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Approaches for the Improvement in Solubility and Dissolution of Poorly Water Soluble Drugs: A Review

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ABSTRACT

Poor aqueous solubility of drugs is a major limiting factor with many new drugs in their successful launch in market in spite of their potential pharmacokinetic activity. Poorly water soluble drugs are becoming a problem in terms of obtaining satisfactory dissolution within the gastro intestinal tract, which is necessary for good bioavailability. Poorly water-soluble drugs are associated with slow drug dissolution followed by slow absorption leading eventually to inadequate and variable bioavailability. Various approaches to overcome the poor aqueous solubility of drugs have been investigated like solid dispersion, spherical agglomeration, nanoparticles, nanosuspensions, nanomorphs, nanocrystals, micronization, polymorphism, co-solvency, pH adjustment, use of surfactants, microemulsion, complexation. In this article, the basic approaches for enhancement of solubility and dissolution of poorly water-soluble drugs have been reviewed with literature-based examples of the formulation options for poorly water-soluble compounds and their practical applications to the industrial practices.

Keywords: Solubility, Dissolution, Techniques.

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INTRODUCTION

Development of new drug entities is posing the real challenge to formulators, particularly due to their poor aqueous solubility which in turn, is a major factor responsible for their poor oral bioavailability. There are many problems arising from the poor solubility of drug in drug development. The aqueous solubility of a drug is a critical determinant of its dissolution rate. According to the Amidon's biopharmaceutical classification system, dissolution in gastrointestinal fluids and permeability through biological membranes are the key parameters in bioavailability of orally administered drugs [1]. The amount of substance that passes into solution in order to establish the equilibrium at constant temperature and pressure, producing a saturated solution is termed as solubility. Temperature, molecular structure of the solute, particle size of the solid, crystal characteristics, nature of the solvent, pH of the sovent, common ion effect, complex formation, solubilizing agents are the factors that affect the solubilities and bioavailability of drugs. The amount of solid substance that goes into solution per unite time under standard conditions of temperature, pH and solvent composition, is a dynamic process **[2].** The limited dissolution rate arising from low solubility, results in the low bioavailability of orally administered drugs. About 40 % of drugs being in the pipeline of pharmaceutical companies are poorly soluble, which emphasizes the need of a technique to overcome such problems **[3].**

Approaches for Improvement of Solubility

Various approaches are practiced to improve the aqueous solubility of poorly soluble drugs. The drug loading should be maximized, particularly for high-dose drugs as to minimize the size of the dosage form. The techniques which are used to improve aqueous solubility of drugs, include

Solid Dispersion

When the drug is dispersed in a biologically inert matrix, the mixture of is called solid dispersion. This can be used to increase the dissolution rate of a drug of low aqueous solubility, thereby improving its oral bioavailability **[4]**. Higher drug dissolution rates from a solid dispersion can be facilitated by optimizing the wetting characteristics of the compound surface, as well as increasing the interfacial area available for drug dissolution **[5]**. The solid dispersion techniques result in reduction in crystallinity of the drug and an increase in amorphous form. It has been observed that the solid dispersion with hydrophilllic polymer show an improvement in solubility and hence bioavailability of the drugs **[6].**

Solvent Evaporation Method

In the solvent evaporation method, the carriers and the active ingredients are dissolved in a suitable

organic solvent and the solvent is evaporated at an elevated temperature or under vacuum. As the solvent is removed, super saturation occurs followed by simultaneously precipitation of the constituents resulting in a solid residue [7]. This method is suitable for those drugs which are thermolabile. Frozen temperatures are used to enhance the integrity of the drug. The limitations of this method are difficulty to find a suitable solvent for dissolve both the drug and the carrier, complete removal of solvent, wastage of organic solvent in evaporation [8]. The solid dispersion of nimodipine made by solvent evaporation method exhibited similar dissolution with drug content up to 20% [7]. The etoricoxib has shown improved dissolution than the physical mixture [9].

Fusion Process (Melt- Mixing)

The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. The physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring [10]. The final solid mass was crushed, pulverized, and sieved. Some systems, such as griseofulvin and citric acid, were found to harden more rapidly if kept at 37°C or higher temperatures. The mixture was cooled with constant stirring to homogeneously disperse the drug throughout the matrix. These systems showed very high drug dissolution rates as compared to control samples [11]. This is a very suitable method for drugs and the carriers that are miscible in molten state and thus many batches can be prepared in a very short time. This method is not suitable for those drugs whose have high melting point above 150 ºC. There is a significant improvement in the dissolution rate of itraconazole prepared by fusion method [5].

