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Review Article

DISSOLUTION AND SOLUBILITY ENHANCEMENT STRATEGIES: CURRENT and NOVEL PROSPECTIVES

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ABSTRACT

The solubility is one of the important parameters to achieve the desired concentration of the drug in the systemic circulation in pharmacological response to be shown. The oral route is the most desirable and preferred method of administering therapeutic agents for their systemic effects, but the poor solubility of the drug is a major challenge for formulation scientist. Close to 40% of orally administered drugs suffer from formulation difficulties related to their water insolubility. Dissolution rate, absorption, distribution, and excretion of a moiety depend upon its solubility characteristics. Although several advantages associated with the oral route, the poorly soluble drugs suffer from slow dissolution and poor bioavailability. Based on solubility, drugs are classified into four classes of the BCS classification. Solubility challenges are faced in ClassII and Class IV of the BCS system this is important because most of the generic and NCE drugs come under class II drugs. The solubility behavior of drugs remains one of the most challenging aspects of formulation development. There are several methods available for solubility and dissolution enhancement of poorly water-soluble drugs. The aim of this clause is to distinguish the techniques of solubilization for the acquisition of effective absorption and improved bioavailability.

Keywords: Solubility, Biopharmaceutical classification (BCS), pH, Dissolution

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INTRODUCTION

The solubility enhancement techniques play a key role to modify the Physio-chemical factors of poorly soluble drugs that which belongs to class II drugs. The low aqueous solubility of lipophilic and hydrophobic drugs creates a problem in the formulation as well as in oral administration. The solubility of a drug is referring to the static property in a saturated solution which will describe relation to the dissolution rate of the poorly soluble drugs and it relates more closely to the dynamic rate of the bioavailability [1].

Table 1: Solubility table in as per USP

Solubility chart	
Different parts of solubility	Parts of one solvent required for one part of the solute
Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	>10,000

Need for solubility

The drugs which have been administered through orally have been considered the main obstacle for the bioavailability of the poorly soluble drugs in the systemic circulation. The drugs will depend on the two intrinsic factors majorly on dissolution rate and permeability the dissolution rate depends upon physical property that refers to the ability to dissolve the solvent in absolute. The second considerable factor that refers to the pharmacokinetics factor (pk) will apply to the orally given drugs that are highly dependable on the permeability of the drug particles in an aqueous medium. Hence 90% of the generic drugs are being reported as hydrophilic in nature and these categories are being estimated as low water solubility and 40% of the new chemical entity (NCE) are screened as the poor aqueous solubility in nature. The pk profile in humans is also regarded as the major hurdle for the oral administration. The rate of absorption and rate of solubility in class II and class IV was highly promulgated to be on the bioavailability and the rate of dissolution [2, 3].

Solubilization theory

The term solubilization is involved in the process of breaking of bonds between the inter-ionic or intermolecular bonds in the solute that separation of the molecules takes place and eventually creates space in the solvent which is dispersed in the solute of the interaction between the solvent and the solute ions [4].

STEP1:-Holes appear in the solvent.

STEP2:-molecules present in the solid will breaks away from the bulk.

STEP3:-the freely available solid molecules will have integrated into the hole in the solvent.

Factors affecting the solubility of a solute [5]

(a) Temperature

Temperature is a primary factor to affect the solubility of a solid in the aqueous medium. In the process of solution, if heat is then absorbed than the solubility of the solutes increases with the increase in temperature, In the case of for most of the salts. If then solute has drawn heat during the process of the solution, the rate of solubility of the solute will eventually decrease with rising in the temperature.

(b) Molecular structure of the solute

If a minute change occurs in the molecular structure of the compound it will affect the marketed formulation, also in its solubility in a given solute.

(c) Solvent nature

Solvent nature has been marked as an important factor that turns relation in solubility parameters. It's also been termed as like dissolves like, it has been made that the mixtures of solvents also been employed. So, like that mixtures have been often used in the field of pharmaceuticals for a purpose to obtain water-based systems. This can be achieved by the addition of excipients such as co-solvents, e. g. Like ethanol, PG, it makes the aqueous phase miscible with other solvents much better.

(d) Crystal characteristics

If crystals show more than one form of the particles of the same substance, those are known as polymorphs, also it possesses various energies in the crystal lattice, and this difference can be reflected by changes in another property. The effect of the polymorphism on the rate of solubility is a predominant from a pharmaceutical point of view. The lack of crystalline structure correlated with so-called amorphous powder, it also escalates in solvable of the drug that is being a similarity to the crystalline shape.

(e) Size of the particles in the solids

The conversion of the interfacial free energy may lead the dissolution of molecules of varying size to cause the solvability of a substance. It will enhance with lowering the size of the particle. When an increase in the solubility with a decrease in the size of the particle will cease the particle has a small radius, if the decrease in any further will lower in size causes a lower solubility.

(f) pH

pH of the solution is either weakly acidic in natured drug or salt form of such drug is reduced by the proportion of un-ionized acid molecules in the solution increases. Consequently, precipitation may occur because of the solubility of the un-ionized species. So, we can say that such precipitation is one of the examples to be encountered in the formulation of liquid medicines.

(g) Formation of complex

In apparent solubility of a solute in an aqueous may be enhanced or may lower by the addition of another substance, which will form an intermolecular complex within the solute. The solubility of the complex determines an evident change in solubility of the salt state.

(h) Polarity

Polarity will affect the solute and solvent of molecules and in turn, the solubility will be affected. Usually, non-polar solute molecules will eventually dissolve in non-polar solvents and in polar solute molecules. It will then disintegrate in polar solvents. Polar solute molecules it has both positive, negative side and when a solvent molecule entices negative sides of the molecules. This is called dipole-dipole interaction movement.

