e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:02/February-2025 Impact Factor- 8.187 www.irjmets.com

METHOD OF ENHANCE SOLUBILITY AND DISSOLUTION RATE OF BCS CLASS || DRUG

Aditi D. Sadgir*1, Sakshi G. Ambre*2, Priya Ambre*3, Pallavi Phalake*4

*1,2,3,4Matoshri Radha College Of Pharmacy Virgaon, Akole, India.

DOI : https://www.doi.org/10.56726/IRJMETS67163

ABSTRACT

A drug's aqueous solubility is defined as the ability to dissolve in a particular solvent, and it is currently a major hurdle in bringing new drug molecules to the market. Traditionally, nearly 40% of the new chemical entities (NCEs) identified by pharmaceutical industry screening programmes have failed to be developed because of poor water-solubility, which makes their formulation difficult or even impossible. The poor aqueous solubility of BCS Class II drug. The purpose of this article is to present various techniques to enhance solubility by novel formulation techniques including Traditional approach. The Traditional techniques that has been discussed in this article includes use of co-solvents, Hydrotropy, micronization, change in dielectric constant of solvent, amorphous forms, chemical modification of drug, use of surfactants, inclusion complex or clathrates, alteration of pH of solvent, use of hydrates or solvates, use of soluble prodrugs, application of ultrasonic waves, functional polymer technology, controlled precipitation technology, evaporative precipitation in aqueous solution, use of precipitation inhibitors, solvent deposition, precipitation, selective adsorption on insoluble carriers. Novel drug delivery technologies developed in recent years for solubility enhancement of insoluble drugs are size reduction technologies, lipid based delivery system, micellar technologies, porous microparticle technology. Solid Dispersion Technique and various types of solid dispersion systems. Keywords: BCS class || , characterization, Method of Solubility Enhencement.

I. INTRODUCTION

BCS stands for Biopharmaceutics Classification System, which is a classification system that categorizes drugs based on their solubility and permeability properties. BCS class II drugs are characterized by high permeability but low solubility. [1] In terms of solubility, BCS class II drugs have low aqueous solubility, meaning they do not easily dissolve in water. This can pose challenges in drug formulation and delivery because drugs need to dissolve in the gastrointestinal fluids in order to be effectively absorbed into the bloodstream. However, BCS class II drugs have high permeability, which means they can easily pass through cell membranes and be absorbed by the body. This is because they have small molecular size and exhibit good membrane transport characteristics. Due to their low solubility, these drugs often have slower dissolution rates and limited bioavailability. In order to improve their oral bioavailability, various techniques are used such as particle size reduction, formulation with solubilizing agents, use of prodrugs, or utilization of lipid-based delivery systems.[2, 3] Due to their low solubility, these drugs often have slower dissolution rates and limited bioavailability. In order to improve their oral bioavailability, various techniques are used such as particle size reduction, formulation with solubilizing agents, use of prodrugs, or utilization of Lipid-based delivery systems.[1, 2]

BCS classification -

The Biopharmaceutics Classification System (BCS) is a system to differentiate drugs on the basis of their solubility and permeability.This system restricts the prediction using the parameters solubility and intestinal permeability. The solubility classification is based on a United States Pharmacopoeia (USP) aperture. The intestinal permeability classification is based on a comparison to the intravenous injection. All those factors are highly important because 85% of the most sold drugs in the United States and Europe are orally administered .[4]

BCS classes

According to the biopharmaceutics Classification System (BCS) drug substances are classified to four classes upon their solubility and permeability.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:02/February-2025 Impact Factor- 8.187 www.irjmets.com

1. Class I - high permeability, high solubility

Example: metoprolol, paracetamol.

Those compounds are well absorbed and their absorption rate is usually higher than excretion.

2. Class II - high permeability, low solubility

Example: glibenclamide, bicalutamide, ezetimibe, aceclofenac

The bioavailability of those products is limited by their solvation rate. A correlation between the in vivo bioavailability and the in vitro solvation can be found.

