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Novel Technologies for Enhancing Solubility of Poorly water soluble drugs

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Abstract: **Solubility is the process of formation of a uniform system, which includes two, parts (solute and Solvent). There are wide varieties of physical and chemical properties that are needed to be considered to determine the solubility for required preparation. Aqueous solubility is one of the key determining factors, lower aqueous solubility leads to issues faced during the studies of newer formulations(1). Many of the newly formulated preparation is practically insoluble in water, which leads to new problems. Numerous techniques are now available in industries to increasing solubility. Methods like particle size reduction, crystal engineering, salt formulation, solid dispersion, use of surfactant, complexation, and many more are used for chemical and physical alteration. Liquisolid technology is a powder solution technology involves the conversion of a poorly water-soluble drug into dry free flowing powder. Excipients play vital role in this novel technology. It also overcome major challenges like bioavailability with low production cost.**

Index terms: Nanocrystals, Nano suspension, Liquisolid Technology *(Keywords)*

I. INTRODUCTION

IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units[1].There are three states of matter mainly – solid, liquid, and gas. The ability of a salute to dissolve in the solvent is known as solubility. The solubility of a substance depends solely on the properties of solvent, temperature and pressure. There is a limit of solute to be dissolved in a solvent and that point is called the point of saturation. The solvent in general are liquids that may be one whole liquid or may have 2 or more component [2]. The bigger portion of the solution is in general liquid, which can be consisting of one or more components. a solution may be of solid and liquid component but rarely have been heard of liquid-gas or solid-gas solutions. The components can be fully soluble (fully miscible) as like ethanol (CH3CH2OH) in water(H2O), can be poorly soluble such as like silver chloride(AgCl) in water (H2O). Condition in which solubility is very bad are known as insoluble[3].Dynamic equilibrium is required for solubility to happen, that can be explained as 2 process step, one step is the simultaneous and opposing processes of dissolution, the other step is phase joining. The rate during the process remains constant. Under specific conditions solubility during the equilibrium can be enhanced giving the supersaturated solution and these are metastable [4].

Solubility can also be interrelated as the quality to dissolve or quality of liquefaction but the in some cases dissolution may not be only cause but other reasons such as chemical reaction should also be considered[5]. The process of solubility is now used in various processes.

The major expression is concentration, either by mass, molarity, molality, mole fraction, or other units. There is specific condition of equilibrium for solubility to occur. The benefits of such is that it is simple, while the only problem is value of this constant is independent of other components [6].Flory-Huggins solution theory is a model to determine the solubility of polymers. Hansen Solubility Parameters and the Hildebrand solubility parameters are considered for the prediction of solubility. Enthalpy of fusion is a possibility to predict solubility via use of physical constant. [7, 8] partition coefficient (log p) is a measure of differential solubility of a compound in a hydrophobic solvent and a hydrophilic solvent. Hansen Solubility Parameters and the Hildebrand solubility parameters [9].

BCS (Biopharmaceutics classification system) is the guidance to be followed under U.S.F.D.A. (U.S. Food and Drug Administration). Parameters that are used are solubility and permeability.

Immediate release products are based on highest dose power of solubility. The intestinal permeability classification is determined by the comparison to the intravenous injections. Majority of the drug used worldwide is oral.

Classes of the drugs are
Class 1 - high solubility and permeability,
Class 2- low solubility and high permeability
Class 3- high solubility and low permeability
Class 4 - low solubility and permeability

II. LITERATURE REVIEW

Oral administration of drug is the most widely and most simple method of administration of drug because of its ease, compliance, good influence on cost, because of these factor many generic formulation are preferred to be oral bioequivalent[10].Solubility is also one of the key factor for consideration of drug that are administered as parenteral preparation[11]. Solubility is important factor to reach the required concentration. Requirement of the drug dose is inversely proportional to the solubility as to achieve the required plasma concentration can't be possible otherwise. lower aqueous solubility is one of the major issue faced during the development and research of the new formulation [12]. Water as the universal solvent is the first choice of solvent in liquid preparation. Many of the new chemical formulation are practically not soluble in the universal choice of solvent, because of the lower absorption leading to the poor and unstable bioavailability. Drug solubility is of the key determining and limiting factor for the orally administered formulation. It is the biggest problem faced by scientist [13].There are various method for the purpose of solubility enhancement that are decided under the perspective of considerable properties. Poor bioavailability is generally caused by lower solubility and poor dissolution

rate of poorly water soluble drugs. Under BCS class 2 (low solubility and high permeability), the bioavailability can be increased by increasing solubility and dissolution rate in the gastro-intestinal fluids [14].

III. SOLUBILITY ENHANCEMENT TECHNIQUES

Solubility improvement techniques are categorized as chemical & physical alteration of drug molecule. There are some other techniques as well.

