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Novel Solubility Enhancement Technique: A Comprehensive Review

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Abstract: Because BCS Class-II medicines have a low solubility and dissolution rate, the main goal of this review was to increase their bioavailability and solubility. One of the important parameters for achieving the intended drug concentration in the systemic circulation and demonstrating a pharmacological response is solubility. Therefore, when developing their formulations, class II medications must improve their solubility and dissolution rate, especially when it comes to solid dosage forms like tablets and capsules.(1) As a result, numerous techniques and more recent technological advancements have been made to improve the solubility and bioavailability of class II medications.(2) This study reviewed the literature on more modern approaches or procedures as well as current studies on the formulation development of class-II medications (3)

Key Words : - Poorly soluble drugs , Solubility enhancement technique , BCS class 2 drugs .

I. INTRODUCTION :

In the formulation design and development process, the field of solubility or dissolution improvement approach continues to present significant challenges for researchers, while being a frequently addressed topic. Dissolution and Solubility, These are the fundamental ideas of all physical and chemical sciences, including how to handle any medication while taking biopharmaceutical and pharmacokinetic factors into account.(1) Because of their biopharmaceutical qualities, more than 40% of newly developed chemical compounds fail before ever reaching the medication development stage. These characteristics include the rate of distribution, the rate and degree of absorption, etc.(2) Solubility can therefore be defined **as "The analytical Composition of saturated solution expressed in terms of IUPAC."**

A common problem in New Chemical Entity (NCE) screening investigations, formulation design, and development is the solubility of a weakly water soluble medication. Its bioavailability property can be enhanced by a variety of approaches. Medication administered orally is fully absorbed, but it also exhibits good bioavailability and fair solubility in the stomach media. However, a number of factors, including as the drug's permeability via lipophilic membranes, affect its bioavailability. Therefore, solubility is challenging to quantify analytically at low concentrations. Consequently, a solubility categorization was

devised to enable the selection of an appropriate formulation method for highly active compounds with good permeability, ensuring speedy and effective formulation development.(4,5)

BCS CLASSIFICATION :

The U.S. FDA released Industry Guidance in August 2000 about the Biopharmaceutical Classification System (BCS). The BCS is a scientific framework that is used to categorize pharmacological substances based on intestinal permeability and equilibrium aqueous solubility. The BCS considers three main factors:

- ✓ intestinal permeability
- ✓ dissolution rate,
- ✓ solubility

when paired with a pharmacological product's in vitro dissolution characteristics. For immediate release solid oral dose forms, these three parameters control the rate and amount of oral medication absorption. Based on the solubility and permeability properties of pharmacological compounds, the BCS classifies them into four categories.(6)

Class	Solubility	Permeability
Class1	high	high
Class2	low	high
Class3	high	low
Class4	low	low

Process of solubilization :

It entails the solute's breakdown of intermolecular or interionic bonds, the solvent's molecules separating to make room for the solute, and the interaction of the solvent with the solute molecule or ion(7) .This process of solubilization is divided into three phases.

- Holes open in solvent
- Molecule of solid breaks away from bulk
- Free solid molecule is integrated in holes of solvent

Factors Affecting Solubilization:

The physical form of the solid, the type and content of the solvent medium, the system's pressure and temperature, and other factors all affect solubility. Let's talk about some of the characteristics that influence solubility, including

1.Particle size :

The solubility of a solid particle is affected by its size because the particle's surface area to volume ratio increases as the particle gets smaller. Greater contact with the solvent is made possible by the bigger surface area.

2.Temperature :

The solubility will rise as the temperature rises since the solution process absorbs energy as it works, but the solubility will fall as the temperature rises if it releases energy. In heated solutions, some solid solutes become less soluble. For instance, solubility of all gases reduces with increasing solution temperature.

3.Pressure:

Changes in pressure essentially have no effect on the solubility of solids or liquid solutes, but for gaseous solutes, an increase in pressure causes a decrease in solubility.