3. Class III - low permeability, high solubility

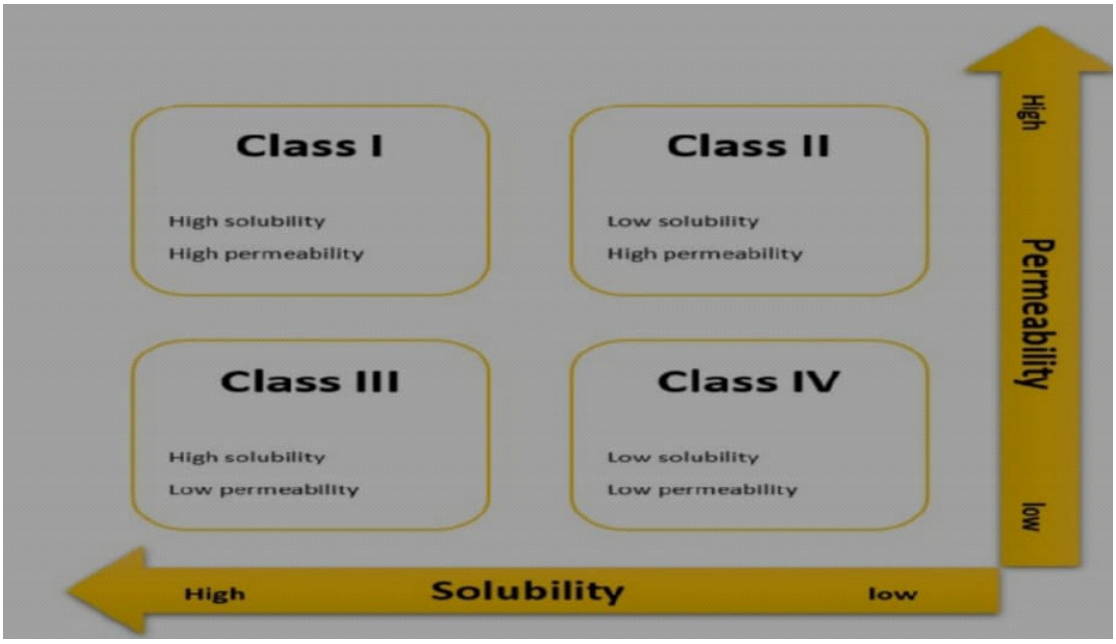
Example: cimetidine

The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then criteria be applied.

Class IV - low permeability, low solubility

Example: Bifonazole

Those compounds have a poor bioavailability. Usually they are not well absorbed over intestinal mucosa and a high variability is expected.[5,6]



A Class II drug will typically exhibit dissolution rate limited absorption and a Class IV drug will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research focus on improving the oral bioavailability of an API . Enhancing solubility and dissolution rate of poorly water-soluble drugsEnhancing permeability of poorly permeable drugs In this article, the various techniques that that can be used for solubility enhancement of BCS Class II drugs are discussed in this article with emphasis on the solid dispersion technique and its application. Formulation of solid dispersion in water-soluble carriers has been widely researched over the past four decades for solubility and related bioavailability enhancement. Despite 40 years of active research, there has not been much products in market based on this technique. The main reason for this being stability and scale up problems associated with this method, as reported by several authors.[7, 8]

Solubility enhancement of BCS class II drug :

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Various techniques are available to improve the solubility of poorly soluble drugs. These techniques can be categorized Solubility Enhancement of BCS Class II Drugs: in three basic approaches:[7, 8,9,10]

A. Traditional Techniques

B. Never and Novel Techniques

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:02/February-2025 Impact Factor- 8.187 www.irjmets.com

C. Solid Dispersion Technique

Traditional Techniques -

- Use of co-solvents
- Hydrotropy
- Micronization
- Change in dielectric constant of solvent
- Amorphous forms
- Chemical modification of drug
- Use of surfactants
- Inclusion complex or clathrates
- Alteration of pH of solvent,
- Use of hydrates or solvates, use of soluble prodrugs,
- Application of ultrasonic waves,
- Functional polymer technology,
- Controlled precipitation technology,

Use of co-solvent :

The solubility of poorly soluble drugs in water can be increased by mixing it with some water miscible solvent in which the drug is readily soluble. This process is known as co-solvency and the solvent used in combination are known as cosolvent.Cosolvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute. It is also commonly referred to as solvent blending. Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen-bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water. By disrupting waters self association, cosolvents reduce waters ability to squeeze out nonpolar, hydrophobic compounds, thus increasing solubility . The advantage of cosolvent technology enhancing drug solubility in a liquid-based formulation includes [8] convenience, removing the need for mixing solvent before administration; safety, avoiding contamination in the dispensing process; inexpensive, no need for expensive pharmaceutical technology for formulation of dosage form. The most frequently used low-toxicity cosolvents for parenteral use are propylene glycol, ethanol, glycerin, polyethylene glycol (PEG), dimethylsulfoxide (DMSO), and dimethylacetoamide

(DMA). [11,12]

Hydrotropic Method :

Hydrotropic solubilization is a technique that can be used to improve the solubility of drugs that are poorly soluble. This technique involves adding a large amount of a second solute, known as a hydrotrope, which increases the aqueous solubility of the poorly soluble drug.[13]

Micronization:

micronization is a common technique used to increase the solubility of BCS class II drugs. Micronization is a process that reduces the average diameter of a solid material's particles to the micrometer or nanometer range. This increases the surface area to volume ratio of the particles, which allows for greater interaction with the solvent and faster dissolution. Micronization improves the bioavailability of poorly soluble drugs by increasing their dissolution rate. It also improves the amorphous property and structural disordering of the drug crystals. Traditional micronization techniques use mechanical means like milling and grinding. Modern techniques use supercritical fluids and manipulate solubility principles.[14,15]

Changing the dielectric constant of solvent:

changing the dielectric constant of a solvent can improve the solubility of BCS Class II drugs. Adding a co-solvent can reduce the dielectric constant of a solvent, which can increase the solubility of hydrophobic molecules .water is a good solvent for polar molecules and has a high dielectric constant. [8]

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:02/February-2025 Impact Factor- 8.187 www.irjmets.com

Chemical modifications of drug:

Add or remove hydrogen bonds: Adding hydrogen bond donors or acceptors, like OH and NH2 groups, can improve aqueous solubility. Removing hydrogen bonds can also increase solubility. Add hydrophilic or ionizable groups: This is a common strategy for improving solubility. [16]