Fusion-Solvent method

In fusion–solvent method, a carrier is melted and the drug is incorporated in the form of a solution. If the carrier is capable of holding a certain proportion of liquid, (yet maintaining its solid properties) and if the liquid is innocuous, the need for solvent removal is eliminated. This method is useful for drugs with high melting points or that are thermo labile. Solvent retention in solid dispersion remains a problem [4].

Kneading Technique

The kneading mixture of gliclazide has shown the improvement in dissolution profile [12]. The percentage release of nevirapine by the kneading method is reached to 62.49% [13]. A mixture of carrier and drug was wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through sieve no. 60 and stored in a dessicator for further evaluation eg. Nimodipine [14].This method is suitable for drugs

that are thermolabile. Frozen temperatures can be used to evaporate the solvent, which can enhance the integrity of the drug [15].

Co precipitation/ Coevaporation /Cogrinding

The procedure includes an intimate mixture comprising the carriers or excipients and a non-aqueous water miscible solvent or combination of solvents and water; co-mixing the intimate mixture with a poorly water soluble drug; then the mixture was sonicated for proper mixing. The solvent was removed using the rotary vaccum evaporation removed the solvent at 50ºC. The prepared dispersion of piroxicam showed improved dissolution rate [16]. In this technique, less solvents and heat are employed as compared to other techniques such as co-evaporation and hence, solvent removal is facilitated.

Characterization of Solid Dispersion

A number of methods have been used to characterize solid dispersions including:- Powder x-ray diffraction (XRD), Microscopically studies, Spectroscopic method, Dissolution Rate determination, Thermodynamic investigation (DSC, TGA DTA) involving determination of the heats of dissolution and the melting points in order to calculate the resulting changes in entropy.

Complexation

Complexation is an effective process to increase solubility of poorly soluble drugs, which refers to the association between two or more molecule to form a non bonded entity with a well defined stoichimetry. Complexation relies on relatively weak forces such as hydrophobic interactions, london forces, hydrogen bonding and inclusion complexes which are formed by the insertion of the nonpolar molecule of one molecule into the cavity of another molecule [17]. Cyclodextrins are commonly used polymer to form complexes with a variety of drug molecules, resulting in an improvement in dissolution and bioavailability due to enhanced solubility and physical stability [18].There are other complexing agent like Caffeiene, Poly Ethylene Glycol, Urea, N-Methyl Glucosamide [19]. Naturally occuring the cyclodextrin are of three types. (i) α- cyclodextrin (ii) β-Cyclodextrin (iii) γ-cyclodextrin. β-Cyclodextrin and its derivatives have been used in pharmaceutical formulations to enhance the solubility [18]. Cyclodextrins are carbohydrate containing an hydrophilic surface, where central cavity is hydrophobic in nature due to the presence of hydroxyl group in the molecule. Inclusion complexes retain a disadvantage that volume of the dosage form is much more as compared to the pure drug [20]. Normally, the dose of the cyclodextrin is non toxic but their derivatives like methyl, hydroxypropyl, sulfoalkylated and suffocated derivatives are toxic in nature [21].

Hydrotropy

In hydrotropy method, the solubility of a drug is increased by addition of a fairly high concentration of hydrotropic agents like urea, sodium citrate, sodium benzoate, sodium acetate sodium alginate etc. The ionic organic salts are commonly called as hydrotropic agents [21]. The formulation formed is called hydrotropes and it is amphiphilic in nature [22]. In mixed hydrotropic solubilization technique, the drug and hydrotropic agent is blended. This technique shows the synergistic improvement in the solubility of a poorly soluble drug and has been used for the formulation of aqueous injection of various poorly soluble drugs. There is an improvement in solubility of aceclofenac is 250 times with hydrotropic agents [23]. The hydrotropic solutions can be used for the poorly aqueous soluble drugs. The solubility of paclitaxel is enhanced by the *N*, *N*-diethylnicotinaamide, *N*, *N*-dimethylbenzamide [24]. The hydrotrops have a wide range of solubilization mechanisms including self aggregations, complexations and changes in the nature of the solvent etc [25]. It is suggested that hydrotropism is a superior techniques over other techniques for solubilization of hydrophobic drugs. In this technique, the chemical modification is not required due to weak interaction between the hydrotropic agent and hydrophobic drugs [21]. Hydrotropic technique has successfully been applied to various drugs likes nifedipine, theophylline, caffeine, riboflavin nimesulide etc [18].