Methods for solubility enhancement

The important factor to be considered for achieving an attainable concentration of drugs in our systemic circulation is solubility. A formulation depends on how efficiently the drug is being soluble in our circulation makes the drug particles available in the site of action. Hence it is necessary to develop solubility of a drug in away such that it should not be lost its any characteristics while administration [5].

Physical modifications

The enhancement of the solubility by altering the physical characteristics of the poorly aqueous-soluble drugs by employing techniques like particle size reduction, micronization, and Nanocrystals, modification of the crystal habitats like polymorphism and drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and recently using cryogenic techniques [6].

Modification of chemically

By changing the pH of the solutions by using of buffered solutions, complexation of the compounds and salt formation of the drugs.

Alteration of the solvent composition

By applying techniques like pH adjustment, co-solvency approach, and by adding the surfactants.

Powder solution technology

Liquisolid compacts and liquiground technique.

By using carrier systems [7]

- Cyclodextrins
- Micelles formation
- Emulsions (micro and nano)
- Liposomes

Micronization

The reduction in the size of the process taken place by a mechanism like compression, friction, attrition, impact or shearing [8].

The term micronization, which reduces particle size down to the micrometer or, in some cases up to the nanometer (1/1000 of a micrometer) size of a particle. It is a prevalent technique for the reduction in size and usually a technique used method for increasing bioavailability and rate of solubility of class II drugs. It is a common technique that refers to the transfer of coarse powder particles to a fine particle to ultrafine powders with a size of the particle ranging from 2 to 5 μm with only a tiny fraction of particles which lies below the 1 μm size range. It is applicable to a wide range of drug types like solid dosages, injectable, ocular, and inhaled products can benefit through micronization [9].

Types of mills used

- Jet Milling
- Bead milling
- Hammer milling

Jet milling

Jet milling doesn't consist any mechanical components, but instead of it, uses the energy of the fluid also known high-pressure air to generate high particle velocity and high energy impact between particles to achieve ultra-fine grinding of pharmaceutical powders. After withdrawing from the jet-mill chamber, the gas which has been processed in the mill is being separated from the solid particles with the help of a cyclone filter. While comparing jet mill to mechanical process it reduces metal combination and, the process temperature remains relatively constant, also can be recommended for drug particles like which are heat-sensitive. The gas left through the mill via tube along with the axis of the cylinder. Presence of solid particles in the mill is subjected to two forces [10].

1. While traveling in circles centrifugal forces have been created by particles.

2. The centripetal force created by drag from the gas and it flows through a nozzle along the wall to the outlet in the centre of the mill.

The drag on the small particles is way lesser than large particles, the derived formula is

Stokes law,

$V= 2/9 (\rho_p-\rho_f)/\mu\ g\ R^2$

Ex: -a study is conducted to assess *in vitro* dissolution rate for low soluble drugs like Glibenclamide was improved by milling through a moderate enhancement of bioavailability was increased through drug Glibenclamide powder were produced by jet milling.

In another study the class II drug ibuprofen was also put through micronization through continuous fluid energy milling, the result was enhanced of dissolution rate with this we can avoid disadvantages of common milling such as clumping, poor flowability, loss of particle range and a high surface area which leads to low dissolution improvement.

Advantages

- Although a process is dry and reduction of the size of micron-sized particles can be achieved with limited size distributions.
- Due to no contamination, it is suitable for heat-sensitive drugs.
- Enhance BA (Bioavailability) through dissolution optimization for oral drugs.

Disadvantages

- This type of milling is not suitable for milling of soft, tacky and fibrous materials.
- Use of inert gas causes the unwanted reaction for sensitive materials.

Ball milling

A pharmaceutical ball milling works on a principle of attrition or shearing usually consist of horizontal and cylindrical shape drums which will rotate on its own axis. The device is filled with materials to be grounded like fibrous coarse particles, etc. The beads like ranging from diameter 12 mm-125 mm. The shell is rotated through a drive gear (30-100rpm) range and large mills shell might be in 3m in DIA and 4.25 m in length. The beads are made up of steel, stainless steel, zirconium etc. The ball mill used for preparation nanosized formulations for low aqueous soluble drugs [11].

Ball mill critical speed

$N_c = 1/2\pi\ (g/R\text{-}r)^{1/2}$

- N_c =critical speed
- R= radii of the ball mill
- r= radii of the beads
- g= acceleration due to gravity

Advantages

- It is also used for size reduction in preparing amorphous powders of drugs if milled together with polymeric compounds.
- It is suitable for materials of all harness of degree. Also for both batches and continuous operations.

Nanomaterials through ball milling

Ball milling can also use for production of nanomaterials at the scale of a lab to batch production. This process can be used in producing carbon nanotubes as well as metallic and ceramic nanomaterials. While these mills are providing with grinding media composed of carbide or steel. The ball mills rotate around a horizontal axis, which is being partially filled with the media to be grounded [12].

Mechanism

The beads will rotate with high energy inside a container and then fall onto the solid particles with the force of gravity and hence crushing the solid particles into nanosized particles.

What can be produced by nano ball-milling?

- Carbon scrolls can be produced by ball milling
- Nanoporous carbon produced by ball milling
- Nucleation and growth of carbon nanotubes via the thermos-mechanical process.
- After grinding and thermal annealing carbon nanotubes formed in graphite sheets.
- Low energy shear milling is a method of preparation for the nanosheets.

In-situ micronization

In-situ micronization is a novel particle engineering technique where micron-sized crystals are obtained during its production itself without the need for any further size reduction. In contrary to the other techniques the external processing conditions like mechanical force, temperature and pressure are required, the obtained drug is micro-sized during the crystal formation. Whereas compared to the SCF requires specialized temperature and pressure to maintain CO_2 at supercritical conditions where these are the major drawbacks in it. In-situ micronization technique is beneficial in above aspects where it requires only mild agitation using magnetic stirrer and processing in less time.