Use of surfactants :

Surfactants, also known as surface active agents, can be used to improve the solubility of poorly water-soluble drugs. Surfactants can do this by Reducing surface tensionSurfactants can lower the surface tension of a solution, which improves the solubility of lipophilic drugs in an aqueous environment. [17]

Application of Ultrasonic waves:

Ultrasonic waves are used to improve the solubility of drugs, especially those that are poorly soluble in water . this is done by reducing the size of the drug particals ,which increase their surface area and their dissolution rate. It also improves the amorphous property and structural disordering of the drug crystals. Traditional micronization techniques use mechanical means like milling and grinding. Modern techniques use supercritical fluids and manipulate solubility principles.[14,15]

Changing the dielectric constant of solvent:

changing the dielectric constant of a solvent can improve the solubility of BCS Class II drugs. Adding a co-solvent can reduce the dielectric constant of a solvent, which can increase the solubility of hydrophobic molecules .water is a good solvent for polar molecules and has a high dielectric constant. [8]

Chemical modifications of drug:

Add or remove hydrogen bonds: Adding hydrogen bond donors or acceptors, like OH and NH2 groups, can improve aqueous solubility. Removing hydrogen bonds can also increase solubility. Add hydrophilic or ionizable groups: This is a common strategy for improving solubility. [16]

Use of surfactants:

Surfactants, also known as surface active agents, can be used to improve the solubility of poorly water-soluble drugs. Surfactants can do this by Reducing surface tensionSurfactants can lower the surface tension of a solution, which improves the solubility of lipophilic drugs in an aqueous environment. [17]

Application of Ultrasonic waves: Ultrasonic waves are used to improve the solubility of drugs, especially those that are poorly soluble in water. This is done by reducing the size of the drug particles, which increases their surface area and improves their dissolution rate. [18]

Alteration Of PH solvent:

Ionic compounds-For ionic compounds with basic anions, solubility increases as the pH of the solution decreases. Weakly basic drugs-The solubility of a weakly basic drug increases as the pH decreases below its basic pKa. Weakly acidic drugs-The solubility of a weakly acidic drug increases as the pH increases beyond its acidic pKa. To improve the solubility of poorly soluble drugs, you can incorporate a pH-modifying material into formulations or tablets. This creates a suitable microenvironment pH that leads to improved solubility. [18]

Inclusion Complete/Clthrates:

Considerable increase in solubility and dissolution of the drug has been achieved by the use of cyclodextrins. These complexes can be prepared with ß-cyclodextrin (ß-CD) and HP-ß-CD; the required quantity of ß-CD is weighed and water added to get tough consistency. To the mass, weighed quantity of the drug is added. The mixture is kneaded in a glass mortar for one hour and then completely dried in hot air oven at 60 0C for 2 hours. The dried mass is sieved through mesh no.120.[19, 20]

Use of Hydrates or Solvates:

A crystalline compound may contain either a stoichiometric or non stoichiometric adducts, such as inclusions, involve entrapped solvent molecules within the crystal lattice. A stoichiometric adducts, commonly referred to as “Solvate”, and is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called as “Hydrate”. A compound not containing any water within its crystal structure is termed “Anhydrous”. Aqueous solubilities of anhydrous forms are higher than the hydrate forms. [21]

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:02/February-2025 Impact Factor- 8.187 www.irjmets.com

Use of Soluble Prodrugs:

The physicochemical properties of the drugs are improved by bioreversible chemical alteration. The most common prodrug strategy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility. The prodrug approach has been successfully used to improve the water solubility of corticosteroids, vitamins and benzodiazepines. Enhancement of rate of dissolution of allopurinol was successfully achieved by prodrug formation.[22,23]

Controlled Precipitation Technology:

In this process, the drug is dissolved in a water miscible organic solvent and then dissolved into aqueous medium containing stabilizers (HPMC, cellulose ethers, gelatin). The solvent dissolves in water and causes precipitation of the drug in the form of micro-crystals. The stabilizers control particle growth and enhance the dissolution rate of poorly soluble drug due to large surface area hydrophilized by the adsorbed stabilizer. For e.g. nanomorph, a patente technology by Solids for controlled crystallization of drugs. [24]

Newer and Novel technology :

Newer and novel drug delivery technologies developed in recent years for solubility enhancement of insoluble drugs.

Nanosuspension:

One of the major problems associated with poorly soluble drugs is very low bioavailability. The problem is even more complex for drugs like itraconazole, simvastatin, and carbamazepine which are poorly soluble in both aqueous and nonaqueous media, belonging to BCS class II as classified by biopharmaceutical classification system. Formulation as nanosuspension is an attractive and promising alternative to solve these problems. Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion. Preparation of nanosuspension is simple and applicable to all drugs which are water insoluble. A nanosuspension not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy.[25,26]

Advantage -

- Enhance the solubility and bioavailability of drugs.
- Suitable for hydrophilic drugs.
- Higher drug loading can be achieved.
- Dose reduction is possible.
- Enhance the physical and chemical stability of drugs.
- Provides a passive drug.

