Microemulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous / transdermal use. A microemulsion is an optically clear pre-concentrate containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent which dissolves a poorly water soluble drug. Upon contact with water, the formulations spontaneously disperse (or 'self emulsifies') to form a very clear emulsion of exceedingly small and uniform oil droplets containing the solubilized poorly soluble drug[56] Microemulsions are potential drug delivery systems for poorly water-soluble drugs due to their ability to solubilize the drugs in the oil phase, thus increasing their dissolution rate. Even if the microemulsions are diluted after oral administration below the critical micelles concentration (CMC), the resultant drug precipitates have a fine particle size allowing enhanced absorption[57].

Advantages of Solubility Enhancement Techniques

In order to increase the bioavailability of poorly water-soluble medications, which make up a sizable percentage of recently created pharmaceutical substances, solubility improvement approaches are crucial. Some popular methods and their benefits are included below, along with reading recommendations.[58]

1 Improved Bioavailability

Drugs that are poorly soluble in water frequently have trouble being absorbed. Techniques for improving solubility speed up dissolution, which is directly related to increased bioavailability.

For example, fenofibrate and other poorly soluble medications' nanocrystals improve their bioavailability.

2 Faster Onset of Action

These methods hasten the beginning of therapeutic effects by speeding up the drug's rate of dissolution. For quick pain relief, paracetamol can be micronised.

3 Reduced Dosage Requirements

Improved solubility minimises adverse effects and drug waste by enabling smaller dosages to produce the intended therapeutic effect.

Example: To improve the solubility of lipophilic medications, lipid-based formulations such as SEDDS are used.

4 Increased Formulation Flexibility

The creation of various dosage forms, including tablets, liquids, and injectables, is made possible by solubility improvement techniques.

For instance, cyclodextrin complexes enable the creation of aqueous solutions for medications that are hydrophobic.[59]

5 Improved Patient Compliance

Oral medications can be made more palatable and flavour masking by using surfactants or reducing the size of the drug particles.

Cyclodextrin inclusion complexes for bitter medications are one example.

6 Minimized Food Effect

By avoiding the solubility issues caused by food, methods such as lipid-based systems can guarantee constant drug absorption regardless of dietary intake.

Antiretroviral medication compositions based on lipids are one example.

7 Targeted Drug Delivery

In addition to increasing solubility, cutting-edge methods like nanotechnology allow for targeted drug administration, which lowers systemic toxicity.

For instance, paclitaxel nanoparticles for anticancer medications.

8 Enhanced Stability

Drugs in their amorphous state are stabilised via solid dispersions and complexation techniques, which decrease degradation and increase shelf life.

For instance, itraconazole amorphous dispersions with HPMC.[60]

Conclusion :

- Solubility enhancement techniques play important role in overcoming the challenges of poorly soluble drug improving bioavailability and enhancing therapeutic efficacy.
- Solubility is most important parameter for oral bioavailability of poorly soluble drug.
- It is now possible to increase solubility of poorly soluble drug with the help of various technique as mention above.

.

REFERENCES

[1] Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility enhancement technique: a review. Journal of pharmaceutical sciences and Research. 2018 Sep 1;10(9):2205-11.

[2] Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancement techniques for hydrophobic drugs. Pharmacie Globale. 2011;3(3):001-7.

[3]. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. International journal of pharmaceutical sciences review and research. 2010 Nov 5;5(1):41-51.

[4]. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. International Scholarly Research Notices. 2012;2012(1):195727.

[5] Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. International Scholarly Research Notices. 2012;2012(1):195727.

[6 Kesarwani P, Rastogi S, Bhalla V, Arora V. Solubility enhancement of poorly water soluble drugs: A review. International Journal of Pharmaceutical Sciences and Research. 2014 Aug 1;5(8):3123
[7] Khatri H, Hussain MS, Tyagi S. Solubility enhancement techniques: an overview. World J Pharmaceut Res. 2022 Mar 3;11:468- 82.
[8] Sikarra D, Shukla V, Kharia AA, Chatterjee DP. Techniques for solubility enhancement of poorly soluble drugs: an overview. JMPAS. 2012;1:1-2
[9] Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancement techniques for hydrophobic drugs. Pharmacie Globale. 2011;3(3):00