Methods of preparation

Solvent change method, pH shift method are the methods are promising in enhancing the flow properties and dissolution rate and stability of poorly soluble compounds.

Solvent change method

In this process, this is most effectively applied to both water-soluble and insoluble drugs. It involves in precipitation in the presence of the protective hydrophilic polymers by drying. Where non-solvent is used as precipitating medium. In low aqueous soluble drugs. The selected drug particles in a suitable solvent the most using stabilizing agents are usually hydrophilic polymers, are to be dissolved in the aqueous solvent which acts as a non-solvent to the drug. After mixing both solutions by batch-wise in a ratio of 1:4 or 1:8 as resulting microcrystals are to be dried using oven or spray dryer. The stabilizers which are present in water phase will adsorb the nucleated phase drug particles which hindering the growth of crystals [13].

Ex: -Gliclazide microcrystals, betamethasone, were prepared by using the solvent change method.

pH shift method

It is well suitable for drugs with pH reliant solubility. The pH of the systems needs to alter slowly from basic to acidic. 0.1 NaOH and 0.1 HCl are used to alter the pH. A high-speed Homogenizer with RPM of 26,000 is employed to prevent aggregation when altering the pH from acidic to basic within a gap time of 5 min for effective microcrystalization [14].

Ex:-Gliclazide microcrystals are being prepared by the pH shift method by using PEG, CMC, and PVP is freeze dried. Similarly, indomethacin was prepared by adding zinc acetate.

Merits: -the produced microcrystals are in-situ surface modified due to the presence of hydrophilic polymers which in turn enhances wettability.

It can also have applied to the pulmonary drugs. Compared to the jet-milled drugs, the respirable fraction of these micro-crystals is increased which can be prevented in a deposition of the throat.

Modern micronization techniques

Apart from traditional micronization techniques, there are modern micronization techniques will promise to enhance low soluble drugs and low solubility. These methods are based upon supercritical fluids to induce a state of supersaturation, it will lead the precipitation of individual drug particles. The commonly used techniques of this category are a rapid expansion of supercritical solution (RESS), the (SAS) method of supercritical anti-solvent, and the (PGSS) method of particles from gas saturated solutions. This technique allows for greater and tenability of the process. Many supercritical fluid techniques can be used for thermolabile materials. Novel techniques involve renewable, non-inflammable and non-toxic chemicals.

Co-crystallization

Although several methods are available for improving solubility enhancement by following existing techniques. But co-crystallization plays a tedious role in BCS class II drugs and hydrophobic drugs, however, these methods having inadequate and drawbacks like employing the high energy of the process also scaling-up issues and

processing are much complicated. For the best, the researchers have developed a method to enhance the rate of solubility known as co-crystallization.

The simple technique that can improve the physicochemical properties of the API. The Co-crystallization technique can be widely applied to acidic, alkaline, and neutral compounds. When this technology can be applied to pharmaceutical substances to improve drug stability through controlled crystallization processes such as by forming metastable polymorphs, high energy amorphous forms, and ultrafine particles can be achieved. It consists of a drug and co-crystal (co-former) with a definite stoichiometric ratio and connected by synthon. Co-crystals can be prepared by several types of interaction, including hydrogen bonding, Vander Waals forces. For compounds like nonionizable co-crystals can rise in pharmaceutical properties by modification of chemical stability, uptake of moisture, mechanical behavior, dissolution rate and bioavailability [15].

A various number of techniques had been investigated to synthesize co-crystals, such as melting extrusion, forming the slurry with ultrasound, particle size reduction, sprays drying, and solvent evaporation and solution method is a more effective and efficient for refinement and furthermore, SE method is commonly used in pharmaceutical industry currently.

Solvent evaporation

The most conventional method in the case of forming crystallization. This technique for the material is mixed with a common solvent and make it evaporate completely. In the stage of the evaporation, the molecules may expect to undergo various hydrogen bonding reactions. While in the case of the co-crystallization which will consist both API and conformers solubility of solvent plays a great role. If the solubility is not similar, then the one with lower solubility than another will precipitate out. If polymorphism existed in the compound the changes are that after co-crystallization may convert into a form which will abridge with co-former.

Hot melt by extrusion

Hot melt extrusion is the helpful technique for the synthesis of cocrystals. Also involves high efficient mixing and surface contacts, in this method, there is no use solvent addition to form co-crystals. This technique majorly depends on the thermodynamic stability of the compound. Hot melt by extrusion method was used in the synthesis of active drug ingredients like carbamazepine-nicotinamide cocrystals with a polymer former. Whereas solvent drop extrusion technique is used to optimize and make the process much flexible and it gives benefit a to carry out the process at even lower temperatures [16].

Sonocrystallization method

For the preparation of organic cocrystals, Sonochemical method is implemented for the making of a finite cocrystal has been done. This was majorly depending on the preparation of nanoparticles. By using ultrasound techniques by combining of caffeine-Maleic acid cocrystals were being to be prepared. Hence this technique proves to be a significant approach.

Ex: -Tegretol (carbamazepine) Prozac (fluoxetine HCl) Sporanox (itraconazole) Aripiprazole (Abilify)

Nanocrystal

Nanotechnology is a tremendously affect our way drug delivery to enhance the solubility as well as the change in a size of particles less than sub-micron level. Transferring of materials to another dimension called as Nano dimension makes particles change their physical properties which were used in the field of pharmaceuticals to be developing an innovation formulation for poorly soluble drugs. Nanosizing is defined as a process which involves reducing the particle size of the API to the nanometer range it means particle size is<1 μm the bioavailability of these preparations is called as nanocrystals [17].

