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Solid Dispersion-A Versatile Technique To Enhance Solubility-A Review.

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ABSTRACT

Since decades, it has become a challenging task to the scientist to enhance the solubility of poorly water-soluble drugs to improve their bioavailability which are given in oral route, by enhancing the dissolution rate which could be the rate-limiting step in the process of absorption of drug from a solid dosage form of insoluble or poorly water-soluble drugs. Based on research, the number of new drug entities which are poorly water-soluble in nature has adequately increased. Currently, 88-90% of new drug candidates which are highly potent are poorly water-soluble. The review article focuses on one of simple, novel technique i.e. solid dispersion to enhance the solubility of poorly water-soluble drugs. The review mainly portrays advantages, disadvantages, various techniques available and applications.

Keywords: Solubility, bioavailability, solid dispersion, absorption, poorly water soluble.

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INTRODUCTION

"Solubility is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature or pressure"[1]. Solubility is fundamentally depends on the solvent system used. Administration of drugs in the oral route is the most common and preferred route of administration due to ease, convenience, flexibility to the consumer but because of many reasons most of the drugs cannot be taken in oral route due to their poor solubility, hence leading to poor bioavailability. Therapeutic effectiveness of a drug depends upon the dissolution, bioavailability and ultimately upon the solubility of drug molecules.[2] Solubility is one of the important ways to achieve the desired concentration of drug in systemic circulation and hence can be defined concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, and in another word can be describe as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.[3]

Advantages of Solid Dispersions[4]**:**

- Change in water solubility will effects on be enhancing drug bioavailability has been possible by solid dispersion.
- Solid dispersion improves wettability of the particle.
- Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate and bioavailability.
- Solid dispersions are more efficient than the traditional techniques, since the latter a particle size reduction limit around 2-5 mm which is not enough to improve considerably the drug solubility or drug release in the small intestine.[1]
- Increased extent of absorption, increase in dissolution rate and reduction in pre-systemic metabolism can be possible.
- Transformation of liquid form of the drug into solid form.[1]
- Parameters, such as carrier molecular weight, composition, drug crystallinity, particle porosity and wettability can be successfully controlled which in turn can produce improvements in bioavailability.

Disadvantages of Solid Dispersions[5]

- Most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate.
- One of the disadvantage of solid dispersions is their poor scale-up for manufacturing.

Applications of Solid Dispersions[6]

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications.

- To achieve a homogeneous distribution of a small quantity of drug in solid state.
- To convert the unstable drug to stable drug.
- To dispense liquid or gaseous compounds in a solid form.
- To formulate a fast release initial dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone. Polymorphs in a given system can be converted into isomorphs, solid solution, eutectic or molecular compounds.
- To increase the solubility of poorly soluble drugs thereby increase the rate of dissolution, absorption, and bioavailability.
- To stabilize unstable drugs against hydrolysis, oxidation, isomerisation, photo oxidation, and other decomposition procedures.
- To reduce side effect of certain drugs.
- Masking of unpleasant taste and smell of drugs.

- Improvement of drug release from ointment, creams, and gels.
- To avoid undesirable incompatibilities.
- To obtain a homogeneous distribution of a small quantity of drug in solid state.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

SOLID DISPERSION SYSTEM

Defining the term solid dispersion as "A dispersion involving the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures." 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 in the amorphous or crystalline form[7]. The drug is either dispersed molecularly in amorphous clusters or crystalline particles. Solid dispersions are categorised into six types based on their molecular arrangement.

1. Simple Eutectic Mixture.
2. Solid Solution
    - Continuous Solid Solution.
    - Discontinuous Solid Solution.
    - Substitutional Crystalline Solid Solution.
    - Interstitial Crystalline Solid Solution.
    - Amorphous Solid Solution.
3. Glass Solution and Glass Suspension
4. Drug dispersion in carriers
    - Hot melt method
    - Hot stage Extrusion
    - Solvent evaporation method
    - Melting –solvent method
5. Use of surfactant
6. Complexation
    - Staching complexes
    - Inclusion complexes
    - β-cyclodextrin inclusion complexes

Simple Eutectic Mixture

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. It is prepared by rapid solidification of fused melt of two components that show complete liquid miscibility but negligible solid-solid solution [8]. Solid eutectic mixtures are generally prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability. [9]

Solid Solution[10]

Solid solutions are compared to liquid solutions, consisting of one phase irrespective of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum *viz.* The molecular dimensions and the dissolution rate is determined by the dissolution rate of the carrier. They are classified according to their miscibility as continuous and discontinuous solid solutions and according to the way in which the solvate molecules are distributed in the solvent as substitutional and interstitial solid solutions

Continuous Solid Solution

Components are miscible in all proportions in continuous solid solutions. Theoretically, the bonding strength of each of the individual component between the molecules is weaker than the bonding strength of molecules between two components.