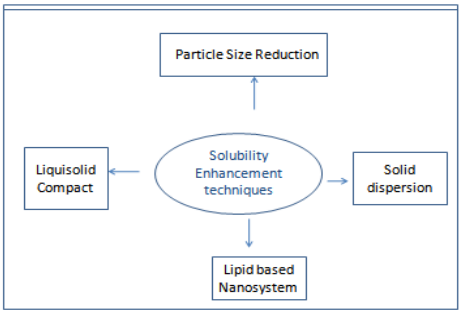

Fig. 1: Solubility enhancement techniques

Particle size reduction-

Particle size is the key determining factor for drug distribution in system as well as solubility within the system, as the surface area increases the absorption increases simultaneously [15]. Particle size reduction can be achieved by methods such combination and spray drying, mechanical stress is used or the purpose of particle size reduction. Particle size reduction is efficient, repeatable, reliable and economic [16, 17].

Micronization

Micronization is one of the other widely used methods for particle size reduction. The advantage of this process is that it helps increasing the rate of dissolution which is in result of increased in surface area but the stability (equilibrium) may not be as such. They technique involved in this are jet mill, rotor stator colloid mills. The saturation solubility becomes a reason micronization becomes an unsuitable option for particle size reduction. The heat produce becomes an issue during the process of spray drying and combination can cause thermos-instability.

Solid dispersions

The method was introduced by Sekiguchi and Obi, during their research the dissolution and generation of eutectic melts of a sulphonamide drug and a water soluble carrier, this assuring the 32s [18]. Solid dispersion is very famous in pharmaceutical technique for increasing the process of dissolution, absorption and therapeutic efficiency of the dosage form. There should be minimum 2 components generally they are a hydrophilic matrix and hydrophobic drug. Commonly used hydrophilic carrier are polyethylene glycols (PEGs), Plasdone-S630 and polyvinyl pyrrolidone (Povidone, PVP) [19, 20].

Hot melt method (fusion method)

The greatest advantage of using this method is its economic value and easy to do. Thai was proposed by Sekiguchi and Obi, their aim was to produce solid quick release medication. Drug with water soluble carrier are heated until they both melts together. Then the mixture is cooled as as it cools it solidifies quickly (ice baths and vigorous stirring). This cooled produce can be molded into tablet by the use of Moulds. The key factor for these formulation is composition, miscibility and the form of substance [21, 22].

Solvent evaporation Method

Tachibana and Nakamura [23] were the first to do this process of dissolve the components and evaporate the solvents under a vacuum to produce a solid formulation. The open the possibilities to manufacture a solid solution of highly water soluble carrier Povidone and highly lipophilic β-carotene. Scientist studied and researched about many other formulation such as naproxen, nimusulide and meloxicam using evaporation solvent. The highest point of advantage is the thermo-stability of drugs during the whole process. It is achieved by using the principle that under vacuum condition the temperature for evaporation decrease quite drastically becoming very lower. The worst possible scenario can be selection of components like volatile component [24].This technique opens the possibility of larger production. The end result is easier to handle a quite efficient with relation to the process of manufacturing [20]

Solid solutions and cryogenic techniques-

Cryogenic technique were developed to improve dissolution by manufacturing nano amorphous drug with more porosity at extremely low temperature. This technique is generally used for injectable (capillary, pneumatic, rotary, ultrasonic nozzle), location (under or above the level of liquid), and composition. Generally after cyrogenesis dry drug powder are obtained

Spray freezing onto cryogenic fluids-

This technique was invented by brigs and Maxwell, in this drug along as a mixture with water is atomized above the refringent.

Spray freezing into vapor over liquid-

Drug in the form of solution is freeze in cryogenic vapors and removal of frozen solvent takes place manufacturing uniform drug particles. Generally medication produced using this technique is highly wettable. The freezing takes place in vapor phase when contact takes place. Drug gets supersaturated in regions where atomized droplet remains unfrozen, drug particle may nucleate and grow [25].

Spray freezing into cryogenic liquid-

This technique is used for production of nanostructured amorphous aggregates, they have high surface area and improved wettable properties. Liquid-liquid impingement in directly incorporated between cryogenic liquid ad feed solution that is automized solution of feed. Because of this good atomization can be achieved which have quicker freeze rate [26].

- Chemical Modification: Change of pH, Use of buffer, Derivatization
- Micellar solubilization

Surfactants are used widely in pharmaceutical industries and they serve their function by improving dissolution performance of the test subject which got poor solubility. Use of surfactant gives reduced surface tension and it is the most aged method as it has been used from a very long time.

They are also used for the purpose of drug suspension. Critical micelle concentration is a point at which surfactants concentration in bulk after which formation of micelle becomes possible. Micelle can entrap the drug moiety inside and can increase the dissolution. Uses of surfactant also improve wettability. They are also used for stabilizing micro-emulsion.

Hydromorphic

It is a process involving solubilization. There is an addition of second solute which results in increased aqueous solubility of first solute. They are organic ionic salts, consisting of many alkali metal salts of organic acids.
The solubility increasing salts are known as 'salt in' and solubility decreasing salts are known as 'salt out' [27].