Spherical Agglomerations

In this method, the drug is dissolved in a organic solvent by gentle warming and the resulting solution is added with stirring to distilled water contained in agglomerating vessel. Chloroform, (agglomerating solvent), is added drop wise and the contents are simultaneously stirred for 30 minutes at a speed of 900 rpm [26]. Similarly the drug is agglomerated using carbon tetrachloride (CCl_4) as the agglomerating solvent at an agitation speed of 650 rpm. This method is useful for drugs with high melting points or that are thermolabile, resulting in improvement of micromeritics, solubility further many batches can be prepared in a very short time [27]. The agglomerates are also prepared by high shear mixing process, where the mixture of melted binder and drug is kept at 70ºC until the addition is initiated. This is done when the product temperature reaches to 55 ºC then rest of the polymer is to be added. During the addition the, impeller speed is to be kept at 900 rpm. Than cooling the agglomerates in liquid nitrogen result in larger agglomerates. The shear mixing process show an increase in dissolution rate of poorly water soluble drug by melt agglomeration with hydrophobic binders [28]. Matrix pellets are prepared by agglomeration in the fluidized bed. The binders affect the size of the agglomerates when acts as a core in the formation of pellets in molten state. The size is also influenced by the volume of the solid particles [29].

Evaporation precipitation into aqueous solutions (EPAS)

The method comprises the dissolution of a drug in organic solvent to form a mixture, spraying the this mixture into an aqueous solution containing the stabilizing agent, and concurrently evaporating the organic solvent in the presence of the aqueous solution to form an aqueous dispersion of the drug particles [30]. The resulting drug particles are in the nanometer to micrometer size range and show enhanced dissolution rates and reduced crystalline when compared to the unprocessed drug. In EPAS technique, it was observed that the nimodipine show an increase in the percentage release of the drug from the formulations. This method is also useful for the drugs with high melting points or that are thermolabile [26].

Microcrystallisation

To enhance the drug dissolution rate using microcrystallisation. The common way for micronization is the milling of previously formed larger crystals. However, milling shows several disadvantages such as the newly created surfaces are thermodynamically activated due to high energy input and have, do not grow naturally. Naturally grown microcrystals are prepared by a precipitation method in the presence of stabilizing agents (e.g. gelatin, chitosan, different types of cellulose ethers) followed by spray-drying of the formed dispersion. In the presence of a stabilizing agent instantaneously mixing of two liquids using the solvent change method is called crystallization. In the first step the drug is dissolved in solvent and the stabilizing agents are dissolved in water. Afterwards, the aqueous solutions are poured into drug solution rapidly under stirring conditions. For comparison of the stabilizing effect, pure water is used and the particle size in the resulting dispersions is determined after 0, 60, and 120 min [31].

Pro-Drug Approaches

The prodrugs are stable in gastric and intestinal fluids; undergo quantative conversion to the parent compound either in the intestinal mucosa, or in plasma or in the liver, or in other organs during absorption. The best example of prodrug design is orally active ampicillin derivative [32]. Its prodrugs, pivampicillin and bacampicillin (both resulting from the esterification of the polar carboxylic group with a lipophilic, enzymatically labile ester) show good absorption (98-99 %). The drugs are given at lower dosage (0.8-1.0 gm daily) than ampicillin (2.0 gm daily).

Polymorphism

Polymorphs are different crystalline forms of a drug with different physicochemical properties and biological activities. The existence of different crystal forms impact on key properties such as shelf life, vapors pressure, solubility, bioavailability, morphology and density[2]. The polymorphs differ from each other with respect to melting points, hardness, compression, solubility, bioavailability,

morphology and density. The existence of the polymers can be determined by using techniques such as optical crystallography, X-ray powder diffraction and differential scanning calorimetry. Therefore, the preparation of drug polymorphs by recrystallisation techniques has emerged as on of the area of active research currently of interest in pharmaceutical field so as to improve the formulation related problems of drug molecule [33] .