4.Nature of solute and solvent :

At room temperature, one gram of lead (II) chloride and 200 grams of zinc chloride may both dissolve in 100 grams of water. These two compounds differ greatly in their natures, which accounts for the large variances in their solubility.

5.Molecular size :

Higher molecular weight and size molecules reduce the solubility of the material since it is harder to surround larger molecules with solvent molecules in order to dissolve the substance. The amount of carbon branching in organic compounds will increase their solubility since it will reduce the size (or volume) of the molecule and facilitate solvent solubility.

6.Polarity :

The solubility will be impacted by the polarity of the solvent and solute molecules. Like dissolves like states that molecules of non-polar solutes will dissolve in non-polar solvents and molecules of polar solutes will dissolve in polar solvents. Therefore, each polar solute molecule has a positive and a negative end. Positive ends of solvent molecules will attract negative ends of solute molecules if the solvent molecule is polar as well.

This kind of force between molecules is called a dipole-dipole interaction. The other force is known as the London dispersion force, and it occurs when the solute molecule's positive nuclei attract the solvent molecule's negative electrons. This allows the molecules of the solute to be solvated by the nonpolar solvent.

7.Polymorph :

Polymorphs' melting points might differ. Polymorphs will have distinct solubility since solubility and melting point of a solid are correlated. Due to very minor variations in free energy, the range of solubility differences between various polymorphs is typically only two to three folds.

8.Rate of solution:

The speed at which chemicals dissolve in solvents is gauged by the rate of solution .

9.Stirring:

Stirring increases the rate of solution by bringing new solvent particles into contact with solute particles, both liquid and solid. (8)

Methods for Improving Solubility and Bioavailability:

There are numerous methods for making poorly soluble medications more soluble. Several contemporary methods and emerging strategies to enhance the solubility include:

1 . Using a surfactant:

Reducing the interfacial tension between the solvent and solute surfaces to improve the wetting salvation contact is a conventional method of solubilizing a poorly soluble material. Many different types of surfactants, such as synthetic block copolymers, Tweens, spans, polyoxyetylene glycerides, and polyoxyetylene stearates, work well as excipients and carriers for improving dissolution.(9)

2 . pH Adjustment:

The simplest and most widely used technique to improve the water solubility behaviour is to modify the ionization behaviour by adjusting the pH of the microenvironment. Therefore, ionization of a molecule depends on the drug's pKa and the pH of the media, according to the pH partition hypothesis and the Handerson-Hesselbatch equation.

Additionally, the ionic compound's alteration may cause the production of in-situ salts. For unionized chemicals, this salt production is therefore not conceivable. In the GIT, the generated salts may potentially reverse to their corresponding acid or basic forms.(10,11)

3 . By changing the solid state:

A drug's crystalline form is important for pharmaceutical purposes due to its stability and bioavailability. Variations in the melting point, density, stability, and drug solubility can result from polymorphism, which is the occurrence of a drug component in numerous crystalline forms. These attributes are dependent on the molecule’s propensity to escape from a certain crystalline structure.

Drugs with the highest degree of crystallinity are typically the most stable since they can exist in various polymorphic forms, which means they have the least amount of free energy. As a result, they have the highest

melting point and the least solubility. Drugs with high free energy can be forced into amorphous or meta-stable forms by manipulating the crystallization process.

They provide the benefit of increased If stabilizers meant to prevent crystal growth aren't included in the formulation,

Polymorphism the existence of a drug substance in multiple crystalline forms can result in variations in the drug's solubility, density, melting point, stability .

Ex : A well-known instance of this is the 1998 removal of ritonavir (Norvir®) capsules from the market due to the discovery of a less soluble (and thus less bioavailable) polymorph that resulted in a reduction in the drug's bioavailability, two years after the product was approved and put on the market. The pharmaceutical sector became more aware of this incidence.(12)

4 . Self- Emulsifying Drug Delivery System:

The idea of an in situ emulsion production in the gastrointestinal tract is the basis of a self-emulsifying, or self-micro emulsifying, system. It can be used to improve lipophilic drug dissolution and absorption.