Solid phospholipid dispersion:

The poor aqueous solubility of BCS Class II drugs represents a major challenge for oral dosage form development. Using celecoxib (CXB) as model drug, the current study adopted a novel solid phospholipid nanoparticle (SPLN) approach and compared the effect of two commonly used industrial manufacturing methods, spray- and freeze-drying, on the solubility and dissolution enhancement of CXB. CXB was formulated with Phospholipoid E80 (PL) and trehalose at different CXB:PL:trehalose ratios, of which 1:10:16 was the optimal formulation. Spherical amorphous SPLNs with average diameters <1 μm were produced by spray-drying; while amorphous 'matrix'-like structures of solid PL dispersion with larger particle sizes were prepared by freezedrying. Formulations from both methods significantly enhanced the dissolution rates, apparent solubility, and molecularly dissolved concentration of CXB in phosphate buffer (PBS, pH 6.5) and in biorelevant fasted state simulated intestinal fluid (FaSSIF, pH 6.5) ($p < 0.05$). While similar dissolution rates were found, the spray-dried SPLNs had a larger enhancement in apparent solubility (29- to 132- fold) as well as molecular solubility (18-fold) of CXB at equilibrium ($p < 0.05$). The strong capability of the spray- dried SPLNs to attain 'true' supersaturation state makes them a promising approach for bioavailability enhancement of poorly soluble drugs.[27, 28]

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:02/February-2025 Impact Factor- 8.187 www.irjmets.com

Solid dispersion:

Solid dispersion (SD) has been widely used to improve the dissolution rate, solubility, and oral absorption of poor watersoluble drugs. SD refers to the group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug; the matrix can be either crystalline or amorphous.Solid dispersion was first introduced to overcome the low bioavailability of lipophilic drugs by forming eutectic mixture of drugs with water soluble carriers[29].Approximate 40% of new chemical entities (NCE) being synthesized by combinatorial screening programs possessing superior pharmacological activities are poorly soluble, which is a great obstacle in formulation development. Biopharmaceutical classification system (BCS) highlights the dissolution as rate limiting step for oral absorption of BCS class 2 and class 4 drugs. BCS class 2 and class 4 drugs have low solubility. [30, 31]

Types of solid dispersion-

1) Based on carrier used - A carrier must meet the following criteria to be appropriate for enhancing the dissolution rate of a drug.

i) freely water-soluble with intrinsic quick-dissolving capabilities

ii) nontoxic and pharmacologically inert

(iii) The melting process must be heat stable and it should have a low melting point

(iv) It must be soluble in a wide range of solvents

(v) It should be able to preferably increase the aqueous solubilityof the drug

(vi) Ideally, it should be able to boost the medication's water solubility and be chemically compatible with the drug and should not form a firmly bound complex with it . [33]

Material of carriers : sugar -Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, and lactose Acid-Citric acid and succinic acid,

Polymeric materials - Polyvinyl pyrrolidine (PVP), polyethene glycol (PEG), hydroxypropyl methylcellulose (HPMC), methylcellulose (MC), hydroxyethyl cellulose. [34] Based on the carrier used, solid dispersions can be classified into the following four generations .[35]

First generation: Solid dispersions were formed as the first carriers to be applied in solid dispersions . In this generation, crystalline carriers are used such as sugars and urea. The disadvatange of the first generation is the presence of crystalline nature of the carrier. In which they are thermodynamically stable, and the drug will not be released as fast as the amorphous form . [36]

Second generation: This generation involves the use of amorphous carriers which are usually polymers . These polymers could be synthetic such as polyethene glycols (PEG), povidone, polyvinyl pyrrolidine, and polymethacrylates or natural-based polymers, such as ethyl cellulose, hydroxypropyl methylcellulose (HPMC), and starch derivatives such as cyclodextrins or hydroxypropyl cellulose .[37]