Discontinuous Solid Solution[11]

The solubility of each of the components in the other component is limited in discontinuous solid solutions. The mutual solubilities of the two components start to decrease below a certain temperature. The term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component.

Substitutional Crystalline Solid Solution

Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

Interstitial Crystalline Solid Solution[12]

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. To occupy interstitial space, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

Amorphous Solid Solution[13]

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Certain carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose.

Glass Solution and Glass Suspension[14]

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature (T_g). On heating, it softens progressively and continuously without a sharp melting point.

Drug dispersion in carriers

Dispersion of drugs in carriers can be achieved by following methods.

- Hot melt method
- Hot melt Extrusion
- Solvent evaporation method
- Melting –solvent method

Hot melt method[15]

The solid dispersion approach to reducing particle size and therefore increase the dissolution rate and absorption of drugs was first recognized in 1961. The term “solid dispersions” refer to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared either by melting (fusion) method

or solvent method or fusion solvent-method. Novel additional preparation techniques have included rapid precipitation by freeze drying and using supercritical fluids and spray drying, often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. The method of preparation includes melting of the drug and carrier in molecular dispersion together and cooling in an ice bath to get supersaturated. Due to solidification dispersed the drug get trapped in a carrier matrix. The resultant solid mass was pulverized and sifted to the required size.

Examples

The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, and Plasdone-S630. Many times surfactants may also be used in the formation of the solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68, and Sodium Lauryl Sulphate used.

Applications

The solubility of etoposide, glyburide, itraconazole, ampelopsin, valdecoxib, celecoxib, and halofantrine can be improved by solid dispersion using suitable hydrophilic carriers.

Hot-melt extrusions

Hot melt extrusion (HME) is the process of applying heat and pressure to melt a polymer and force it through an orifice in a continuous process. HME is a well-known process, developed to produce polymer products of uniform shape and density. It is one of the most widely applied processing technologies in the plastic, rubber and food industries and is used to prepare more than half of all plastic products including bags, films, sheets, tubes, fibres, foams, and pipes. HME has more recently been applied to the health-care industry where it is used to manufacture medical devices and to mix active pharmaceutical ingredients (APIs) with polymers to enhance the API's bioavailability [16].

Advantages [17]

- This technique protects drug susceptible to oxidation and hydrolysis by complete elimination of oxygen as well as moisture from the mixture [1].
- Improve the solubility and bioavailability of poorly soluble compounds.
- Processing in the absence of solvents and water.
- Economical process with reduced production time, fewer processing steps, and continuous operation.
- Uniform dispersion of the fine particle occurs.
- Good stability at varying pH and moisture levels.
- Safe application in humans due to their non-swellable and water insoluble nature.

Disadvantages [18]

- Not applicable to heat sensitive material.
- A limited number of the available polymers.
- This method requires high energy input.
- HME is complex mixture of the active drug and excipient.

Examples of general excipients used in HME Polyethylene glycol, Polyethylene oxide, Hydroxypropyl cellulose, Hydroxypropyl methyl cellulose, Poly(dimethylamino ethyl methacrylate-co-methacrylate ester), Ammonio-co-methacrylate copolymer and cross-povidone.

Application of HME [19]

- To mask the bitter taste of an active drug.
- Formation of polymer-drug solutions/dispersions which increased drug solubility and increased drug dissolution rate.

- Formulation of controlled release dosage forms (including implants).
- Formulation of targeted release dosage forms.
- Prednisolone, Carbamazepine, and Nifedipine were developed in HME to increase the solubility.

Solvent evaporation method[20]

The drug and carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. An important prerequisite for the manufacture of a solid dispersion using the solvent evaporation method is that both the drug and the carrier are sufficiently soluble in the solvent. The solvent can be removed by various methods like by spray-drying or by freeze-drying Temperatures used for solvent evaporation generally lie in the range 23-65℃.