[10] Jatwani S, Rana AC, Singh G, Aggarwal G. An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach. International journal of pharmaceutical Sciences and Research. 2012 Apr 1;3(4):942.
[11] Jatwani S, Rana AC, Singh G, Aggarwal G. An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach. International journal of pharmaceutical Sciences and Research. 2012 Apr 1;3(4):942.
[12] Gupta SK, Gupta RK, Pandey NK, Singh SK, Kumar B. Solubility enhancement techniques: A comparative study. Int J Res Anal Rev. 2018;5:73.
[13] Jatwani S, Rana AC, Singh G, Aggarwal G. An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach. International journal of pharmaceutical Sciences and Research. 2012 Apr 1;3(4):942.
[14] Jain S, Patel N, Lin S. Solubility and dissolution enhancement strategies: current understanding and recent trends. Drug development and industrial pharmacy. 2015 Jun 3;41(6):875-87.
[15.] Deshmukh AS, Tiwari KJ, Mahajan VR. Solubility enhancement techniques for poorly water-soluble drugs. Int. J. Pharm. Sci. Nanotechnol. 2017 May 31;10(8).
[16] Khatri H, Hussain MS, Tyagi S. Solubility enhancement techniques: an overview. World J Pharmaceut Res. 2022 Mar 3;11:468- 82.
[17] Kadam SV, Shinkar DM, Saudagar RB. Review on solubility enhancement techniques. IJPBS. 2013 Jul;3(3):462-75.
[18] Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility enhancement technique: a review. Journal of pharmaceutical sciences and Research. 2018 Sep 1;10(9):2205-11.
[19] Gaikwad SS, Mhalaskar RS, Mahale YD, Jain NP. Review on: solubility enhancement of poorly water soluble drug. Indo Am J Pharm Res. 2014;4(11):5530-41.
[20] Mahapatra AP, Patil V, Patil R. Solubility enhancement of poorly soluble drugs by using novel techniques: A comprehensive review. Int. J. PharmTech Res. 2020;13(2):80-93.
[21] Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. International journal of pharmaceutical sciences review and research. 2010 Nov 5;5(1):41-51.
[22] Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility enhancement technique: a review. Journal of pharmaceutical sciences and Research. 2018 Sep 1;10(9):2205-11.
[23] MS AK, Rajesh M, Subramanian L. Solubility enhancement techniques: A comprehensive review. World Journal of Biology Pharmacy and Health Sciences. 2023;13(3):141-9.
[24] Kumar P, Singh C. A study on solubility enhancement methods for poorly water soluble drugs. American Journal of Pharmacological Sciences. 2013;1(4):67-73.
[25] Kumar S, Bhargava D, Thakkar A, Arora S. Drug carrier systems for solubility enhancement of BCS class II drugs: a critical review. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2013;30(3).
[26] Gupta SK, Gupta RK, Pandey NK, Singh SK, Kumar B. Solubility enhancement techniques: A comparative study. Int J Res Anal Rev. 2018;5:73.
[27] Sarfraz RM, Bashir S, Mahmood A, Ahsan H, Riaz H, Raza H, Rashid Z, Raza SA, Abrar MA, Abbas K, Yasmeen T. Application of various polymers and polymers based techniques used to improve solubility of poorly water soluble drugs: A review. Acta Pol. Pharm. 2017 Mar 1;74:347-56.
[28] Patel A, Patel S, Dwivedi N, Patel S, Kaurav N. Solubility enhancement technologies and research emerged. International Journal of Pharmaceutical & Biological. 2017;8(2):1-1.
[29] Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. International journal of pharmaceutical sciences review and research. 2010 Nov 5;5(1):41-51.
[30] Deshmukh AS, Tiwari KJ, Mahajan VR. Solubility enhancement techniques for poorly water-soluble drugs. Int. J. Pharm. Sci. Nanotechnol. 2017 May 31;10(8).
[31] Sareen S, Mathew G, Joseph L. Improvement in solubility of poor water-soluble drugs by solid dispersion. International journal of pharmaceutical investigation. 2012 Jan;2(1):12.
[32] Sikarra D, Shukla V, Kharia AA, Chatterjee DP. Techniques for solubility enhancement of poorly soluble drugs: an overview. JMPAS. 2012;1:1-22.
[33] Namdev B, Venkatachalam S, Jawahar N, Chorsiya A. A brief review on solubility enhancement technique: hydrotropy. Indian J Pharm Educ Res. 2022 Apr 1;56(2):347-55.
[34] Jagtap S, Magdum C, Jadge D, Jagtap R. Solubility enhancement technique: a review. Journal of pharmaceutical sciences and Research. 2018 Sep 1;10(9):2205-11.