Depending on the production technology, processing of the drug microcrystals of drug nanoparticles can lead to an either crystalline or to an amorphous product, when applying precipitation. Such an amorphous drug nanoparticle should not be called nanocrystal. It often refers to nanocrystals in the amorphous state [18].

There two approaches to prepare drug nanocrystals; they are top-down approaches and bottom-up techniques. However, top-down techniques have been employed successfully in both lab-scale and commercial scale formulations. Bottom-up approaches have not been yet used at a commercial level, these techniques have been found to be to produce applied sized distribution nanocrystals using simplest methods [19].

Bottom-up techniques

These techniques are also referred to as precipitation techniques as nano-sized drug particles are formed by precipitation which will be crystalline or amorphous. In these techniques drug is precipitated from supersaturated solution or by solvent evaporation with a non-solvent.

(a) Precipitation by addition of liquid antisolvent

To obtain nanosized particles by precipitating of a drug from its solution by the addition of an antisolvent is an effective way to obtain drug nanocrystals. The size of the particles and the morphology of the final product can be controlled. In this method, a drug is dissolved in a solvent and then mixed with another the which is miscible with the first solvent but acts as Antisolvent. Then obtained the result is increased super-saturation of the solution due to diffusion of solvent into the antisolvent and nucleation of particles will occur. This process of formation of particle growth and nucleation can be competed by a process called Ostwald ripening.

(b) A simple mixing method using a static mixer

Nanosized of drug particles are produced by mixing the drug solution and antisolvent using mixing forces. Here solvent plays a key role in the production of submicron particles as it should solubilize drug particles and accelerates a fast diffusion rate towards the antisolvent. The solvents used for the preparation of drug solution can be organic, e. g. Ethanol, methanol, IPA, acetone, etc., And co-solvents like e, g. Polyethene glycol or propylene glycol. Solvents like PEG are being chosen which are environmentally friendly. Static mixers have been described in the literature as simple mixing equipment. It offers over several advantages on other mixing equipment like low cost, low energy, and homogenous mixing of miscible solvents.

Top-down techniques

These have become an increasingly recognized by industries as well narrow, wide of distribution of the drug particles. Currently there few marketed formulations are being prepared by top-down techniques. These techniques are high energy processes which will break down the particle size of drugs to nm size by application of friction. These include techniques like media milling, high-pressure homogenization (HPH) etc. These two techniques have been widely accepted by regulatory authorities [20].

(a) Media Milling

This technique is developed by Liversidge *et al.* In 1992 is commercially known as Nanocrystal® technology; it is well known nanosizing technology which is most successful. It is a current version of wet ball techniques. The wet ball technique involves low energy milling in which jar is filled with a milling medium and drug dispersion is either aqueous or non-aqueous media and is subjected to a milling operation. Shear forces of impact are generated by the movement of the milling media, and it will lead to particle size reduction. While in contrast to high-pressure homogenization, it is a low energy milling technique. Milling media use small or large milling pearls. It consists of ceramics, stainless steel or highly crosslinked polystyrene resin-coated beads. Erosion is the main problem while milling the material. To avoid the impurities caused by erosion of the media can be overcome by the coating of the media balls. Two basic principles are for milling either the milling is an agitator or complete container is moved in a complex movement which leads to movement of media. The milling time depends on

factors such as surfactant content, thehardness of the drug, viscosity, temperature, energy input, size of the milling media. The current Nanocrystal technology involves high energy wet ball milling.

(c) High-pressure homogenization (HPH)

This method for production of nanosuspensions was patented by Muller *et al.* In 1994 and it is the second most important technique for production of the drug nanocrystals. The homogenization employs two techniques, namely, i.e. microfluidizer technology (IDD-P™ technology), piston gap homogenization in water (Dissocubes®). The IDD-P technique was developed by Skye pharma. I.e. Is the insoluble drug delivery microparticle technology. The microfluidizer technology can generate small particles by a frontal collision of two fluid streams under pressures up to 1700bar thus it leads automatically to particle collision, by shear forces and cavitation occurs, it is based on the principle of jet-stream homogenization where the drug suspension is homogenized at a higher velocity and pressure by a homogenizing chamber. In this technique, two types of chambers are being used, i.e. Y type and z type. In the z chamber, the direction of the flow of suspension changes which in particle collision and shear forces and finally particle reduction occurs. In the Y type chamber, the suspension flows in two streams which collide with each other, resulting in particle collision and particle breaks down [21].

(d) Dissocubes homogenization technique

In, this contrast to this Dissocubes employs piston-gap Homogenizers. This technology was also introduced by Skye Pharma PLC. It is a production of nanoparticle suspensions with water at room temperature. The drug is mixed in an aqueous solution of surfactant along with stabilizers and the resulting dispersion is passed through a narrow gap which having diameter 25 μm and subsequently forced by a piston with a very high pressure ranging from 500 to 1500 bars. Then the suspension of the drug passed through the Homogenizer repeatedly to achieve the desired particle size and therefore the pressure is increased in a stepwise manner. As the width of the gap is very narrow in a micrometer, hence it is recommended that the starting drug product is advised to pre-micronize using fluid energy mill to prevent clogging in the gap and it reduces the milling time [21].

Finally, the drug is in a closed system, the pressure in it maintains constant as soon as it passes through a narrow gap, an increase of the dynamic pressure of the liquid it develops, as a result, the static pressure of the liquid falls below the vapor pressure which in result in boiling of the liquid and formation of bubbles will occur. As soon as the mixture leaves the narrow gap, the gas bubbles will collapse due to normal conditions and formation of nanosized drug particles are achieved by cavitation forces and shear forces and collide.

HPH can be used for both laboratory and commercial purpose as it is a scalable process since it cannot generate any impurities due to abrasion or shear forces are developed in HPH, it can also use to produce parenteral nanosuspensions.