It is defined as a mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents, and co-solvent that forms a transparent isotropic solution in the absence of an external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT. Thus The ease with which water penetrates the different liquid phases that develop on the droplet's surface, whether they are crystalline or gel, may be related to the ease of emulsification.

The GIT becomes irritated by the high surfactant content (30–60%) in self-emulsifying formulations. Because most self-emulsifying systems include liquid products, they can only be administered in soft or hard-shelled gelatine capsules that are filled with lipids.

It is important to take into account how the emulsion and capsule shell interact to keep the hygroscopic contents from drying out or settling inside the capsule shell .

A typical example of a self-micro emulsifying drug delivery system (SMEDDS) is the Neoral®. The relative bioavailability of cyclosporine A given as Neoral® may range from 174% to 239% of that of cyclosporine A from Sandimmune®, the formulation that was first put on the market. This depends on the dose level. Drug bioavailability from emulsion formulations is significantly influenced by emulsion droplet size, with small droplet radii improving the medication levels in the plasma, partly as a result of direct lymphatic absorption. SMEDDS should only be used orally because of their high surfactant concentration. Because they may cause diarrhoea over time, long-term usage of SMEDDS may not be advised.(13,14)

Advantages:

1) They develop spontaneously upon mixing their components under gentle agitation, which is advantageous for both manufacturing and scale-up.

2) Thermodynamic stability exists for them.

Drawbacks:

1) It involves elevated surfactant concentrations and medication chemical instability

5 . Microemulsion :

A micro emulsion is a translucent, optically clear, isotropic, thermodynamically stable system that dissolves a poorly water soluble medication.

It is composed of a combination of oil, hydrophilic surfactant, and hydrophilic solvent. The formulation self-emulsifies or spontaneously disperses when it comes into contact with water, creating a very transparent emulsion of uniformly sized, minuscule oil droplets that contain the poorly soluble medication. These systems have been used to include proteins for oral, parenteral, percutaneous, or transdermal usage, as well as to enhance the solubility of many temperatures that are virtually insoluble in water.

A broad variety of surfactant concentrations and low viscosity fluid ratios can be used to create these homogenous systems. In order to increase the solubility of medications that are prepared as microemulsions, a number of parameters including co-surfactants, surfactant mixtures, and surfactants count.

Surfactants such as Brij 35, polyoxy ethylene surfactants, sugar esters like sorbitan monooleate (Span 80), cationic or anionic substances like sodium dodecyl sulphate and alkyltrimethyl ammonium bromide, or zwitter ionic substances like phospholipids like lecithin are preferred because of their superior performance.(17,18,19)

6 . Particle Size Reduction:

By reducing the particle size to a submicron level, micronization, also known as nanoization, is one of the most promising methods for increasing the bioavailability of lipophilic medicines.

In the course of the Preformulation Particle size is a crucial parameter in formulation research that needs to be tightly regulated. Reducing the particle size is a successful method of increasing solubility, but if it is done in an unregulated or suboptimal manner, the medication may recrystallize and reaggregate when stored. This calls for a comprehensive investigation into the particle size and physical stability. It is not feasible to reduce size to the submicron range using current methods.(21)

7 . Complexation:

The enzymatic breakdown of starch yields cyclic oligosaccharides known as cyclodextrins.