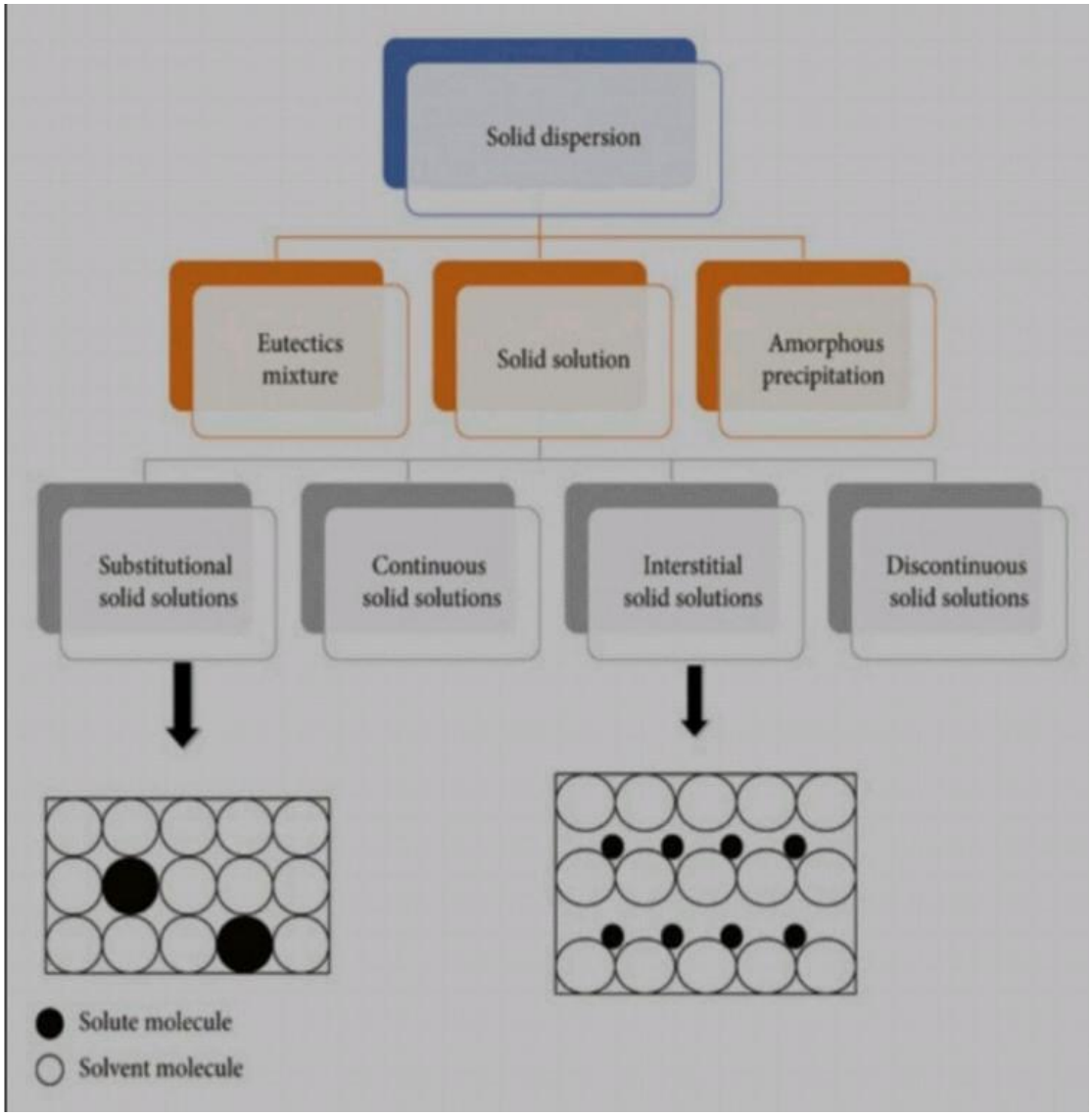
Third generation: It has been proved that the dissolution profile can be enhanced by using a carrier with surface active agent properties. As a result, the use of surface-active agents such as poloxamer 407, compritol 888, ATO, inutec SP1, gelucire 44/14, and inulin as carriers was revealed to be effective in achieving a high purity level of the polymorphic and for increasing in vivo bioavailability [38]

Fourth generation: This type of dispersion is described as controlled release solid dispersion. It contains poorly watersoluble drugs with a short biological half-life. The carriers used are either water-soluble carriers or insoluble water carriers. Solubility enhancement and extended drug release in a controlled manner are the two targets in controlled-release solid dispersion. The water-soluble carriers used in controlled-release solid dispersion include ethyl cellulose, Eudragit, Hydroxypropyl cellulose, and cellulose. [39]

2) Bases on their Molecular structure-Solid dispersions can be categorized into the following types.

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:02/February-2025 Impact Factor- 8.187 www.irjmets.com

Table 1: Types of soliddispersion Based on Their Molecular Structure.



1. Eutectics Systems

This mixture composes of two compounds in the liquid state that are completely miscible but in the solid state only to a very limited extent. It is prepared through fast solidification of the fused melt of the two compounds, giving a complete liquid miscible product and very little solid-solid solubility. Such a system is thermodynamically intimately mixed with the physical mixture of its two crystalline compounds [40].

2. Glass Solution and Suspensions

Glass solution refers to the homogeneous glassy system in which a solute is dissolved in a glass carrier, whereas the glass suspensions, in which the precipitated particles are present, are suspended in glass solvent. The lattice energy in such systems is low, and the melting point is not sharp, examples of carriers that form glass solutions and suspensions are urea, citric acid, polyethene glycol, polyvinyl pyrrolidine, and sugars such as dextrose, sucrose, and galactose [40].

3. Solid Solution

In this system, when the two components crystallize together, they form a single homogeneous phase system. The drug particle size is decreased to its molecular size in the solid solution. As a result, a faster rate of dissolution will be achieved in the solid solution than in the corresponding eutectic mixture. The solution can be categorized (as continuous or discontinuous) depending on the level of miscibility of the two compounds or how the solvate molecules are circulated (substitutional, interstitial, or amorphous) [40].

