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Solubility enhancement (Solid Dispersions) novel boon to increase bioavailability

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ABSTRACT

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Solubility is essential for the therapeutic effectiveness of the drug, independent of the route of administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. Poorly soluble drugs are often a challenging task for formulators in the industry Conventional approaches for enhancement of solubility have limited applicability, especially when the drugs are poorly soluble simultaneously in aqueous and in non-aqueous media. Drug with poor water solubility cause slow dissolution rates, generally show erratic and incomplete absorption leading to low bioavailability when administered orally. Solubilization may be affected by cosolvent water interaction, micellar solubilization, reduction in particle size, inclusion complexes, solid dispersion, and change in polymorph. Some new technologies are also available to increase the solubility like micro emulsion, self-emulsifying drug delivery system and supercritical fluid technology. This present review details about the different approaches used for the enhancement of the solubility of poorly water-soluble drugs include particle size reduction, nanonization, pH adjustment, solid dispersion, complexation, co-solvency, hydrotropy etc. The purpose of this article is to describe the techniques of solubilization for the attainment of effective absorption and improved bioavailability.

Keywords: Solubility, Solubility Enhancement, bioavailability, solid dispersion, Solid Dispersion, Solubilization.

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INTRODUCTION

It has been estimated that nearly 35-40 % of drugs suffer from poor aqueous solubility and it affects the absorption of drug from gastrointestinal tract that leads to high inter and intra subject variability, poor oral bioavailability, increase in dose, reduction in therapeutic efficiency and finally failure in formulation development[2,4]. Various formulation strategies like micronization, solubilization, complexation, dendrimers for drug solubilization, formation of solid solutions/dispersions with hydrophilic carriers, self-micro emulsifying drug delivery systems (SMEDDS). Nano particulate approaches spray drying, pro-drug approaches and salt synthesis had been attempted for solubility enhancement[12]. An attractive possibility would be represented by implementing a simple solid dispersion technique by utilizing several hydrophilic carriers. Such technique impart a means of reducing particle size to a nearly molecular level, presenting a variety of processing and excipients options which allow for flaccidity when formulating oral delivery systems of low water soluble drugs with cost effectiveness and denoting dose reduction. Solubility and dissolution. The solubility behaviour of a drug is a crucial determinant of its oral bioavailability[1]. There have been always certain drugs, for which solubility has conferred a challenge to the development of a suitable formulation for oral administration. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug moieties has increased suddenly and thus the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry[6]. The free energy (G) is a measure of the energy available to the system to perform work. Its value decreases during a continuously occurring process unless and until an equilibrium position is achieved when no further energy can be made available, i.e., $\Delta G=0$ at equilibrium[2,3,5]. The solution was developed when equilibrium is established between un-dissolved and dissolved solute components in a dissolution process is termed as saturated solution. The amount of substance that

passes into solution in order to establish the equilibrium at constant pressure and temperature and so produced a saturated solution is known as the solubility of the Consideration of the modified Noyes-Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral bioavailability of substance[5,6].

$$dC/dt = AD (Cs - C)/h$$

Where, dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, Cs is the solubility of the compound in a dissolution medium, C is the concentration of drug present in the medium at a time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound[12].The main possibilities or improving dissolution according to this analysis are to increase the surface area available for dissolution by decreasing the size of the particles present in the solid compound by optimizing the wetting phenomenon of the compound surface, to decrease the boundary layer thickness, to ensure sink conditions for dissolution and, last but not definitely the least, to enhance the apparent solubility of the drug molecules under physiologically relevant conditions[11,16]. The absorption of drug from the gastrointestinal (GI) tract can be limited by several factors with the most important contributors being poor aqueous solubility and/or poor membrane permeability of the drug molecule. While delivering an active agent orally, it is very much important that it must dissolve in gastric and/or intestinal fluids before it can reach systemic circulation through GI membrane permeability. Hence, a drug with poor aqueous solubility will exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will basically exhibit permeation rate limited absorption. Thus, two areas of pharmaceutical research that focus on improving the oral bioavailability of the active agents include enhancing solubility and dissolution rate of poorly water-soluble drugs and increasing the permeability of poorly permeable drugs. Several Approaches for enhancement of drug dissolution/ bioavailability of poorly soluble drugs[17,43]