The α, β, and ώ-cyclodextrins are the three main types. Six, Seven, and Eight D-(+) glucopyranose units make up CD. With their primary and secondary hydroxyl groups pointed outwards, these agents have a torus-shaped structure. The hydrophilic surface and hydrophobic interior chamber of cyclodextrins are important characteristics. In order to improve the water solubility, rate of dissolution, and bioavailability of lipophilic medicines for oral or parentral administration, CD and its derivatives have been used as complexing agents. Through cyclodextrin complexation, a larger relative solubility augmentation can be achieved when the pure drug's water solubility is low(25). Several factors have been identified as crucial in the development of complexation, including:

1. The exclusion of high energy water from the cavity,
2. The release of ring strain particularly in the case of -CD,
3. Hydrogen and hydrophobic bindings
4. Van der Wal‟s interactions,(26)

The most commonly utilized natural cyclodextrin is β-CD, yet its usage in pharmaceutical applications is limited due to its low solubility in water (1.85 g/100 ml, 250C), toxicity profile, and low solubility in water of the complexes that are generated. Derivatives like hydroxypropyl β-CD and sulphobutylether-β-CD have been produced in order to produce less poisonous and more water soluble entities. The most popular approach is this one.

to employ cyclodextrins to improve the stability and water solubility of hydrophobic medications. The following techniques can be used to create solid dispersion complexes.

8 . Kneading Method:

Using this method, water is injected into cyclodextrin (CD) to create a paste. Subsequently, the medicine is added and mixed for a designated duration. Next, the kneaded dough is added, dried, and, if necessary, put through a sieve.(27)

9 . Lyophilization/freeze-drying technique:

This method involves first freezing the solution and then drying it at low pressure to eliminate the solvent system from the mixture that contains the medication and CD. This technique effectively converts thermolabile materials into complex forms.(28)

10 . Supercritical anti solvent technique :

Supercritical Carbon Dioxide is proposed as a new complexation medium in the Supercritical Anti-Solvent Technique because of its enhanced solvating power and better mass transfer. One of the most cutting-edge techniques for creating the drug's inclusion complex with CD in the solid form is this one.(29)

Benefits:

1. The method is non-toxic.
2. Quick procedure, extremely low maintenance costs, and encouraging outcomes.

Drawbacks:

1) It has a high upfront cost

11 . Microwave Irradiation Method:

This method makes use of a microwave oven to induce a reaction between the drug and complexing agent using microwave irradiation . The medication and CD are dissolved in a solution of water and organic solvent in a predetermined ratio and added to a round-bottom flask. The mixture reacts in the microwave oven for a brief period of time—roughly one to two minutes at 60 0 C. To eliminate any remaining uncomplexed free drug and CD, a sufficient amount of solvent mixture is added to the reaction mixture or solution mentioned

above once the reaction is finished. Subsequently, the residual precipitate is removed using Whatman filter paper and dried for 48 hours at 400 C in a vacuum oven.(30)

12. Hydrotrophy :

This process of solubilization occurs when a large amount of a second solute is added, increasing the solute's solubility in water. It refers to the rise in solubility in water caused by a high concentration of chemicals. Regarding the mechanism, it is more directly associated with complexation, which is a weak contact between the poorly soluble medicines and hydrotropic agents such as sodium benzoate, sodium acetate, sodium alginate, and urea.31 Alkali metal salts of different organic acids make up the solute. Ionic organic salts are hydrotropic agents. Salts or additives that increase a solute's solubility in a particular solvent are referred to as "salt in" solutes, whereas salts that decrease solubility are referred to as "salt out" solutes.

The term "hydrotropism" refers to the "salting in" of non-electrolytes caused by a number of salts with big anions or cations that are highly soluble in water. On the other hand, hydrotropic solutions have a weak contact between the hydrotropic agent and the solute and do not exhibit colloidal features. A few specific examples may be ethanol, salicylates, different alkaloids like caffeine and nicotine, ionic surfactants like diacides, SDS, and dodecylated oxydibenzene, and aromatic alcohols like resorsinol, pyrogallol, catechol, and b-napthols.(32)