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:07/Issue:02/February-2025 Impact Factor- 8.187 www.irjmets.com

(i) Continuous solid solutions:The components are miscible in all proportions in a continuous solid solution. Hypothetically, this indicates that the bonding strength between the two components is greater than the bonding strength between the molecules of each individual component. However, solid solutions of this type have not been reported in the pharmaceutical world to date. [41]

(ii) Discontinuous solid solutions:In the case of discontinuous solid solutions, the solubility of each component in the other component is limited .[41]

(iii) Substitutional solid solutions:This type of solid solution occurs only if the size of the solute molecules is variable by less than 15% or so from the solvent particles .[42]

(iv) Interstitial solid solutions:In interstitial solid solutions, the soluble particles fill the interstitial gaps between the solvent molecules in the crystal lattice. Therefore, the solute molecule diameter should be less than 0.59 times that of the solvent molecular diameter . [42]

METHODS OF SOLID DISPERSION

a) Fusion method: it is also known as melt method when the starting materials used are crystalline. Sekiguchi et al. in 1961 were the first to use melting method which involved melting the drug within the carrier followed by cooling and pulverization of the obtained product. Ex. Albendazole and urea solid dispersion was prepared by this method. The main advantages of this method are its simplicity and economy. is However it has few limitations like it is applied only when the drug and the matrix are compatible and when they mix well at the heating temperature. Phase separation may also occur during cooling, the drug matrix miscibility changes. [42]

b) Solvent Evaporation method: the drug and thecarrier are completely dissolved in an organic solvent, the solvent is evaporated. The obtained solid mass is ground, sieved and dried. Ex. Solid dispersion of ofloxacin with PEG by solvent evaporation method. [43]

c) Modified Solvent Evaporation method: drug is dissolved in organic solvent at its saturation solubility with continuous stirring for some time. The polymer is suspended in sufficient amount of water. The drug solution is poured at once into polymer suspension. The entire solvent is evaporated. The mass obtained

is dried. [44,45]

d) Melting Solvent method: it is a combination of two methods which involves dissolving the drug in a suitable solvent and mixing it with molten carrier followed by cooling. The solidified mass is crushed, pulverized and passed through sieve. The advantage of this method is it reduces maximum temperature and results in less decomposition of thermolabile drugs.[45]

e) Kneading method: A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved. Ex. furosemide and crospovidone solid dispersion was prepared by this method .[46]

f) Co-precipitation method: the carrier is dissolved in water and drug in organic solvent, then the aqueous solution of carried is poured into organic solution of drug. During the addition of nonsolvent the drug and carrier are co-precipitated to form micro particles. The resultant micro particle suspension isfiltered and dried (solid dispersion) . [44]

g) Spray drying method: here the solution of drug substance and carrier is evaporated by spraying the solution as fine droplets chamber with maintained temperature, humidity and airflow. The principle involved is evaporation of the solvent from the mixture until the desired moisture content is obtained. It is advantageous for weight and volume reduction . Rankell et al. prepared solid dispersion of Loperamide with PEG 6000 21. [47]

h) Lyophillization technique: it has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. [48]

i) Hot Melt Extrusion :The hot-melt extrusion method is the modern version of the fusion method in which the extruder induces intense mixing of the components. Compared with the traditional fusion method, melt extrusion offers the potential to shape the molten drug-polymer mixture into implants, pellets, or oral dosage forms . However, this method requires the complete miscibility of the drug and the polymer in the molten state. Solubility parameter phase diagrams can be used to predict miscibility and to rationally select the compatible polymer [43, 49]

This process has various advantages, which includes the following :

(1) Fewer processing steps because the components are not compressed and the product is not dried, making this procedure simple, continuous, and efficient.

(2) Entire mixing at a high shear rate and temperature disaggregates the particles, resulting in a uniform distribution of tiny drug particles in the polymer matrix and molecular level dispersion.

(3) In addition, unlike the classical fusion approach, this technique allows for continuous manufacturing, making it appropriate for large-scale production. HPMC, HPMCAS, PVP, PVP, vinyl acetate, and polyethylene oxide are some of the most often utilized polymeric materials in hot-melt extrusion . [50]

II. CONCLUSION

In this review we focused on the method of enhance solubility of BCS class || drug. Therefore, improving the solubility of poorly water-soluble drugs is a large challenge in the pharmaceutical industry. To overcome this problem, various methods such as complexation, lipid-based systems, SD, micronization, nanonization, and cocrystallization were developed for clinical use.It is considered a promising technique to overcome problems related to poor aqueous solubility and poor Bioavailability. By improving wettability of drugs and surface area, drug solubility and dissolution were increased.

III. REFERENCES

[1] Kunde D. S., Sh, B., Godbole A.M.,andGajreP.etal.(2015).'Biopharmaceutical classificationsystem': a brief acount. Int J Res Meth, 1(1), 20-46.

[2] Peeush Singhal, Ritu Singhal et al. (2017). 'The Biopharmaceutics Classification System' (BCS): Review.World Journal Of Pharmacy And Pharmaceutical Sciences, Volume 7, Issue 1, 269-283 ISSN 2278 – 4357.

[3] Wagh M. P. , & Patel J. S. et al. (2010). Biopharmaceutical classification system: scientific basis for biowaiver extensions. International Journal of Pharmacy and Pharmaceutical Sciences, vol-2 (Issue-1), PP-12-19.

[4] Yasir M., Asif M., Kumar A., & Aggarval A. et al. (2010). Biopharmaceutical classification system: An account. International Journal of Pharm Tech Research, 2(3), PP-1681- 1690. 5) Chavda V, Patel N. et al. (2010). 'Biopharmaceutics Classification System' Vol 1, Issue 1

[5] Muthukumaran M., Krishnamoorthy B., et al. (2015). 'Biopharmaceutical Classification System' (BCS): Concept and Development Strategies in Drug Delivery System. International Journal of advancd Pharmaceutical Genuine Research, 3(1), 12-25, ISSN 2347-5102.