Some of the known technologies used for the production of nanocrystals areNanopure™ technology

Modified mixing methods

These methods involve precipitation of a drug by external features. For example, the addition of ultrasonic waves or alteration in the environment of precipitation, e. g. The spray drying, freeze drying, or high gravity precipitation, may produces smaller particles when compared to conventional methods.

- Sonoprecipitation
- High gravity controlled precipitation technique (HGCP)
- Supercritical fluid technique (SCF)
- Rapid expansion of supercritical solutions (RESS)
- Spray freezing into liquid (SFL)

Combination technique

Various combination techniques and high energy process have been used to prepare drugs nanoparticles. By using these techniques, significant reductions in processing times can be achieved by subjecting the drug to precipitation before processing through a top-down process. This technique includes

- Nanoedge™ technology
- H69, H42, H96 are the combination techniques.

Co-milling process: a technique for process optimization

The term co-milling and milling refers to a drug in the presence of occupants which are well-known techniques that have a potential to enhance solubility and dissolution of the drug particles. It is a simple, efficient and economical process which does not require any sophisticated equipment and it is an environmental friendly which does not require any organic solvent. While in process of wet milling or solid dispersions co-milling combines the advantages of particle size reduction and amorphization of milling will makebenefit of improved solubilization/micellization is provided by the co-milled excipient. Co-milling has also been used for improving the characteristics of different drugs which are in amorphous, and drugs which are prone to heat degradation.

Powder solution technology: (Liquisolid technology)

The powder solution technique (Liquisolid technique) is an innovative approach to enhance the dissolution property will increase the rate of bioavailability of the poorly water-soluble drug particles in systemic circulation. It is patented by Spireas et. al in 1996. Basically, liquisolid is based upon dissolving an insoluble drug particle into soluble by the addition of non-volatile solvent and admixtures of drug loaded solutions by adding proper carrier and coating materials to convert into acceptable flowing and compressible powders. By this technique, liquid medications are also being converted into free-flowing powders by adding suitable non-volatile solvents and excipients to it to make free flowing powders. Liquisolid systems also involve conversion of lipophilic drugs or water-insoluble solid drugs dissolved in a non-volatile solvent and these medications can be converted into free-flowing and nonadherent, dry looking, and ready to compressible compacts [22].

Formulation is based upon ^{liquis} ^{o}^{lid} compacts will be classified into

- Liquisolidcompacts
- Liquisolid microsystems

Components used in liquisolid

Carrier material

These are enhancing the compressing properties and having relatively large, and porous in nature with sufficient absorption property which in turn contributes to absorption of liquisolid. E. g. Different types of cellulose derivatives, starch, lactose, sorbitol, avicelpH101, 102and Eudragit RLandRS etc [23].

Coating of material

Coating of materials will enhance the flow and very fine in diameter, the absorption is very high in coating particles which favorable in covering the wet carrier particles a dry looking powder by adsorbing off any excess liquid. E. g. Silica of various grades like cab-o-sil M5, Aerosil 200.

Non-volatile solvents

These solvents are very inert and preferably water-miscible and not high in viscous organic solvent systems. Various solvents like polyethylene glycol 200and400, glycerin, liquid polyethylene glycol, polysorbates, fixed oils etc.

Disintegrants

These are used in dissolving the particles quickly disintegrates like sodium starch glycolate (explotab13, Pumogel, etc.)

Designing the liquisolid compacts by implementing mathematical model: -

To desired for obtaining good flow behavior and compressibility of liquisolid systems or compacts a mathematical model is used to

design for selecting of suitable carriers, solvents, and coating materials were proposed by Spireas

A mathematical model is based on new fundamental properties of powder called flowable liquid retention potential (Ψ value) the Ψ value is defined as the max weight of the liquid that can be retained per unit [24, 25].

The excipient ratio (R) or the carrier:

The coating material ratio is represented as follows: R=Q/q (1)

Where R is a ratio of the carrier (Q) and coating materials (q).

For, a successful formulation design, this ratio R be suitably selected.

Another term called liquid load factor (Lf) is defined as the ratio of a weight of liquid medication (W) to the weight of carrier material (Q) in systems.

Lf = W/Q (2) the Ψ value was used to calculate excipient quantities.

The derived equation for this as follows: Lf = Ψ+Ψ (1/R) where, Ψ and Ψ are the constant Ψ values of the carrier and coating materials, respectively. By calculating Lf and W, we can calculate the amount of Q and q required for the liquisolid system [26].

The mechanism for enhancing the release of the drug from liquisolid systems

1) Increased Aqueous Solubility

2) Increased Drug Surface Area

3) Increased Wettability [27]

Alteration of solvent composition

Adjustment of pH

Low water-soluble drugs with a part of the molecule might be a base or acid, it will potentially dissolve in water by applying for pH change. Then the adjustment of pH can be used for both oral and intravenous administrations. The solubility of the compounds might be precipitated blood and with a presence of the strong buffer with a pH of 7.2 to 7.4 will be considered the capacity of the buffer and tolerability of the pH selected are best suited. By pH. Partition hypothesis and Henderson Hesselbach equation, the compound is ionized also dependent on pH media and drug pKa [28].

Advantages

- Requires small quantities of the compound.
- Simple to produce and fast track.
- Easy to formulate and to analyze.

Disadvantages:

- Upon dilution may cause precipitation.
- The compound is much less soluble in aqueous media pH.

Use of surfactants

The surfactant is used to reduce the interfacial tension between two immiscible layers of the liquid emulsions. These are useful for enhancing of the absorption to increase both rates of dissolution also the permeability of the drug. It enhances the dissolution rate by promoting wetting properties of penetrating the dissolved fluid into solid drug particles.

E. g. By enhancing the solubility of drug name called enrofloxacin derivative from norfloxacin by employing a series of co-solvents and surfactants the aqueous solubility of enrofloxacin increase 26 times.