13. Solid Dispersion:

Sekiguchi and obi were the first to suggest the idea of solid dispersion. They studied the formation and dissolution behavior of eutectic melts of a sulfonamide medication and a water soluble carrier in the early 1960s.33 This method improves the drug's solubility by dispersing a poorly soluble medication within a highly soluble solid hydrophilic matrix. Eutectic (non-Molecular Lebel mixing) or solid solution (Molecular Lebel mixing) products can be produced using the solid dispersion process.Homogeneous dispersions of crystalline or amorphous medication in crystalline or amorphous carrier are known as eutectic dispersions. The solid dispersion technology hasn't gained traction despite the promising element of dissolution enhancement and idea simplicity due to manufacturing, scale-up, and stability issues.(34,35)

One helpful pharmaceutical method for improving a drug's dosage form dissolving is solid dispersion. The pharmaceutical business uses a variety of hydrophilic carriers, such as polyvinyl pyrolidone, PEG, Plasdone, Tween 80, SLSA, and others. Many techniques, including the Holt Melt method (Fusion Method), the Solvent Evaporation Method, and the Hot Melt Extrusion Method, are employed to improve the water solubility of hydrophobic drugs.

14. Hot Melt Method (Fusion Method):

This method involves heating a physical mixture of a drug and a water-soluble carrier until it melts. The melted mixture is then quickly cooled and solidified in an ice bath while being vigorously stirred. The final solid mass is then crushed, pulverized, and sieved, and it can be compressed into tablets with the aid of a tablet excipient.(36)

15. Solvent Evaporation Method:

Using this method, the medication and carrier were both dissolved in a single solvent, which was then vacuum-sealed to create a solid solution. Using this method, numerous researchers investigated the solid dispersion of Meloxicam 15, Nimuselide, and Naproxen.

16. Hot Melt Extrusion:

With the exception of the extruder's strong component mixing, this is virtually the same as the fusion method. Miscibility of the medication and matrix can be an issue, just like in a typical fusion procedure. Moreover, large shear forces cause a high local temperature in the extruder for heat-sensitive materials.

17. Nano- Suspension:

A drugstore In order to stabilize nano-sized drug particles for oral, topical, parenteral, or pulmonary delivery, surfactants are used in a biphasic system called nano-suspension. This technique has been developed as a possible effective option for hydrophobic medication delivery.(44)Drugs that are poorly soluble and insoluble in both water and oils are treated using this method.

With an average particle size spanning between 200 and 600 nm, the solid particles in nano-suspensions typically have a particle size distribution of less than one micron. Media milling (Nanocrystals), high pressure homogenization in water (Dissocubes), high pressure homogenization in nonaqueous media (Nanopure), and the combination of precipitation and high pressure homogenization (Nanoedege) are some of the methods used to prepare nano-suspension.(45)Of these, some techniques are discussed here.

A) Precipitation Technique:

Using this method, the medication is dissolved in a solvent and then mixed with a non-solvent to form the crystal precipitate. This method is used in the preparation of medications like Danazol, Naproxen, and others to increase their oral bioavailability and rate of dissolution.

B) Nano –Crystals or Nano systems (Media Milling):

Using this method, high shear media mills are used to prepare nano-suspensions. First, the milling chamber, which is filled with the stabiliser, medication, water, and milling media, is rotated for several days (at least two to seven days) at a very high shear rate at regulated temperatures.Because glass, zirconium oxide, or highly cross-linked polystyrene resin make up the milling medium.

18. Nano-Crystallization:

The process of reducing drug particles to a size range of 1 to 1000 nanometers is known as nanocrystallization. To produce nanocrystals, two different approaches are employed, referred to as "bottom-up" and "top-down" development. The top-down processes (high pressure homogenization and milling) begin at the macroscopic level, such as a micron-sized powder. Atomic and molecular components are combined chemically to create nanoscale materials using bottom-up techniques (such as precipitation and cryovacuum procedures).

19. Milling:

Wet milling is a method that can be used to create nanoscale particles. Impact and attrition forces are used in ball mills to reduce particle size. The two most popular types are the stirred media mill and the tumbling ball mill. This process has issues with mill surface degradation and consequent contamination of the suspension.