[6] Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995 Mar;12(3):413-20. doi: 10.1023/a:1016212804288. PMID: 7617530.

[7] Babu, V.R., Areefulla, S.H., Mallikarjun, V., 2010. Solubility and Dissolution Enhancement: An overview. J Pharm Research 3(1),141-145.

[8] Ahuja, N., Katare, O.P., Singh, B.,2007. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. Eur. J. PharmBiopharm. 65,26-38.

[9] Chaumeil, J.C., 1998. Micronisation: a method of improving the bioavailability of poorly soluble drugs, Methods and Findings in Experimental and Clinical Pharmacology. 20, 211-215.

[10] Amin K, Dannenfelser R M, Zielinski J, Wang B. Lyophilization of polyethyleneglycol mixtures. J. Pharm. Sci. 2004, 93:22442249.

[11] Yalkowsky, S.H., Roseman, T.J., 1981. Solubilization of drugs by cosolvents. In: Yalkowsky, S.H. Ed. Techniques of Soluhilization of Drugs. Dekker, New York.

[12] C. Neuberg, Hydrotropic phenomena, Biochem. Z. 76 (1916) 107.

[13] Khadka, P.; Ro, J.; Kim, H.; Kim, I.; Kim, J.T.; Kim, H.; Cho, J.M.; Yun, G.; Lee J. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian J. Pharm. Sci.,2014, 9, 304–316.

[14] Midoux, N.; Hosek, P.; Pailleres, L.; Authelin, J. Micronization of pharmaceutical substances in a spiral jet mill. Powder Technol.,1999,104, 113–120.

[15] Kumar S, Singh P, Various techniques for solubility enhancement: An overview. The Pharma Innovation Journal 2016; 5(1):23-28.

[16] Bakatselou, V., Oppenheim, R.C., Dressman, J.B., 1991. Solubilization and wetting effects of bile salts on the dissolution of steroids. Pharm Res. 8, 1461-1469.

[17] Wen X, Tan F, Jing Z, Liu Z. Preparation and study the 1:2 inclusion complex of carvedilol with β-cyclodextrin. Journal of Pharmaceutical and Biomedical Analysis. 2004;34(3):517–523. doi: 10.1016/s0731-7085(03)00576-4. [DOI] [PubMed] [Google Scholar]

[18] Talari, R., Varshosaz, J., Mostafavi, S.A., Nokhodchi, A., 2009. Dissolution Enhancement of Gliclazide Using pH Change Approach in Presence of Twelve Stabilizers with Various PhysicoChemical Properties. J Pharm Pharmaceut Sci. 12(3), 250 – 265.

[19] Challa, R., Ahuja, A., Ali, J., Khar, R.K., 2005. Cyclodextrins in Drug Delivery: An Updated Review. AAPS PharmSciTech. 6 (2), 29-57.

[20] Lachman, L., Lieberman, H.A., Kanig, J.L., 1990. The Theory and Practice of Industrial Pharmacy. 3rd ed. Varghese Publishing House, Bombay. 177.

[21] Huttunen K., Raunio H., Rautio J. Prodrugs: Design and clinical applications. Pharmacol. Rev. 2011;63:750–771. doi: 10.1124/pr.110.003459. [DOI] [PubMed] [Google Scholar]

[22] Stella V.J., Nti-Addae K.W. Prodrug strategies to overcome poor water solubility. Adv. Drug Deliv. Rev. 2007;59:677–694. doi:

[23] Merisko-Liversidge E., Liversidge G.G., Cooper E.R. Nanosizing: A formulation approach for poorly-watersoluble compounds. Eur. J. Pharm. Sci. 2003;18:113–120. doi: 10.1016/S0928- 0987(02)00251-8. [DOI] [PubMed] [Google Scholar].

[24] Chingunpitak J. Nanosuspension Technology for Drug Delivery. Walailak J. Sci. Technol. 2006;4:139–153. doi: 10.2004/wjst.v4i2.94. [DOI] [Google Scholar]

[25] Muller R. Nanosuspension for the Formulation of Poorly Soluble Drugs. In: Neilloud F., Marti-Mestres G., editors. Pharmaceutical Emulsion and Suspension. Routledge; London, UK: 2000. [Google Scholar].

[26] U. Brinkmann-Trettenes Solid phospholipid nano-particles: investigations into formulation and dissolution properties of griseofulvin Int. J. Pharm.(2014)

[27] O.A. Abu-Diak An investigation into the dissolution properties of celecoxib melt extrudates: understanding the role of polymer type and concentration in stabilizing supersaturated drug concentrationsMol. Pharm. (2011)

[28] Chiou W. L. and Riegelman S., Pharmaceutical applications of solid dispersion systems, Journal of Pharmaceutical Sciences. (1971) 60, no. 9, 1281–1302.

[29] Greeshmika P., Kavya S., Sayeeda S., Hemalatha B., and Padmalatha K., Solid dispersion: strategy to enhance solubility, Indo-American Journal of Pharmaceutical Sciences. (2021) 8, 1812–1823.