Disadvantages

- Effect of solvents on the environment and high cost of production due to the extra facility for removal of solvents.
- Due to the toxicity potential of organic solvents employed in the solvent evaporation method, hot melt extrusion method is preferred in preparing solid solutions.

Application

The solid dispersion of the 5- lipoxygenase/cyclooxygenase inhibitor ER- 34122 shown improved *in-vitro* dissolution rate compared to the crystalline drug substance which was prepared by solvent evaporation.

Melting –solvent method[21]

A drug is first dissolved in a suitable liquid solvent and then this solution is incorporated into the melt of polyethylene glycol, obtainable below 70°C without removing the liquid solvent. The selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also polymorphic form of the drug precipitated in the solid dispersion may get affected by the liquid solvent used.

Use of Surfactants[22]

The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent. Surfactants are amphiphilic in nature having a polar end (the circular head) and non-polar end (the tail). Most surfactants consist of a hydrocarbon segment connected to a polar group can be anionic, cationic, zwitterionic or nonionic. Small molecules of polar molecules can be accumulated into the hydrophobic core of micelles[7]. When a surfactant such as Tween-80, sodium lauryl sulfate is placed in water, it will form micelles. A nonpolar drug will partition into the hydrophobic core of the micelle and the polar tail will solubulize the complex. This has been illustrated improvement of wetting characteristics and micellar solubilization.

Advantage Biodegradable biosurfactants gives low toxicity, better surface area, and interfacial activity.

Disadvantage Patent rights, scale-up manufacturing process may not be possible.

Complexation

Complexation is the association between two or more molecules to form a non-bonded entity with London forces, hydrogen bonding and hydrophobic interactions [9]. There are many types of complexing agents and major three are listed below.

- Staching complexation
- Inclusion complexation
- Cyclodextrin Inclusion Complexes

Staching complexation[11,12]

Staching complexes are formed by the overlap of the planar regions of aromatic molecules. Nonpolar moieties tend to be squeezed out of the water by the strong hydrogen bonding interactions of water and causes some molecules to minimize the contact with water by aggregation of their H-C moieties and the phenomenon is called as self-association. This aggregation is favored by large planar non-polar regions in the molecule. Stached complexes can be homogeneous or mixed.[12].

Examples: For staching complexes are as Nicotinamide, Anthracene, Pyrene, Methylene blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene, etc.

Preparation: Considerable increase in solubility and dissolution rate of the drug has been achieved by the use of cyclodextrins. These complexes can be prepared with ß-cyclodextrin (ß-CD) and HP-ß-CD, the required quantity of ß-CD is weighed and water added to get tough consistency. To the mass, weighed quantity of the drug is added. The mixture is kneaded in a glass mortar for one hour and then completely dried in hot air oven at 60°C for 2 hours. The dried mass is sieved through the proper mesh.

Inclusion complexation[23]

Inclusion complexes are formed by the insertion of the non-polar molecule or the non-polar region of one molecule (known as a guest) into the cavity of another molecule or group of molecules (known as a host). The major structural requirement for inclusion complexation is a comfortable fit of the guest into the cavity of host molecule. The cavity of the host molecule must be large enough to accommodate the guest and small enough to eliminate water as well so that the total contact between the water and the non-polar regions of the host and the guest is reduced [6,11].

Cyclodextrin Inclusion Complexes

Cyclodextrins (CD) are bucket-shaped cyclic oligosaccharides composed of 6,8 dextrose units (α, β, γ CD) respectively joined through C-C double bonds. The interior of these molecules is lipophilic, and exterior of these molecules is hydrophobic. Lipophilic molecules can be incorporated into the interior cavity of CD leading to better stability, high water solubility, and increased bioavailability or decreased undesirable side effects. The presence of hydroxyl groups on the external surface of the CD molecule increases the possibility of hydrogen bonding with the drug molecules resulting in the formation of non-inclusion complexes as well.

Examples: 2-hydroxypropyl- β cyclodextrin, methyl β cyclodextrin etc., are widely used due to high water solubility and low toxicity.

Applications: The complex of praziquantel with β CD showed significantly improved dissolution profile compared with that of the pure drug, here hydrophobic CD can act as sustained release carriers for water-soluble drugs. The inclusion complexes of aceclofenac with hydroxypropyl-β-cyclodextrin provided increased dissolution rates as well as improved therapeutic effect [24].