20. High pressure homogenization:

In high pressure homogenization, a crystalline drug particle aqueous dispersion is forced through a small homogenization gap at a very high speed under high pressure. It is possible to homogenize in water, nonaqueous media, or media with reduced water content. Cavitations and shear forces break apart the particles. The liquid boils as a result of the static pressure applied to it, producing gas bubbles. Under standard air pressure, gas bubbles burst as they leave the space. Shock waves are created as a result, causing the crystals to clash and the particles to break apart. When working with temperature-sensitive materials, a heat exchanger should be employed since high pressure homogenization raises the sample temperature.

The type of medication, the amount of pressure used, and the quantity of homogenization cycles all have a major influence on the final particle size that is produced during the procedure.

21. Precipitation:

The precipitation process begins with dissolving the material in a solvent to create a diluted solution.

After that, the drug solution is injected into water, which serves as an unfavorable solvent. For the material to precipitate as nanocrystals during injection, the water must be effectively agitated. Filtering can be used to extract nanocrystals from the solution, which can then be dried in the open.

22. Modern Methods for Increasing Solubility and Bioavailability:

These days, a key instrument in the pharmaceutical industry is the New Chemical Entity (NCE) for demonstrating their therapeutic activity to raise the frequency of poorly soluble drugs. Due to their poor dissolving properties, these medications are exceedingly challenging to process and deliver to patients.

The scientist's task is to make a medicine that isn't very soluble in water more soluble. There are numerous approaches or strategies available to increase a drug's solubility that isn't very soluble in water. Following are some of the methods that are covered in this discussion:

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23. Liquisolid Technique:

This system describes formulations that are created by blending liquid drugs, drug solutions, or drug suspensions in nonvolatile solvents into dry, free-flowing, non-adherent powder and stable mixtures by employing the appropriate carriers and coating materials. Different grades of cellulose, lactose, and starch are available and can be employed as carriers. Additionally, if silica powder is utilized in a very fine grade, it can be a good coating material. The emulsification procedure can result in an increase in the drug release profile

from the appropriate vehicle by increasing the surface area of the particles. The surfactant acts as an imp in this. The rate and extent of drug absorption are affected if the dissolution as well as solubilization characteristics of hydrophobic drug are changed. This is because of a role that can mimic the formation of micelles in bile salts and because of this solubility characteristics of poorly water soluble drug increases.(46)

24. Liquisolid Tablets:

It is a recent method that Spireas and colleagues devised.47 Liquisolid technique was demonstrated as an Imp. technology for increasing the rate at which water-insoluble medications dissolve. This system demonstrated both good compressibility and an acceptable flow property. Drugs that are liquid lipophilic, also known as water insoluble, are dissolved in a nonvolatile solvent. With the use of an appropriate carrier and coating material, this liquid form can be changed into a dry, non-adherent, free-flowing, and easily compressible powder blend.

Since liquid medications are known to be either solubilized or molecularly dispersed, increasing their surface area and wetting time will aid in the dissolution of liquid solid tablets containing water-insoluble drugs, resulting in better or improved dissolving characteristics and improved bioavailability.Because of this system's low manufacturing costs, the majority of pharmaceutical companies use it in their production today.(48)

25. Glassy Solid Solution:

It is a particular type of solid dispersions technique in which a medication is molecularly dissolved in an amorphous carrier. When isomalt is used as the carrier, hot stage microscopy (HSM), dissolution tests, and differential scanning calorimetry (DSC) are utilized to discriminate between solid suspensions and solid solutions. Mostly employed in the making of sugar-free hard candies, the carrier isomalt (1-O-α-Dglucopyranosyl-D-mannit dihydrate/6-O-α-Dglucopyranosyl-Dsorbit) is registered as a sugar substitute. It is possible to heat isomalt above its melting point without it breaking down. The melt solidifies amorphously at ambient temperature, transitioning to glass around 60°C. Glass transition temperature (Tg) values for other sugar polyols are lower; for example, mannitol and sorbitol have reported values of 10.7°C and 0°C, respectively. Because of this, glassy systems containing isomalt ought to be more stable than those including other polyols. (49)