pH adjustment

Since the majority of drugs are either weak acids or weak bases. This makes it convenient to increase the aqueous solubility of drugs by adjusting the pH. A slight modification of Nerst-Brunner equation shows that the increase in pH results in increase in the dissolution rate of a weak acid and decrease in the case of a weak base. A classical example is the addition of a buffering agent (such as sodium bicarbonate) to aspirin formulations in order to raise the pH of the microenvironment of the dissolving solid particle, resulting in enhanced drug dissolution and thus oral absorption [34]. The salt formation of meloxicam with ethanolamine show significant enhancement in the dissolution rate of meloxicam at pH 6.8. The diethanolamine salts of meloxaicam favours the rapid absorption of meloxicam [35]. The formation of double salt of calcium sulphate and sodium carbonate, it is believed that two salts have high porosity and specific area [36]. The chitosan and its glutamates and hydrochloride salt of naproxen influenced the dissolution rate and permeation across Calo-2 cells [37]. Due to the common ion effect of chloride, there was decrease in the solubility of hydrochloride salts at lower pH values. The study of pH solubility profile of hydrochloride salts was done which show the apparent dissolution rate and solubility of these hydrochlorides was less in the pH range of the stomach 1.0-2.0. This show that salt formation does not show always better results for enhancement of solubility and dissolution rate [38].

Surfactants

The use of surface active ingredients in formulations is generating more and more interest. These vehicles combine the aspects of high solubilizing potential, incorporation of the compound into micellar structures and absorption enhancing effects. Sodium dodecyl sulfates (0.05%) show the improvement of solubility due to their high wettability and reduced the interfacial tension between the nimodipine and aqueous media [39]. Tween 80 (i.e. polysorbate 80) is reported to increase the solubility and dissolution profile of CI-1041 and Flurbiprofen [40]. Natural surfactants like bile salts have been reported to be suitable for the oral administration of sparingly soluble compounds [41]. As the formulation with sodium lauryl sulfate show a significant increase in solubility of the drug as compared to the pure drug. In the solid dispersion, the carriers show improvement in the dissolution rate of the drug due to its wettability and more exposure of surface area to the drug

with the dissolution media [8]. Carbamazepine and nifedipine show the improvement in dissolution rate with hydrophilic non-volatile solvent onto carriers with a large surface area e.g. dissolving the drug in hydrophilic liquid (PEG-400) and adsorbing the solution on to the surface of the silica [42].

Nanoformulations

Nanocrystal

The nanocrystals are prepared by modified anti-solvent recrystallization followed by high pressure homogenization. The drug dissolves in ethanol, poured into 1000 ml aqueous solution containing a stabilizer and stirred with stirrer at 1600 rpm for 5 min. The obtained suspension of microcrystalline is then homogenized by high pres-sure homogenization. At first, 5 cycles at 200 bars were conducted as pre-milling step, and then 10 cycles at 1000 bar were run to obtain the nanocrystal dispersion. After centrifugation using an ultracentrifuge at the rotate speed of 10 000 rpm for 10 min (15 ◦C), the upper clear liquid is removed and the remaining residue is dried in a heated vacuum desiccators at 40 ◦C for 24 h [43]. No substantial crystalline change was observed after nanocrystal formation. The nanocrystal containing only trace of stabilizer also exhibited an enhanced dissolution rate and significantly improved oral bioavailability of the drug. Nanocrystals are particles made from almost 100% drug, stabilized by a small amount of surfactants or polymeric stabilizers [44].

Nanohybrid

The nanohybrid was prepared by the direct co precipitation method, by dispersing the drug in deionized water and titrated with a NaOH solution to give a solution of drug at pH 10.0±0.2. The whole process was performed under a nitrogen atmosphere at 60 ◦C. The resulting precipitate was collected by filtration and washed with deionized water, followed by 50% ethanol solution. To prepare the non-coated nanohybrids, the resulting precipitate was dispersed in a mixture of methylene chloride and ethanol and spray dried under the following condition: atomizing pressure, 130 kPa; blower speed, 0.30m/min; inlet temperature: 80 ◦C; and outlet temperature: 40–50 ◦C [45]. This method was different from the conventional strategies mostly relying on the physical methods, such as milling of drug, co-grinding of drug and water-soluble polymer and using biopolymers as drug carrier [44].

Nanosuspensions

Nanosuspensions can be defined as colloidal dispersions of nano-sized drug particles that are produced by a suitable method and stabilized by a suitable stabilizer. There are two approaches to prepare drug nanosuspensions; precipitation method (bottom-up) and disintegration method (top-down) [46]. Dried drug nanosuspensions are prepared by acid–base neutralization combined with spray drying which may be a promising method for the enhancement of oral bioavailability of

poorly soluble drugs with pH-dependent solubility [47]. Nanosuspensions preserves the high dissolution rate for the enhancement of oral bioavailability of poorly water soluble drugs. Nanosuspensions are thermodynamic unstable and often associated with stability issues including Ostwald ripening, aggregation and crystalline transformation [48].