I. PHYSICAL MODIFICATIONS [15,18]

- Particle size
- Micronization
- Nanoionization
- Modifications of the crystal habit
- ✓ Polymorphs
- ✓ Pseudo polymorphs (including solvates)
- Complexation/solubilization
- ✓ Utilization of surfactants
- ✓ Utilization of cyclodextrines
- Dispersion of Drug in a carrier
- ✓ Solid dispersions (non-molecular)
- ✓ Solid solutions

II. Chemical modifications [22,26]

- Salt formation
- Co Solvency
- Co-Crystallization
- Nano technology
- Hydrotrophy
- Solubilizing Agent

III. Other [17,19]

- Hot Melt Extrusion
- High Pressure Homogenization
- Solvent Evaporation Method
- Polymeric Alteration
- Super Critical Method
- Electrostatic Sppining Method
- Spray Freezing in to liquid & Lyphophillization Tech.
- Lyphophilization Tech.
- Direct Capsule Filling
- Inclusion Complexes
- ✓ Kneading Method
- ✓ Co-precipitation
- ✓ Spray Drying

Physical Modifications

(a) Particle Size Reduction

The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound[14,18]. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermo sensitive or unstable active compounds. Using traditional approaches for nearly insoluble drugs may not be able to enhance the solubility up to desired level[8,29.]

(b) Micronization

Micronization is another conventional technique for the particle size reduction. Micronization increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility. Decreasing the particle size of these drugs, which cause increase in surface area, improve their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so forth micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug[13,14].

(c) Nanosuspension

Nanosuspension technology is important tool for solubility enhancement of poorly soluble drug. A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspensions is between 200 and 600 nm[12,42.] In nanosuspension the particle size of drug reduce which

increase the surface area and therefore the dissolution rate and solubility increases which enhance bioavailability. Basically Nanosuspension is submicron colloidal dispersion of pure particles of drug which is stabilized by surfactants. Compounds that are insoluble in water (but are soluble in oil) with high log P value, high melting point and high doses for that nanosuspension is favourable method. Nanosuspension technology can also be applicable for drugs which are insoluble in both water and organic solvents[16,17,30].

Advantages of nanosuspension

1. This method improves the solubility and bioavailability of drug which gives rapid onset of action.

2. To increase the bioavailability of drugs with high log P value can be formulated as nanosuspensions.

3. Dose reduction is possible.

(d) Modification of Crystal Habit[22]

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability[41,44]. Similarly amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase in surface area. Order for dissolution of different solid forms of drug.

Amorphous >Metastable polymorph >Stable polymorph

(e) Complexation

Complexation is the association between two or more molecules to form a non bonded entity with a well defined stichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Ex. of complexing agents are; chelates- EDTA, EGTA, molecular complexes- polymers, inclusion complexes cyclodextrins[22,23].

(f) Solubilisation by Surfactants

Surfactants are molecules with distinctpolar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or non-ionic. When smallpolar molecules are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension but increases solubility of drug within an organic solvent.

II CHEMICAL MODIFICATIONS[16,33]

(a) Salt Formation

Salt formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt having more solubility than respective drug. Ex. Aspirin, Theophylline, Barbiturates.

(b) Co-crystallization

New approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. A co-crystals may be defined as crystalline material that consist of two or more molecular (and electrical neutral) species held together by non-covalent forces. It can be prepared by evaporation of a heteromeric solution or by grinding the components together or by sublimation, growth from the melt and slurry preparation. It is increasingly important as an alternative to salt formation, particularly for neutral compounds[20,24].