However, by combining of co-solvents alone produced only a small rise insolubility of low soluble drugs in a formulation can be achieved. Here ionic surfactants were found to be much better solubilizing than nonionic surfactants. When ionic surfactants are compared with the cationic surfactants were high in the amount of anionic surfactant.

Use of co-solvents

The use of co-solvent is one of the technique to approach to enhance the solubility of poorly water-soluble drugs in formulations. The solubility of insoluble water drugs can be enhanced by the addition of the water-miscible solvent in good solubility has seen are known as co-solvents, these are the mixtures of water and one or more water-miscible solvents that used to create a solution have property to enhance the solubility of poorly soluble compounds [29].

E. g. PEG300, propylene glycol, ethanol

Low soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture is suitable to co-solvent approach. Co-solvents can increase the folds of the drugs into several thousand times when compared to the aqueous solubility of the drug alone. Co-solvents may be combined with other solubilization techniques with pH adjustment may further increase the solubility of poorly water-soluble compounds.

Advantages

- Simple but rapid procedure to formulate.

Disadvantages

- Toxicity and tolerability are well with all excipients.
- The solvent level to be considered upon administration.
- Upon on dilution, precipitation occurs.

Cosolvents products: -Nimotop by Bayer (Nimodipine IV) Lanoxin, GSK (Digoxin elixir)

Carrier systems (complexation of compounds)

Complexation is associated with inclusion of compound is being two or more molecules to form a non-bonded entity with a well-defined stoichiometry. The forces presented in complexation are relatively weak forces such as London forces, hydrogen bonding, hydrophobic interactions are involved. Inclusion compounds are formed by insertion of a nonpolar molecule of one molecule into the cavity of another molecule or group of molecules (known as the host). Most commonly used are Cyclodextrins, these are nonreducing, crystalline, water-soluble, and cyclic oligosaccharides consisting of glucose monomers arranged in a shape of donut having a hydrophobic cavity and hydrophilic outer surface. Three types of naturally occurring Cyclodextrins are α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin. The surface of the CD is water soluble, but the cavity is hydrophobic it provides a microenvironment for appropriate size for non-polar molecules. Based on the structure and properties of drug molecules it can form 1:1 or 1:2 complex [30].

Types of methods to form complexation

(a) Kneading method

(b) Lyophilization/freeze-drying technique

(c) Microwave irradiation method

Micellar solubilization approach

Surfactants are compounds will have two molecular regions: A hydrophilic head (polar head) also a hydrophobic head (non-polar head). Use of the surfactants will improve the solubility of drugs and improve the characteristics of low soluble drugs. It has a low-tension property and increases the rate of dissolution of high lipophilic drugs in the aqueous medium [31].

Traditional surfactants

a) Anionic surfactant: the hydrophilic group having a negative charge, e. g. SLS, potassium laurate.

b) Cationic surfactant: a hydrophilic group having a positive charge, e. g. cetrimide, benzalkonium chloride.

c) Zwitterion surfactant: molecules having both positive and negative charges e. g. N-dodecyl-N, N-dimethyl betaine.

Nontraditional surfactant

a) Nonionic surfactant: -poloxamers (Pluronics).

b) Ampholytic surfactant (zwitterionic surfactant):-molecule carries both negative and positive charges. E. g. N-dodecyl-N, N-dimethyl betaine

The above-mentioned surfactants are also used to stabilize a suspension when the concentrations of these surfactants exceed the critical micellar concentration (CMC) the micelle formation occurs, thus entrapping the drugs within micelles.

The micellar approach is divided into 2 types

- Mixed micelles approach
- Polymeric micelles approach

Micro-emulsions

The microemulsion is an approach to solubilize the low soluble drugs via phase mixing of the oil and aqueous by adding of surfactant and co-solvent by mixing, which in turn reduces interfacial tension forming like small and uniformly oil droplets which will contain poorly solubilized drugs in it. it enhances the solubility of many drugs which faces practically insoluble in an aqueous phase and is well established by the large amounts of two immiscible liquids. These microemulsions are optically crystal clear in nature with concentrate in a mixture of oil and water. These are isotropic in nature and thermodynamically stable and translucent systems. The droplets with arranging size of 20-200 nanometers [32].

Method of preparation of micro-emulsion [33]

a) Phase titration method

b) Phase inversion method

Factors affecting the microemulsion [34]

- Packing ratio.
- Property of surfactant, the oil phase, and temperature.

Theories of microemulsion formation: -

Basically, three approaches are being explained by the formation of microemulsion formation and stability are:

- Interfacial and film mixed theories
- Theories of solubilization
- Thermodynamic properties

The free energy of micro-emulsion can be considered and depend to a certain extent at which lowers the surfactant surface tension between the oil and aqueous phase also change in entropy of the system [34].

$Gf = \gamma a – T S$

- Where Gf = free energy formation
- A = change in the interfacial area of the microemulsion
- S = change in entropy of the system
- T = temperature
- γ = surface tension of oil-water interphase

Components of the microemulsion

The oil and surfactant are more in abundance, but in use is restricted because of their toxicity and potential of their irritation also their mechanism of action is so far unclear. The use of surfactants (tension reducing agents) and oils are being used in the formulation for micro-emulsions should be biologically compatible and should not be toxic in nature, acceptable by clinically and approved and compounds should be certified as (GRAS) [35].