Lipid based Nano systems

For the preparation of lipid based Nano system, lipids are proved to be beneficial due to their ability to solubilize lipophilic molecules or their low harmful effects in the prepared formulation. Lipids are utilized for preparation of solid lipid Nanoparticles as well as nanostructured lipid carriers. The development of lipid based Nano system using DOE approach assures the quality of the final formulation [28-29]

Lipid Nanoparticles- Lipid Nanoparticles namely solid lipid Nano-carriers and nanostructured lipid carriers are easy to formulate on an industrial scale. As they have high stability, loading capacity and it provide control release of nanoparticles encapsulated in lipids.SLN is an aqueous dispersion made up of solid lipid, with one or more emulsifying agents which acts as stabilizers whereas nanostructured lipids are made up of oil as well as solid lipid which is further stabilized by an emulsifying agent.

Different variables with their effects on the responses are further confirmed via performing analysis of variance test. Various cubic and quadratic mathematical equations are made. The following table no. 1show recent studies on SLNs and NLCs [30]

Table 1. Formulations of solid lipid nanoparticles and nanostructured lipid carriers

S. No	Formulation	Variables	Remarks	Ref.
1	ofecoxib LSC	Liquid loading factor, Hardness of Tablet	Lf has great impact on in vitro release	39
2	Embelin LSC	Liquid loading factor, Angle of Repose	Angle of Repose also great influence	40
3	oClonazepam LSC	Conc. Of drug in PG, Disintegration time	PG conct. Effect on DT and Release	41

Nano suspension

Nano suspensions contain submicron colloidal dispersion of pharmaceutical active ingredient particles in a liquid phase stabilized by surfactants. Production of drugs as
Nano suspensions has been developed for drug delivery systems as an oral formulation and non-oral administration. Formulation has very poor solubility and Nano suspension indicates that the drug is the nano particle range, these nano particle are made stable by the use of surfactant for oral, parenteral, topical or pulmonary application [33].

Nano emulsion

These are thermodynamically unstable water-in-oil (w/o) or oil-in-water (o/w) nanoparticles emulsions which is stabilized by emulsifying agents and having a milky appearance. These systems can be formulated by applying similar design of experiment approach. Various formulations are:

Table 2. Various formulation of nanoemulsion

S. No	Formulation	Variables	Remarks	Ref.
1	Rifampicin loaded SLN	Drug conc., Particle Size	Particle size decreased with high concentration of emulsifying agent and homogenization pressure.	31
2	Budesonide loaded NLC	• Drug Conc. •Emulsifying agent, Particle Size	With higher conc. Of emulsifying agent and co-emulsifying agent, particle size decreased while high conc. Of drug, particle size increased.	32

Liquisolid Technology

Liquisolid technique act as a favorable technique for crushing challenges like solubility and bioavailability. These tasks are enhanced as rise in wetting properties and surface area of the drug usable for dissolution medium. It has good production capability and formulations are of lower cost. Patient compliance in oral route grabby the technology will be high. This study proves that Liquisolid technology can be used effectively for the poorly soluble drugs and this technique is truly favorable for BCS class II and class IV drugs [37] by using Liquisolid formulations, rapid release ratesof drug are obtained. Act as weapon to enhance the bioavailability ofhydrophobic drugs. They are used in probiotics. They possess good flow ability and compressibility [38].

Table 3. Various formulation of liquisolid compacts

S. No	Formulation	Variables	Remarks	Ref.
1	Doxorubicin loaded nanoemulsions	Lipid conc., Encapsulation efficiency .	A mixture of emulsifying agents, lipids and co-emulsifying agents concentration were significantly effective for higher entrapment efficiency	34
2	Epleregnone loaded nanoemulsion	Oil Conc. , Globule size	With higher concentration of oil, globule size increased	**35**
3	Eugenol loaded nanoemulsions	Oil Conc. , Globule size	High concentration of oil decreased Polydispersibility index,	**36**

Crystal Engineering

Surface area of a drug available is inversely proportional to particle size which means lower the particle size greater the surface area of drug. Particle size is a very important factor in determining dissolution rate and is dependent on crystallization. Common techniques are able to produce particle that have greater heterogeneity and cohesive. Crystal engineering was developed for the controlled and determined crystallization that produce highly efficient and pure drugs formulation. Polymorphs are produced by changing the crystallization techniques. As a result, drug with similar physiochemical properties may have different structure. For the market most thermodynamically stable formulation is selected [42-44].

IV. CONCLUSION

In oral formulation, dissolution is key factor for the measurement of therapeutic efficiency. Oral route of administration is the most preferred and simplest method of medicine administration. The methods and technology used discussed above gives us an idea about the increasing formulations dissolution. The properties of raw material describes the requirement for the processes such as equipment that are to be used, methods to be implemented. The efficient and defined selection of everything leads to uniform dosing and better patient compliance which also helps in the economic factors of pharmaceutical industries. Several properties are to be considered for choosing the method for the purpose of solubility enhancement such as solubility, physical and chemical properties, melting and boiling point, pharmacokinetic and pharmacodynamics nature etc. ,

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