(c) Co-solvent

It is well-known that the addition of an organic co-solvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water by the adding water miscible solvent in which the drug has good solubility the solubility of a poorly water soluble drug can be increased frequently known as co solvents also known as solvent blending. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterally[29-30]. It is also commonly referred to as solvent blending. Most co solvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water[19,25]. By disrupting waters self-association, co solvents reduce waters ability to squeeze out nonpolar, hydrophobic compounds, thus increasing solubility.

Advantages

1. Compared to other solubilisation approaches very high drug concentrations of poorly soluble compounds can be dissolved.

2. Co- Solvents can enhance the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent.

3. It is Simple and rapid method to formulate and produce.

(d) Hydrotropy[33]

It designates to increase in solubility in water due to presence of large amount of additives.It improves solubility by complexation involving weak interaction between hydrophobic agents (Sodium benzoate, sodium alginate, urea) and solute. Ex.Sublimation ofTheophylline with Sodium acetate and Sodium alginate[26].

(e) Solubilising agents

The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. PEG 400 is improving the solubility of hydrochlorothiazide.

(f) Nanotechnology Approach

Nanotechnology will be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometres (nm) or less[20].

SOLID DISPERSION

Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs. Sekiguchi and Obi were the first to describe on solid dispersions in 1961. Solid dispersion is one of the important strategies to tackle dissolution rate limited oral absorption of poorly soluble compounds. Formulation of poorly soluble compounds as solid dispersions might lead to particle size reduction, improved wetting, reduced agglomeration, changeability in the physical state of the drug molecules and possibly a dispersion in the molecular level, according to the physical state of the solid dispersion. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a

hydrophobic drug. The matrix can be either crystalline or amorphous[24,25]. The drugs can be dispersed molecularly, either in amorphous particles (clusters) or in crystalline particles. Solid dispersion Solid dispersions are classified by various ways, on the basis of their solid state structure as well as on the basis of carrier used. It is relevant to classify various systems of solid dispersion as per as their fast release mechanisms are concerned. Riegelman and Chiou classified solid dispersions into the following six representative types: Simple eutectic mixtures, amorphous precipitations in a crystalline carrier, solid solutions, glass solutions and glass suspensions, compound or complex formation, and combinations of the previous five types.

Classification of Solid Dispersion[12,27,33]

Solid dispersion classified in 3 groups.

1. First generation solid dispersions: In first generation solid dispersion, formulation of eutectic mixtures or molecular dispersion improved the rate of drug release which in turn increases the bioavailability of poorly water soluble drugs. Disadvantage related formulation of crystalline solid does not release drug quickly. Example: Crystalline carriers: Urea, Sugars and Organic acids.

2. Second generation solid dispersion: In second generation we use amorphous state of carrier which improves drug release; likes fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), ethylcellulose or hydroxypropyl cellulose or starch derivates, like cyclodextrins.

3. Third generation solid dispersion: In third generation we use carrier which have surface activity and self-emulsifying property. The surfactants decrease the recrystallization of drug and thus improve the solubility of drug. Example: Surface active self-emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14[27].

Types of solid dispersions [16-32]

a. Simple eutectic mixture: An eutectic mixture of a sparingly water soluble drug and a highly water soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component. The increase in surface area is mainly responsible for increased rate of dissolution. This led to a conclusion that the increase in dissolution was mainly due to decreased particle size.

b. Solid solutions: Solid solutions consist of a solid solute dissolved in a solid solvent. A mixed crystal is formed because the two components crystallize togetherin a homogenous one-phase system. Hence, this system would be expected to yield much higher rates of dissolution than simple eutectic systems

c. Glass solution of suspension: A glass solution is a homogenous system in which a glassy or a vitreous of the carrier solubilizer drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent.

d. Compound or complex formation: This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of the drug from the complex is dependent on the solubility dissociation constant and the intrinsic absorption rate of the complex[31].

e. Amorphous precipitation: Amorphous precipitation occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug[19,27].

Advantages of solid dispersion

1. Reduction in particle size: different carrier use in solid dispersion reduces particle size of drug particle which improve solubility and bioavailability.