26. Spherical Agglomeration:

It is a process that combines the agglomeration, spheronization, and crystallization unit processes. One can refer to the resulting crystals as spherical agglomerates. The obtained crystals' spherical shape contributes to their enhanced flowability and compressibility, making them more suitable for direct tableting or coating without additional steps. This is demonstrated by their simple fusion with Gelure 44/14, which demonstrated a three-hour residence time with 100% drug release. Three procedures were used to make furosemide granules with Hydroxylpropyl β-cyclodextrin: kneading, physical mixing, and solvent evaporation, which resulted in a complete dissolution in 30 minutes.(50,51)

27. Sono Crystallization :

This procedure involves changing the crystalline nucleation by the use of ultrasonic energy. Ultrasound energy causes both expansion and compression. It develops and creates bubbles when a few cycles are finished, and then it collapses. The energy created by the generated bubbles collapsing contributes to the enhancement of the nucleation process, resulting in a highly predictable and reproducible crystallization process.

The following is the significance of using ultrasound in crystallization:

1. It reduces the width of the metastable zone,
2. It reduces the particle size distribution,
3. Reduces the amount of cooling required to achieve crystallization,
4. The procedure is quite predictable and reproducible.
5. Manages the transformations.

Two techniques are employed on an industrial scale for the development of inhaled medication delivery: dispersive ultrasound crystallization (DISCUS) and ultrasound-mediated amorphous to crystalline transition (UMAX).(52)

28. By using Prodrug:

A prodrug is a drug molecule that is covalently attached to a pharmacologically inactive moiety, also referred to as a promoiety, with the intention of overcoming the parent drug's numerous physicochemical and biopharmaceutical limitations in order to realize the drug's therapeutic effect. A prodrug must reasonably undergo a chemical or biological change to the parent drug within the body in order to yield an accurate pharmacological result or effect. Improving the solubility of a class II or IV poorly soluble medication is a major goal when applying. Specifically, a prodrug must be sufficiently soluble to be mixed into a solution for intravenous delivery.

moreover respectable solution stability to offer a suitable product shelf life and the quick conversion to the parent medication that is pharmacologically active. Furthermore, the promotions need to demonstrate that they are safe. Prodrugs of weakly soluble drugs that are soluble in water, including sodium hemisuccinate esters and sodium phosphate esters, are effective examples of using these medicines for intravenous (IV) delivery.(53,54)

29. Combination With Other Drug:

There are several solubilizing agents on the market, and each of them has a number of noteworthy drawbacks. Combining two or more medications with complementary modes of action has the potential to increase solubility while also producing an additive therapeutic impact. In one study, the solubility of both clarithromycin and prednisolone was dramatically increased up to an optimal concentration of paracetamol when coupled with paracetamol, caffeine, and ibuprofen. Comparatively speaking, prednisolone's solubility improvement was less than that of clarethromycin.(55,56)

Conclusion:

The solubility of the medication molecule is the most important factor in the formulation development process. Since it is the primary factor governing both the drug's therapeutic efficacy and formulation. Since the rate at which a drug dissolves during oral absorption is determined by this process, solubility is a crucial need for the formulation and production of various therapeutic dosage forms.

Several methods have been discussed here, either separately or in combination, to improve or enhance solubility. The selection of the procedure varies depending on the excipients' biocompatibility and effectiveness as well as safety When it comes to medications taken orally, solubility is one of the key limiting factors in reaching the required concentration in the systemic circulation to produce a pharmacological reaction. Enhancing solubility is important and required since many medications that have a bioavailability issue become less effective when administered. Therefore, using the many methods that were previously explained, it is now possible to increase the solubility of poorly water soluble drugs.

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