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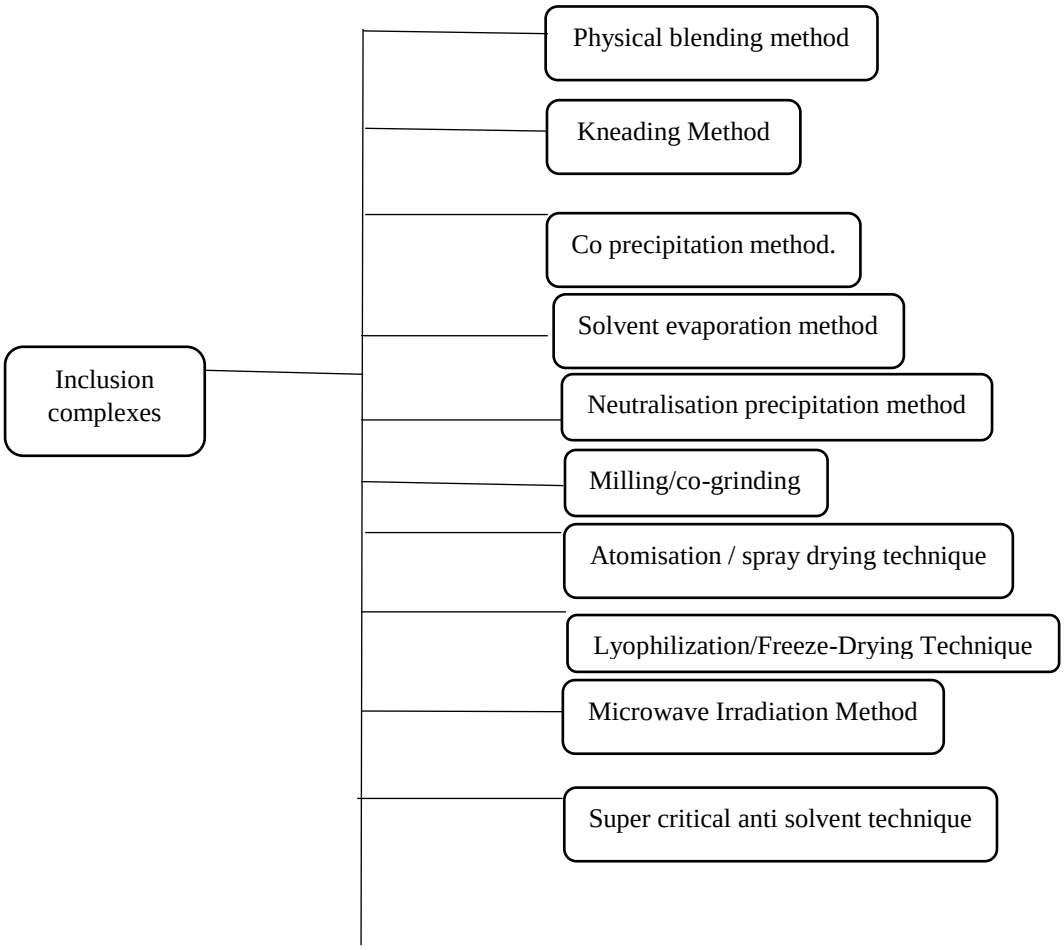
APPROACHES FOR MAKING OF INCLUSION COMPLEXES[25]

Preparation: The drug – CD complexes are prepared by following approaches



Physical blending method

The drug and cyclodextrins are mixed physically by trituration method using mortar and pestle, sifted to get the desired size under lab scale. The drug and cyclodextrin are blended extensively in rapid mass granulator for 30 min, sifted to get desired sized particles under large scale. The prepared mixtures are stored at controlled temperature and humidity conditions.

Kneading method

Mixing of CD with a small amount of water or hydro-alcoholic solvent to form a paste, add the drug to it and knead for a particular period of time. The mixture is dried, comminuted, sifted by using mortar and pestle in laboratory scale. Extruders are used to do the kneading and to form inclusion complexes.

Co-precipitation technique

This involves co precipitation of drug and cyclodextrin in a complex. To the CD required quantity of drug is added under agitation and mixture is protected from sunlight. The precipitate so formed is vacuum filtered, dried at room temperature. This method gives drug-cyclodextrin complexations and abrupt changes of temperature with organic solvent addition giving to precipitate of material. This method is little attracted in large scale production due to its high yield, usage of organic solvent and larger preparation time.