2. Improve wettability of particle: solid dispersion improves wettability of particle.

3. Improve porosity: Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate

4. Improve dissolution which ultimately improves the solubility and bioavailability.

Disadvantages of solid dispersion

1. Instability due moisture content.

2. Difficulty in incorporating into formulation of dosage forms

Manufacturing methods of solid dispersion

1. **Solvent evaporation method:** In solvent evaporation method we dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. Tachibechi and Nakumara were the first to dissolve both the drug (β-carotene and the carrier PVP) in a common solvent and then evaporate the solvent under vacuum to produce a solid dispersion. Commonly use solvent such as ethanol, chloroform, or a mixture of ethanol and dichloromethane. In some case cosolvant may use because large volume of solvents as well as heating may be required to enable complete dissolution of drug and carrier. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. The disadvantages of solvent method such as; expensive, ecological, and difficult to find common and removable solvents, difficulty in completely removing liquid solvent, difficulty of reproducing crystal form[24,27].

2. **Fusion/melting method[39]:** The physical mixture of a drug and a water-soluble carrier was heated directly until it gets melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved which improve the solubility and bioavailability of drug. Limitation regarding this method is at high temperature many drug may get degraded.

3. **Hot melt extrusion[30-38]:** HME can be simply defined as the process of forming a new material (the extrude) by forcing it through an orifice or die under controlled conditions, such as temperature, mixing, feed-rate and pressure. HME differs from simple extrusion in that, polymer, drug and excipients blends are mixed thoroughly in the molten state in this process, needing no solvents for granulation. The molten polymer serves as the thermal binder[19,23].

Advantage of HME

1. Improve the solubility and bioavailability of poorly soluble compounds.

2. Processing in the absence of solvents and water.

3. Economical process with reduced production time, fewer processing steps, and a continuous operation.

4. Uniform dispersion of fine particle occurs.

5. Good stability at varying pH and moisture levels.

6. Safe application in humans due to their non swellable and water insoluble nature.

Disadvantages of HME

1. Not applicable to heat sensitive material.

2. Limited number of available polymer.

3. This method requires high energy input.

Application of HME

1) Masking the bitter taste of an active drug.

2) Formation of polymer-drug solutions/dispersions which increased drug solubility and increased drug dissolution rate.

3) Formulation of controlled release dosage forms (including implants).

4) Formulation of targeted release dosage forms.

4. **Super Critical Fluid Method:** (SCF) Super critical fluid is fluid which exists as single fluid above its critical temperature and pressure.SCF shows the properties of both a liquid and a gas above its critical condition. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drug particles are solubilised within SCF, they may be re-crystallized at greatly reduced particle sizes[27].Carbon dioxide is the most commonly used SCF because it is chemically inert, non toxic and non flammable. Other supercritical solvents include nitrous oxide, ethylene, propylene, propane, npentane, ethanol, ammonia, and water.

5. **Liquisolid method:** In liquisolid technique liquid may be transfer into free flowing, readily compressible and apparently dry powder by simple blending with selected carrier and coating material. The liquid portion which can be liquid drug, drug suspension or drug solution in a suitable non volatile liquid vehicle can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. The acceptable flowing and compressible powder form of liquid medication is liquisolid compact. The liquisolid is newer and promising approach because of simple manufacturing process, low production coast, and applicable for industry due to good flow and compact property of liquisolid formulation[28-33.] When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibers in its interior as cellulose, both absorption and adsorption take place; i.e. the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics[19,23].

The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. Non-volatile solvent present in the liquisolid system facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface.

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Classification of liquisolid system[26-40]

Classification based on type of liquid medication contain there in:

1. Powdered drug solutions.

2. Powdered drug suspensions.

3. Powdered liquid drugs.

Classification based on technique use for formulation

1. Liquisolid compacts.

2. Liquisolid Microsystems

Advantages of liquisolid method:

1. Method improves the solubility and bioavailability of orally administered water insoluble or poorly soluble drugs.

2. Method is applicable in industry.

3. Useful for the formulation of oily drugs/liquid drugs.

4. By using different carrier and additives drug release can be modified like PVP, PEG 60000, Hydroxy Propyl Methyl Cellulose and Eudragit etc.