Nanoparticle

Nanoparticle are solid colloidal is a microscopic particles ranging in size from 10nm to 1000nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. They consist of macromolecular materials in which the active principle is dissolved, entrapped or encapsulated. Nanoparticles have been prepared by three methods: (1) dispersion of preformed polymers; (2) polymerization of monomers; and (3) ionic gelation or coacervation of hydrophilic polymers. The major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen [49].

Microemulsion

SMEDDS

Self microemulsifying drug delivery system is a isotropic mixture of an oil, co surfactants and the drug [50]. The drug ibuprofen was dissolved by co surfactant and oil (accurately weighted) in the glass vials. The compound was mixed by gentle stirring at 37°C. e.g. Simvastatin [51] Seccalcitol [52]. It has been focused that enhancing the solubility of poorly aqueous soluble drugs by the SEMDDS of results in improvement of the bioavailability and clinical efficacy of the drug**.** Dry emulsion: the dry emulsion has been successfully applied for a potential oral drug delivery for the poorly hydrophobic drugs. The dry emulsion is prepared by spray drying the oil in water emulsion of drugs e.g. Amlodipine [53].

Micronisation

A decrease in particle size results in an increase in specific surface area leading to increased solubility and dissolution rate of the drug [54]. The methods employed for decreasing particle size of the drug are: Trituration and grinding, ball milling, spray drying, freeze drying, fluid energy micronization, ultrasonic waves, super critical fluid, controlled precipitation change [55]. There are certain conventional methods which used for the particle size reduction of the drugs like, Jet-milling, High Pressure Homogenization, Supercritical fluid technology, Spray drying etc

Microparticles

The microparticles are produced by the static mixer technique of drug oxcabazepine. This technique was previously used by Gassman. The method consists of two steps i.e. (a) Drug is to be

dissolved in a water miscible solvent. (b) The resulted solution is mixed with the aqueous solvent containing the stabilizing agent, the precipitate obtained are microparticles and a called as microcrystal [56]. The drug particles are covered by a hydrophilic polymer layers which are protective in nature. The polymer present on the surface of the drug reduces the particle size and inhibits the crystal growth. The microparticles of the Griseofulvin were prepared using the hydrophilic surfactant (poloxamer-407) which increases the wetting efficiency of the drug [57] e.g. Ethenamide and Flubiprofen [58]. The microparticle is also generated by the compressed gas precipitation techniques which enhances in the dissolution rate of poorly water soluble drug [59]. Using hammer jet milling, there was a significant increase in the dissolution of the drug cilostazole by reducing the particle size [60]. Air jet milling of Levonorgestrol by milling pressure at 4.2 Kg/cm² (as primary pressure) and 4.0 Kg/cm² secondary pressure, with a speed of screwfull of 5 rpm [6]. Enteric microparticles were formulated by dissolving the drug in eduragit in ethanol: acetone mixtures and then emulsification of the resultant solution with the liquid paraffin contain the sorbitan sesquioleate, at a speed of 1000 rpm [61].

Silica lipid hybrid microcapsules (SLH)

It is composed of silica nanoparticles, medium chain triglycerides and lecithin. It is a two steps process (a) Homogenization (b) Spray drying. The o/w emulsion was prepared by dissolving lecithin in oil followed by the addition of drug. The coarse mixture was homogenized (by homogenizer) and the silica sterilize emulsion are spray dried to form SLH –microcapsules. The celecoxib showed the improved therapeutic effectiveness by LH-microcapsules whereas, reduced the cost of poorly soluble drugs [62].

Approaches used for the dissolution and bioavailability enhancement of poorly water soluble drugs with different polymers

Approaches	Drug	Polymer/Surfactant
Solid Dispersion (S. E.)	Etorocoxib[9]	Sucrose, Lactose, Mannitol
(S. E.)	Nevirapine[13]	PVP K-30
(S. E.)	Nimodipine[7]	PEG-4000
(S. E.)	Mefenamic Acid[8]	PEG-4000
S.E.	Ketoprofen[63]	Gelucire 44/14
S.E.	Famotidine[64]	PEG-4000, 6000
K.M	Aceclofenac[6]	Mannitol,Urea, Lactose
K.M	Gliclazide[12]	PVP-K30, HPMC
K.M.	Nimodipine[14]	Gum Karaya
K.M.	Aceclofenac[65]	Croscamellose
K.M.	Famotidine[64]	PEG-4000, 6000
Coevaporation Method	Piroxicam[16]	MC, Potato starch