Solution/solvent evaporation method

This is an alternative method for spray drying technique. This involves dissolving or molecular dispersion of drug and CD agitated separately into a mutually miscible solvent, agitated for 24 hrs, finally evaporation of the solvent under vacuum at 45℃ to get inclusion compounds. Generally aqueous or hydro-alcoholic solvents are used. The dried powdered mass was obtained so was pulverized and sifted through 60 mesh sieve.

Neutralization precipitation method

This relies on inclusion compound achieved by neutralization. This method involves dissolving of the drug in alkaline solution ($NaOH/NH_4OH$) and mixing it with an aqueous solution of CD. The resultant solution is agitated with acid till endpoint is reached. Consequently, a white color precipitate is formed corresponds to the formation of the inclusion compound. The precipitate so obtained is filtered and dried. The drugs susceptible to acid or alkaline undergoes degradation is the only limitation with this method.

Milling/Co-grinding technique

This method involves milling and grinding of drug and CD with the help of mechanical devices to form solid binary inclusion compounds. Drug and cyclodextrins are physically mixed, ground for certain time by using mortar and pestle or ball milling to attain a binary mixture and sifted to achieve the desired size.

Atomization/Spray drying method

In pharmaceuticals, spray drying is a common technique used to convert liquid phase to solid dry powder form. By employing this method inclusion complex can be produced from a solution. The mixture of the drug and carrier are passed through fast solvent elimination system. The particles so obtained are in solid state and shows the drug release in a controlled manner, in turn, improves the rate of dissolution, increases shelf life and stability due to the elimination of maximum quantity of water.

Lyophilization/ Freeze drying technique

This is an alternative method to solvent evaporation. In this method solvent system is removed from frozen state by primary drying under pressure. A drug which is thermo labile in nature can be successfully made in this method. It is a poor yielding and tedious process. CD inclusion complexes prepared by freeze drying will give amorphous, porous powder with a higher degree of interaction.

Microwave irradiation method

This method involves a reaction between the drug and carrier in a definite molar ratio by microwave irradiation using a microwave oven at different frequency and time. The drug and carrier mixture can be dissolved in aqueous or organic solvent and reacted for a short period of time at 60℃ in a microwave oven. Uncomplexed free drug can be removed out by adding the required amount of solvent mixture to the reaction mixture. The precipitated residue was separated using what Mann filter paper, dried, pulverized, and stored.

Supercritical anti solvent technique

In the supercritical fluid anti-solvent technique, carbon dioxide is used as anti-solvent for the solute but as a solvent with respect to the organic solvent[26]. In pharmaceuticals, the thermo labile substance can be handled easily by low critical temperature and pressure used in supercritical carbon dioxide. It is easily removed from the polymeric material, non-toxic, non-flammable, inexpensive, and safe technique. This is an alternative method for cyclodextrin complexation. Supercritical carbon dioxide is suggested as a new complexation medium due to its properties of improved mass transfer and increased solvating power. This method constitutes one of the most innovators methods to prepare the inclusion complex of the drug with CD in solid state[27]. This is a non-toxic method as it is not utilizing any organic solvent, fast process, maintenance cost is low with promising

results, but it requires a quite high initial cost. 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[28]. When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent. Because of the supercritical fluid the 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[29].

CONCLUSION

The review concludes that rate-determining step for the poorly water-soluble drug is dissolution. Various techniques have been discussed above to enhance the poorly soluble/insoluble drugs. The abovesaid techniques either alone or in combination can be used. Successful improvement of aqueous solubility mainly depends on the method we choose. CD inclusion complexes are most new, safe, industrially applicable techniques. Solubility enhancement of any drug depends upon drug characteristics like physical nature, chemical nature, pharmacokinetic behavior, solubility, melting point, absorption site. They can be formulated into any dosage form like a tablet, capsule, immediate release or sustained/controlled release with different strengths and doses to reduce dosing frequency, finally to improve accuracy and therapeutic efficacy.

FUTURE SCOPE

Though solid dispersions are having excellent solubility enhancement ability and many advantages, there are certain limitations exist to scale up, stability, manufacturing technique, formulation, reproducibility and stability of commercially available dosage forms of poorly water-soluble or insoluble drugs. Nowadays due to the availability of surface active agents and self-emulsifying carriers with low melting points, development of solid dispersions for preclinical, clinical and commercial use had been feasible.

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