5. A number of poorly soluble drugs can be formulated in to the system.

6. Production cost is low compared to that of preparation of soft gelatin capsules

7. This system is specifically for the powdered liquid medications.

Disadvantages of liquid solid method

1) High solubility of drug in the non-volatile liquid drugs for the improvement of dissolution rate and bioavailability.

2) It requires recipients of high adsorption properties and high specific surface area.

3) It is not applicable to high dose insoluble drugs (>100 mg).

4) During compression sometimes liquid drug may be squeezed out of the tablet result in improper hardness[21-27].

6. **Self-emulsifying system:** SEDDS or SMEDDS are the important method to improve the solubility and bioavailability of poorly water soluble drug. SEDDS are define as isotropic mixture natural or synthetic oils, solid or liquid surfactant, or alternative, one or more hydrophilic solvent and co-solvent/surfactant[22-40]. SEDDSs typically produce emulsions with a droplet size between 100–300 nm while self-micro-emulsifying drug delivery systems

(SMEDDSs) form transparent micro-emulsions with a droplet size of less than 50 nm. Upon mild agitation followed by dilution in aqueous media, such as GI fluids, these systems can form fine oil–in–water (o/w) emulsions or micro-emulsions (SMEDDS).Self emulsifying formulations spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification[23,27]. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDS are physically stable formulations that are easy to manufacture.

Composition of SEDDS:[36-37] The composition of self emulsifying system is simple combination of drug, oils, surfactant and co surfactant or co-solvent. The self-emulsifying process depends on: The nature of the oil and surfactant. The concentration of surfactant The temperature at which self-emulsification occurs

1**. Oils:** Oils can solubilise the lipophilic drug in a specific amount. Oil can facilitate self-emulsifying and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, increasing absorption from GIT. Example; olive oil, oleic oil, sesame oil.

2. **Surfactant:** Non-ionic surfactant with high hydrophiliclipophilic balances (HLB) value is used in the formulation of SEDDS. High HLB and hydrophilicity of surfactant assists the immediate formulation of o/w droplets and rapid spreading of formulation in the aqueous media. Example; Tween, Labrasol, cremophore etc.

3. **Co-surfactant/ co-solvent:** Dissolve large amount of hydrophilic surfactant or hydrophobic drugs in lipid phase. It increases fluidity of the interfacial film. Example: ethanol, propylene glycol, polyethylene glycol, polyoxyethlene, propylene carbonate tetrahydrofurfuryl alcohol, Glycofurol etc. Mechanism of self emulsification: Self-emulsification takes place when the entropy change favouring dispersion is greater than the energy required to increase the surface area of the dispersion[23-37.]

The type of self emulsifying dosage form includes Self emulsifying tablet, capsule, pellets, solid dispersion, powder ets. Method use for preparation of self emulsifying system is melt granulation, spray drying, capsule filling, and melt extrusion ets.

Advantages of Self Emulsifying system[19,23]

a. Improvement in oral bioavailability enabling reduction in dose.

b. Ease of manufacturing and scale up.

c. High drug loading efficiency.

d. Protection of drugs from the gut environment

e. More consistent and reproducible profile of drug absorption and blood time profile.

Disadvantages of Self Emulsifying system

a. High surfactant concentration irritates the GIT.

b. Chemical instability of drug and surfactant in formulation

7.Complexation: Complexation is the association between two or more molecules to form a non bonded entity with a well definedstochiometry. In Complexation relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions involved.

Two type of complex available [20-35]

1. Stacking complexes: It is driven by association of non polar area of drug and complexes agent this results in exclusion of the non polar area from contact with water, thereby reducing total energy of the system. Stacking can be homogeneous or mixed, but results in clear solution.