Cogrinding	Griseofulvin[66]	PEG-6000
Cogrinding	Indomethacin[66]	PEG-6000
P.M.	Meloxicam[67]	Skimmed Milk
P.M.	Diclofenac[68]	PEG-6000, Gelucire 50/13
Shear Pelletization	Itraconazole[11]	Eduragit E100
Lyophilization	Fenofibrate[69]	Poloxamer 407
PM, SE, KM	Lovastatin[70]	Locust Bean Gum
Supercritical Anti-solvent Precipitation	Felodipine[71]	HPMC
Complexation	Carbamazepine[72]	2-hydroxypropyl+-cyclodextrin
Complexation	Loratadine [73]	Hydroxypropyl-β-cyclodextrin
Complexation	Clofibrate[74]	Cyclodextrin
Complexation	Gliclazide[75]	Cyclodextrin
Complexation	Nicardipine[76]	Cyclodextrin
Complexation	Amiodarone[77]	Cyclodextrin
Complexation	Oxazepam[78]	Cyclodextrin
Complexation	Albendazole[79]	Cyclodextrin
Cosolvency	Valdecoxib[72]	Cyclodextrin
Nanomatrix	Fenofibrate[44]	Polymethylacrylate
Ultra-rapid freezing	Danazol[80]	Polyvinylpyrrolidone
Liposomes	Fenofibrate[40]	Bile salt
Nanoparticles	Cyclosporin-A[81]	Chitosan
Nanoparticles	Spironolactone[82]	HPMC
Nanosuspensions	Nitrendipine[83]	PEG-200+Acetone
Melt Agglomeration	Diazepam[28]	PEG-3000
Matrix pellets	Theophylline[29]	Microcrystalline Wax
Spherical Agglomerates	Mefenamic Acid[8]	HPMC
SphericalAgglomerates	Nimodipine[26]	HPMC
Microcrystals (Static mixer process)	Oxcarbazepine[56]	Methyl Cellulose
Microparticles	Phenytoin[59]	PVP K-30
(SMEDDS)	Simvastatin[51]	Carpryol, Cremophor EL
Dry emulsion	Amlodipine[53]	
Microemulsion	Docetaxel[84]	Cremophor EL
Salt formation	Phenazopyridine Hcl.[38]	Sodiumacetate-Hcl. acid buffer
Salt formation	Meloxicam[35]	Ethanolamines
Salt formation	Naproxen[37]	Chitosan and its glutamate
Cogrinding	Gliclazide[85]	PVP -30K
Cogrinding	Albendazole,Danazol [86]	Lactose, PVP, HPMC
Novel lipid-based formulations	Piroxicam[87]	PEG-4600
Solvent change approach	Aceclofenac[88]	Chitosan
Evaporative Precipitation into Aqueous Solution (EPAS)	Cabmazepine[30]	PVP
(EPAS)	Danazol[89]	Hydroxypropyl-b-cyclodextrin
(EPAS)	Mefenamic Acid[8]	SLS, HPMC, PVP
(EPAS)	Nimodipine[26]	SLS,HPMC,PVP
Solvent Change Approach	Aceclofenac[88]	Chitosan

Hydrophilic Silica Aerogels	Ketoprofen[90]	Silica aerogel
Hydrophilic Silica Aerogels	Griseofulvin[90]	Silica aerogel
Nanocrystalline (Spray Drying)	COX-2[84]	Poloxamer-407

S.E. (Solvent Evaporation), P.M. (Physical Mixture), K.M. (Kneeding Method), EPAS (Evaporative Precipitation Techniques in Aqueous Solution, SMEDDS (Semi-microemulsifying Drug Delivery System), PEG (Poly Ethylene Glycol), PVP (Polyvinyl Pyrrolidone), HPMC (Hydroxy Propyl Methyl Cellulose)

SUMMARY

The delivery of poorly water soluble drugs has been the subject of much research, because due to solubility problem of many drugs, the bioavailability gets affected and hence solubility enhancements become necessary. The increases in the percentage of new chemical entities demand such technologies as to reduce the dose of the drug and increase their efficacy with dissolution enhancement. We conclude that with the help of present techniques, and with some modification, we can search the future prospective methods for solubility enhancement.

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