[35] 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 (0428-0296). 2021 Jul 1;68(3).
[36] Minocha S, Pahwa S, Arora V. SOlubility enhancement of poorly water soluble drugs by various techniques. J Biomed Pharma Res. 2019:13-9.
[37] F. L. O. Da Silva, M. B. D. F. Marques, K. C. Kato, and G. Carneiro, "Nanonization techniques to overcome poor water-solubility with drugs," Jul. 02, 2020, *Taylor and Francis Ltd*. doi: 10.1080/17460441.2020.1750591.
[38] P. Vinod, P. Sunil, P. Sonali, P. Tejaswini, P. Sachinkumar, and P. Shitalkumar, "Solubility Enhancement of Poorly Soluble Drugs by Using Novel Techniques: A Review," 2014. [Online]. Available: www.jcpronline.in
[39] M. Sheetal and Z. Godse, "Techniques for solubility enhancement of Hydrophobic drugs: A Review." [Online]. Available: www.japer.in
[40] P. Kumar and C. Singh, "A Study on Solubility Enhancement Methods for Poorly Water Soluble Drugs," *Am J Pharmacol Sci*, vol. 1, no. 4, pp. 67–73, Sep. 2013, doi: 10.12691/ajps-1-4-5.
[41] M. Amrit, K. Patel, and A. Kabri, "International Journal of Advance THE IMPORTANCE OF DRUG SOLUBILITY AND TECHNIQUES FOR SOLUBILITY ENHANCEMENT", [Online]. Available: www.ijaar.co.in
[42] K. T. Savjani, A. K. Gajjar, and J. K. Savjani, "Drug Solubility: Importance and Enhancement Techniques," *ISRN Pharm*, vol. 2012, pp. 1–10, Jul. 2012, doi: 10.5402/2012/195727.
[43] K. T. Savjani, A. K. Gajjar, and J. K. Savjani, "Drug Solubility: Importance and Enhancement Techniques," *ISRN Pharm*, vol. 2012, pp. 1–10, Jul. 2012, doi: 10.5402/2012/195727.
[44] Kamalakkannan V, Puratchikody A, Masilamani K, Senthilnathan B. Solubility enhancement of poorly soluble drugs by solid dispersion technique–A review. J. Pharm. Res. 2010 Sep;3(9):2314-21.
[45] Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. International Scholarly Research Notices. 2012;2012(1):195727.
[46] Chaturvedi AK, Verma A. Solubility enhancement of poorly water soluble drugs by solid dispersion. International Journal of Pharmaceutical Sciences and Research. 2012 Jan 1;3(1):26.
[47] Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. International Scholarly Research Notices. 2012;2012(1):195727.
[48] Jatwani S, Rana AC, Singh G, Aggarwal G. An overview on solubility enhancement techniques for poorly soluble drugs and solid dispersion as an eminent strategic approach. International journal of pharmaceutical Sciences and Research. 2012 Apr 1;3(4):942.
[49] Kamalakkannan V, Puratchikody A, Masilamani K, Senthilnathan B. Solubility enhancement of poorly soluble drugs by solid dispersion technique–A review. J. Pharm. Res. 2010 Sep;3(9):2314-21.
[50] Kaur J, Aggarwal G, Singh G, Rana AC. Improvement of drug solubility using solid dispersion. Int J Pharm Pharm Sci. 2012;4(2):47-53.
[51] Wairkar SM, Gaud RS. Solid dispersions: Solubility enhancement technique for poorly soluble drugs. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2013 Jul;4(3):847.
[52] Attia MS, Hasan AA, Ghazy FE, Gomaa E, Attia M. 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. 2021 Apr 1;55(13):103.
[53] Kumar S, Singh P. Various techniques for solubility enhancement: An overview. The Pharma Innovation. 2016;5(1, Part A):23.
[54] Kumar A, Sahoo SK, Padhee K, Kochar PS, Sathapathy A, Pathak N. Review on solubility enhancement techniques for hydrophobic drugs. Pharmacie Globale. 2011;3(3):001-7.
[55] 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.
[56] Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. International journal of pharmaceutical sciences review and research. 2010 Nov 5;5(1):41-51.
[57] Thorat YS, Gonjari ID, Hosmani AH. Solubility enhancement techniques: a review on conventional and novel approaches. International journal of pharmaceutical sciences and research. 2011 Oct 1;2(10):2501.
[58] Patel VR, Agrawal YK. Nanosuspension: An approach to enhance solubility of drugs. Journal of advanced pharmaceutical technology & research. 2011 Apr 1;2(2):81-7.
[59] Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. International journal of pharmaceutical sciences review and research. 2010 Nov 5;5(1):41-51.
[60] Ramesh V, Meenakshi S, Jyothirmayee N, Bullebbai M, Noorjahan SK, Rajeswari G, Nagesh Babu G, Madhavi D. Enhancement of solubility, dissolution rate and bioavailability of BCS Class II Drugs. Int J Pharma Chem Res. 2016 Apr;2(2):80-95.