2. Inclusion complexes: It is formed by the inserting the nonpolar molecule or the nonpolar region of one molecule into the cavity of another molecule or group of molecules. There are no forces involved between them and therefore there are no bond is also called as no-bond complexes[33-36]. Cyclodextrins are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α, ß, and γ-CD are composed of six, seven, and eight D-(+) -glucopyranose units[13,14]. Cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. Cyclodextrine and their derivatives commonly use in Complexation. They form complex with drug and improve the solubility and bioavailability of poorly soluble drug. Derivatives of R-cyclodextrin with increased water solubility (e.g. hydroxypropyl-Rcyclodextrin HP-R-CD) are most commonly used in pharmaceutical formulation. The forces driving complexation were attributed to:

1. The exclusion of high energy water from the cavity.

2. The release of ring strain particularly in the case of –CD.

3. Van Der Val's interactions.

4. Hydrogen and hydrophobic bindings.

Solid inclusion complexes can be prepared by using following methods

1. **Kneading method:** This method is based on impregnating the CDs with little amount of water or hydro alcoholic solutions to converted into a paste. The drug is then added to the above paste and kneaded for a specified time. The kneaded mixture is then dried and passed through sieve.

2. **Co-precipitation:** In this method, in the solution of CDs the required amount of drug is added. The complex kept under magnetic agitation with controlled process parameters. The complex is protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex. This method is applicable to industry [6,13].

3. **Physical blending method:** It is simple trituration method. In this method the CDs and drug are mixed together thoroughly by trituration in a mortar and passes through appropriate sieve to get the desired particle size in the final product[11].

4. **Neutralization method:** In this method precipitation of inclusion compounds by neutralization technique take place .in this dissolve the drug in alkaline solutions like sodium/ammonium hydroxide and mix with an aqueous solution of CDs. The clear solution is obtained. This solution is neutralising under agitation using hydrochloric acid solution till reaching the equivalence point. A white precipitate is being formed at this moment. This precipitate is filtered and dried[13,14.]

5. **Milling/Co-grinding technique:** By using this method a solid binary inclusion compounds of drug and CD is prepared. In this method Drug and CDs are mixed intimately and the physical mixture is introduced in an oscillatory mill and grinded for suitable time. Ball mill is also use for preparation of binary complex[13,14].

6. **Lyophilisation/ Freeze drying technique:** Lyophilisation/ freeze drying technique is considered as a suitable technique to get a porous, amorphous powder with high degree of interaction between drug & CD[13,14,15]. This technique is suitable for thermo labile substances. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug & CD at reduced pressure is form.

7. **Microwave irradiation method:** In this technique the microwave irradiation reaction between drug and complexing agent takes place using a microwave oven. The drug and CD in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for short time of about one to two minutes at 60ºC in the microwave oven[16,17]. After the reaction completes, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual, uncomplexed free drug and CD. The precipitate so obtained is separated using whatman filter paper, and dried in vacuum oven at 40ºC for 48 hrs. Microwave irradiation method is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of the product[31.]

8. **Supercritical antisolvent technique:** In the supercritical fluid antisolvent technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heatlabile pharmaceuticals. This method is important for improving bioavailability of pharmaceutically active compounds. Supercritical carbon dioxide due to its properties of improved mass transfer and increased solvating power it proved as a new complexation medium[22,18]. In this technique, first, drug and CD are dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti-solvent). When the solution is sprayed into supercritical fluid antisolvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent[29-30]. Because of the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow.

CONCLUSION

Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. The basic approaches followed by all the currently available technologies engaged in the solubility and dissolution enhancement is to maximize the bioavailability and therapeutic efficacy. To overcome the solubility problem various solubility enhancement methods are develop today which is industrial applicable. By using newer techniques which are discussed above it is possible to improve solubility of poorly water soluble drugs. By this article we conclude that, Solubility is the most important physical characteristic of a drug for its oral bioavailability, formulation, development of different dosage form of different drugs, therapeutic efficacy of the drug and for quantitative analysis. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, reduce frequency of dosing and better patient compliance combined with a low cost of production. The different techniques described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds increase in solubility. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

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