- Oil phase (lipid phase)
- Aqueous phase (water phase)
- Primary surfactant
- Secondary surfactant
- Co-solvent (addition of solvent)

Marketed formulations

Table 2: marketed formulations of the microemulsion in current market [35]

S. No.	Brand name	Active ingredient	Manufacturer
1	Sandimmune neural	cyclosporine A	Novartis
2	Fortovase	Saquinavir	Roche Laboratories
3	Norvir	Ritonavir	Roche Laboratories
4	White Glow	Mulberry extract	Lotus herbals

Liposomes

The name liposomes derive from two Greek words: Lipos means fat and soma means body these were first described by British hematologist Dr. Alec D Bangham in the year 1961 at the Babraham Institute. These are simple microscopic vesicles in which presented like lipid bilayer structure is present in an aqueous volume entirely enclosed by a membrane, composed of lipid molecules. Several components are in liposomes, phospholipid and cholesterol are the main components. These liposomal particles can characterize in advanced technology for delivering active ingredients to the particular site of action. After huge research and innovation that leads to liposomal technology had progressed called as conventional vesicles. Generally, liposomes are spherical in shape vesicles with size ranging from 30 nm to several micrometers. These vesicles are prepared as artificially like a spherical vesicle composed of the lipid bilayer [36].

The classification of liposomes is based upon lamellae, composition, a method of preparation and its size

Table 3: Classification of different types of liposomes [37]

S. No.	Types	Size
1.	Multilamellar large vesicles (MLV)	(>0.5 μm)
2.	Oligolamellar vesicles (OLV)	0.1-1 μm
3.	Unilamellar vesicles (UV)	All Sizes
4.	Small Unilamellar vesicles (SUV)	20-100 nm
5.	Medium sized Unilamellar vesicles (MSUV)	-
6.	Large Unilamellar vesicles (LUV)	>100 nm
7.	Glant Unilamellar vesicles (GUV)	>1 μm
8.	Multivesicular vesicles MV)	More than>1 μm

Methods of liposomes production

Passive loading techniques

a) Mechanical dispersion methods:

b) Lipid film hydration by handshaking and non-hand shaking or freeze drying

c) Micro emulsification

d) Sonication

e) French pressure cell

f) Membrane extrusion

g) Dried reconstituted vesicles

h) Freeze-thawed liposomes

Solvent dispersion methods

a) Ethanol injection

b) Ether injection

c) Double emulsion

d) Reverse phase evaporation studies

e) Stable pluri lamellar vesicles

Detergent removal methods:

a) Dialysis

b) Column chromatography

c) Dilution

d) Reconstituted Sendai virus enveloped [37].

Applications of liposomes

- Cancer chemotherapy
- Gene delivery
- Liposomes for topical applications
- Liposomes for pulmonary delivery
- Liposomes for nasal administration
- Liposomes in parasitic diseases
- Ophthalmic delivery of drugs
- Liposomes for brain targeting

Advantages

- These are biocompatible and completely biodegradable, non-toxic in nature
- These are suitable for delivery of hydrophobic, amphipathic drugs
- It reduces exposure of sensitive tissue to toxic drugs

Disadvantages

- The production cost is high
- Occurrence leakages also a fusion of particles with encapsulated drugs to other molecules may happen
- Lysosomes have very short t1/2 life (half-life) in the RES system (reticuloendothelial systems) and cells in the liver like Kupffer cells may remove from the hepatic circulation.
- Limitations in liposomal technology:
- Stability issues
- Sterilization problems
- Affecting efficiency of encapsulation
- Actively targeted
- Degradation may occur in lysosomal particles.
- Chemical modifications:

Prodrug approach

The prodrug is used to improve physiochemical properties of drug to modify the chemically, enzymatically of the drug delivery is the prodrug approach is inactive, a bioreversible derivative of active drug molecules that goes under enzymatic/or chemical transformation in the body to release the active ingredient called parent drug which elicits the desired pharmacological action in the body. This approach the prodrugs needs carrier or promoiety and as a result of modification in molecular level of the prodrug itself to the formation of a new active compound. To avoid the unnecessary toxicities and to overcome the drug loading the prodrug approach can be used to enhance the solubility of the heavy doses as well as poorly soluble drugs [38].

Ex: -

- levodopa: active form (dopamine)
- Enalapril: active form (Enalaprilat)
- S-methyldopa: active form (alpha-methyl norepinephrine)
- dipivefrine: active form (epinephrine)
- Sulindac: active form (Sulfide metabolites)
- Hydrazide MAO inhibitors: active form (hydrazine derivatives)

Conversion in salt form

Most common process and effective method of enhancing the solubility enhancement in poorly water-soluble drugs. By conversion of acid or base in salt form shows more stability than the respective drug, for conversion into the salt form of a drug, the ionizable groups should assist in the selection of the salt. The formation criteria should be: -the difference between drug and counterion should be 2 to 3 pKa units. The decrease in crystal lattice force is seen in counterion. For the production of these processes, it should be approved by health agencies like FDA also data like toxicological studies should be supported for the selection of the counterion [39].

E. g. Aspirin, theophylline, barbiturates.

Recent and current trends in solubility enhancement techniques

a) Melt-sonocrystallization

b) Cavitation

c) Floating granules

d) Cryogenic techniques

e) Plasma irradiation

f) electrospinning

g) Cellulose nanofibers

h) Crystal co-agglomeration technique

i) Fluidized bed-coating on sugar beads

Melt-sonocrystallization

This is an innovative and novelty in creating a particle engineering technique to enhance the solubility of a water-insoluble (hydrophobic) drugs which will affect the crystal habitat of the drug. It can be imparting a wide variety of the desirable characteristics of a highly valued product in industries. The chemical company named Dow, following this technology for rapid acid crystallization, but it is closely safeguarded. By implementing this technique impurity are reduced from 800 ppm to less than 50 ppm [40].

Cavitation

This technique is generally being defined by forming of cavities, subsequently by forming and collapsing of cavities formed with a density of high energy ranging 1 to 1018kW/m^3energy is applied to

form the cavities that occur at variously like millions of locations that formed in reactor simultaneously it generates conditions of high energy and pressures. Thus, chemical reactions require the stringent environment in the process is generated due to the chemical reactions or certain unexpected reactions. It can also tend to generate of local turbulence and acoustic streaming in the reactor, which in turn enhance the rate of transport [41].