[30] Savjani K. T., Gajjar A. K., and Savjani J. K., Drug solubility: importance and enhancement techniques, ISRN Pharmaceutics. (2012) 2012, 10, 195727.

[31] Verma S., Kumar I., and Chaudhary A., Solid dispersion: different methods of enhancing solubility and classification of solid dispersion, International Journal of Advance Research, Ideas and Innovations in Technology. (2019)

[32] Dixit K., Singh P., and Stuti S., Solid dispersion-a strategy for improving the solubility of poorly soluble drugs, IInternational Journal of Research in Pharmaceutical and Biomedical Sciences. (2012) 3, 90–964.

[33] Poddar K., Solid dispersions: an approach towards enhancing dissolution rate, International Journal of Pharmacy and Pharmaceutical Sciences. (2011) 3, 9–19.

[34] Bhawana K., Ramandeep K., Sukhdeep K., Sukhkaran K., and Himani B., Solid dispersion: an evolutionary approach for solubility enhancement of poorly water soluble drugs, International Journal of Recent Advances in Pharmaceutical Research. (2012) 2, 1–6.

[35] Zhang Z., Li W., Wang G., Qu Y. L., and Yu D. G., Electrospun 4th-generation solid dispersions of poorly water-soluble drug utilizing two different processes, Journal of Nanomaterials. (2018) 2018, 10, 2012140.

[36] Alshehri S., Imam S. S., Hussain A., Altamimi M. A., Alruwaili N. K., Alotaibi F., Alanazi A., and Shakeel F., Potential of solid dispersions to enhance solubility, bioavailability, and therapeutic efficacy of poorly

water-soluble drugs: newer formulation techniques, current marketed scenario and patents, Drug Delivery. (2020) 27, no. 1, 1625–1643.

[37] Mande P. P., Bachhav S. S., and Devarajan P. V., Bioenhanced advanced third generation solid dispersion of tadalafil: repurposing with improved therapy in pyelonephritis, Asian Journal of Pharmaceutical Sciences. (2017) 12, no. 6, 569–579.

[38] Nair A. R., Lakshman Y. D., Anand V. S. K., Sree K. S. N., Bhat K., and Dengale S. J., Overview of extensively employed polymeric carriers in solid dispersion technology, AAPS PharmSciTech. (2020) 21, no. 8, 309–320.

[39] Bhut Z., Prajapati B., Patel N., Patel A., and Patel A., Solid dispersion as a strategy to enhance solubility: a reviewarticle, International Journal for Pharmaceutical Research Scholars. (2012) 3, 277–283.

[40] Leuner C. and Dressman J., Improving drug solubility for oral delivery using solid dispersions, European Journal of Pharmaceutics and Biopharmaceutics. (2000) 50, no. 1, 47–60.

[41] Rahul M., Patil A., and Maniyar H., Solid diperstion: strategy to enhance solubility, International Journal of Pharmaceutical Sciences Review and Research. (2011) 8, 66–73.

[42] Baghel S., Cathcart H., and O'Reilly N. J., Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs, Journal of Pharmaceutical Sciences. (2016) 105, no. 9, 2527–2544.

[43] Anupama K. and Neena B., Formulation and evaluation of mouth dissolving tablets of oxcarbazepine|request PDF, International Journal of Pharmacy and Pharmaceutical Sciences. (2009) s1, 12–23.

[44] Chavan R. B., Lodagekar A., Yadav B., and Shastri N. R., Amorphous solid dispersion of nisoldipine by solvent evaporation technique: preparation, characterization, in vitro, in vivo evaluation, and scale up feasibility study, Drug Delivery and Translational Research. (2020) 10, no. 4, 903–918

[45] Baboota S., Dhaliwal M., and Kohli K., Physicochemical characterization, in vitro dissolution behavior, and pharmacodynamic studies of rofecoxibcyclodextrin inclusion compounds preparation and properties of rofecoxib hydroxypropyl β-cyclodextrin inclusion complex: a technical note, AAPS PharmSciTech. (2005) 6, no. 1, E83–E90.

[46] Patel B. B., Patel J. K., Chakraborty S., and Shukla D., Revealing facts behind spray dried solid dispersion technology used for solubility enhancement, Saudi Pharmaceutical Journal. (2015) 23, no. 4, 352–365.

[47] Lin, Y.E. and Wilken, L.O. (1980) some effects of a mod-ified lyophilization procedure on dissolution and other properties of digoxin powders and tablets. M.S. Thesis. Auburn University, AL, p. 63.

[48] Vasoya J. M., Desai H. H., Gumaste S. G., Tillotson J., Kelemen D., Dalrymple D. M., and Serajuddin A. T, Development of solid dispersion by hot melt extrusion using mixtures of polyoxylglycerides with polymers as carriers for increasing dissolution rate of a poorly soluble drug model, Journal of Pharmaceutical Sciences. (2019) 108, no. 2, 888–896.

[49] Repka M. A., Majumdar S., Kumar Battu S., Srirangam R., and Upadhye S. B., Applications of hot-melt extrusion for drug delivery, Expert Opinion on Drug Delivery. (2008) 5, no. 12, 1357–1376