Floating granules

These dosages can be converted into tablet form or capsule by addition suitable excipients as well as by incorporating certain gas-generating agents are being added in the formulation. Which in result gives a floating effect on the surface of the GI fluids called buoyancy. The excipients used are lightweight of the polymers like poloxamer 188, hydroxypropyl methylcellulose, polyethene glycol 6000, polyenyl acetate, polymethyl methacrylate, alginate beads are used in a dosage form. In drug having high permeability and it remains 99.9% unionized. At this time dug goes into systemic circulation like small intestine where it can be solubilized. So, for this reason, this dosage form can be recommended [42].

Cryogenic techniques

The word cryogenic means the liquids which are under lower than Celsius scale which will rapidly freeze any material this technique is being developed and created for increasing the solubility and quicker rate of dissolution for drugs which are poorly water soluble. It contains several parts like injection device, the location of the nozzle, also a composition of cryogenic liquids [43].

E. g. Hydro fluoroalkanes, liquid nitrogen etc.

After processing of the powder, it can be obtained by a various process like lyophilization and some techniques are mentioned below:

Various techniques like

a) Ultra rapidly freezing.

b) Spray freezing into liquid over vapor.

c) Spray freezingly into liquid cryogenic.

d) Spray freezingly onto liquid cryogenic.

Plasma irradiation

Plasma irradiation is a feasible technique for enhancement of low soluble drugs after the huge investigation. The plasma itself contains an equal numbered of negative ions and positive ions in a unionized neutral species such as we called them like molecules, atoms, and radicals, etc. The plasma is created by subjecting to a gas to a radio-frequency potential in a vacuum chamber. Optimally, it leads to the production of electrons, which are accelerated in an electric field and to collide with neutral molecules to produce a free radical. During at this treatment, these O_2radicals will react with chemical groups and on the surface, while exposed sample will lead to the formation of an O_2functional group. Production of these groups will enhance the properties like wettability and increase effectively the surface area for better dissolution, in turn, increase the rate of dissolution and better solubility [44].

Electrospinning method

This entire technique was patented by J. F. Cooley in May 1900 and by W. J Morton onJuly 1902. It is also likely to the cellulose nanofibers which is likely to draw a charged thread using electric forces from a solution of polymers to produce fibers likely up to some hundreds of nanometers. Although this process was invented earlier than the recent technique of production of nanofibers by Turbak, Synder, and Sandberg in the late 1970s. The advantage of this technique is this technology does not require any high energy or coagulation chemistry or high temperatures to produce a solid thread from solution. This technology combines polymers with solid dispersion with nanotechnology to produce fiber threads. In this process, a liquid stream of a drug/polymer solution is subjected to potential energy between 5 and 30kw. The fibers of submicron threads were formed when electrically charged forces will overcome and causes surface tension in the solution with air interface will produce nanofibers [45].

Cellulose nanofibers

The word cellulose nanofibers were first coined by some workers called Turbak, Synder, and Sandberg in the year of 1970s in a lab called ITT Rayonier located in Whippany, new jersey in the USA. They described a product which has been prepared by them a material which is a like gel type that's been passed through a Gaulin milk type Homogenizer at parameters like high temperatures and followed by an ejection of a hard impact on the hard surface. A facile method was developed and produced by cellulose nanofibers/nanofibers with a single-step procedure by milling process with ball-mill equipment. By mechanical and chemical actions of this technique, the nanofibers were produced at length of 20 nm wide and several micrometers long were yielded. Having surface properties was perfectly tailored. Also, can choose by adding any type of modifying reagent. By adding reagent called succinic anhydride can be modified a cellulose nanofiber shows an increased and enhanced property of hydrophilicity. These nanofibers can be readily dispersed in H_2O or dimethyl sulfoxide (DMSO), at the zeta potential of-38.7Mv and forming the carboxyl groups on the surface. Likely a modified dodecyl succinic anhydride, cellulose nanofiber shows good dispersibility in o-oxylene and excellent compatibility with polyethene. These nanofiber composites will enhance overall in mechanical properties and a new pathway to the production of these complete functioned of nanofibers [46].

Crystal co-agglomeration technique

Since spherical agglomeration is being restricted to only poorly water-soluble drugs because of the excipients like Disintegrants agents and diluents are being in hydrophilic in nature with agglomeration of these excipients the bridging of organic liquids is difficult. To overcome this a novel technique is developed by Kadam et. Al was known as crystal co-agglomeration. It is a slight modification of spherical crystallization and used for size enlargements of alow and high dose, in this technique a single generated step and it is recently utilized to improve the micromeritic properties [47].

Fluidized bed-coating on sugar beads

In this technique fluidized bed will coat on the sugar beads, on a drug-carrier mixture solution was sprayed onto surface of the granular beads of excipient or spherical sugar beads to skip processing for the single-step process for compaction of the tablets and being applicable to the process for encapsulation and can be applied to existing dosage forms like immediate and controlled release forms. Coated with spherical sugar beads [48].

E. g. Milling antifungal agent (itraconazole) manufactured by Janssen Pharmaceuticals in the brand name of Sporanox which is available in capsule form.

CONCLUSION

By this article, we conclude that by the implementation of various methods to enhance the solubility by modification of physical, chemical and carrier systems. Although solubility enhancement characteristics depend upon physical nature, chemical nature, melting point, site of absorption, etc. The rate of dissolution is determining step for oral absorption of the poorly water-soluble drugs by describing various techniques above articles gives a modification in certain characteristics by increasing the number of folds insolubility. Finally, this article concludes that solubility of low water-soluble drugs isan important to reach into systemic circulation to elicit its pharmacological response.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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