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Review Article

A Systematic Review on Solid Dispersion: Enhancing the Solubility of Poorly Soluble Drug

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Abstract

Oral route is mostly preferred route for administering drugs to patient. But due to the poor solubility many drug has limited used in oral administration. Enhancement of water solubility of poor water soluble drug is a main target in a pharmaceutical field. Solubility is a one of the most important factor which affects dissolution rate and bioavailability. Solid dispersion technique used for increasing the solubility of poor soluble drugs resulting enhancing the dissolution rate and bioavailability by using various polymer. In this review focused on methods used in solid dispersion, also focused on characterization of solid dispersions.

Keywords: BCS classification; Solid dispersion; Solubility; Dissolution; Bioavailability

Introduction

Oral route is mostly preferred route for administering drugs to patient. But due to the poor solubility many drug has limited used in oral administration. Poor solubility is mostly effects on dissolution rate and bioavailability of drugs. Biopharmaceutical Classification System (BCS) categorized the drugs into four subclasses according to solubility and permeability. BCS class II and IV belonging drugs have poor solubility problem. It is most challenges to enhance the solubility of this BCS II and IV belonging drugs. For this purpose, various approaches are used such as solid dispersion, reduction of particle size (Micronization and Nanonization), formation of salts, alteration of pH, formation of polymorphs and pseudo polymorphs, by complexation method, by using surfactant and co-solvent. But among of this approaches solid dispersion is easy and give the high accuracy result of enhancement of solubility.

Solubility and its types

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution [1].

Absolute/Intrinsic solubility: The maximum amount of solute dissolved in a given solvent under slandered conditions of temperature, pressure and pH is called as absolute or intrinsic solubility. It is a static property.

Saturated solubility: A maximum amount of solute dissolved in a given solvent up to its saturated level. Additional solute will not dissolve in solvent Table 1.

Importance of Solubility

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug product [2].

Table 1: USP and BP solubility criteria.

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practically insoluble	10000 and over

However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. Solubility also plays a major role for other dosage forms like Parenteral formulations as well [3]. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response [4]. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility. More than 40% NCEs (New Chemical Entities)

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developed in pharmaceutical industry are practically insoluble in water. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastro intestinal mucosal toxicity. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist [5]. The improvement of drug solubility thereby its oral bioavailability remains one of the most challenging aspects of drug development process especially for oral-drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected, and nature of intended dosage form. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs [6,7].

Biopharmaceutical classification system (BCS) [8]

Amidon et al., developed the Biopharmaceutical Classification System (BCS). The BCS classification of a drug depends upon its three key parameters that control absorption- solubility, dissolution rate and permeability. BCS classified the drugs into one of the 4 groups which is as follows Table 2.

Methods of solubility enhancement of poor water soluble drugs [9]

There are several ways by which drug solubility and dissolution rate can be enhanced, which can be categorized in to physical modification, chemical modifications of the drug substance, and other techniques.

Particle size reduction: The solubility of a drug is intrinsically related to the particle size. Reduction of particle size of a drug by various means such as jet mill, rotor stator colloidal mill, ball mill, etc. leads to increase in surface area with enhanced dissolution. But limitation of this process includes thermal and physical stress on drug product that leads to degradation. Other disadvantages include limited opportunity to control important characteristics of final product such as shape, size, morphology, surface properties, and electrostatic charges. Also, amorphous region are thermodynamically unstable and susceptible to recrystallization on in hot and humid condition [10,11].

Nanosuspension technology: Nanosuspension technology has been developed as a promising candidate for effective delivery of poor water-soluble drug. It is sub-micron colloidal dispersion of pure particles of drugs, which is stabilized by surfactants for either topical or oral use or parentral or pulmonary administration. In nanosuspension, particle size is usually less than one micron ranging between 200 and 600 nm [12]. Media milling, high pressure homogenization in water, high pressure homogenization in non-aqueous media and

Table 2: BCS classification of Drugs.

Class	Permeability	Solubility	Examples
Class I	High	High	Diltizem, propranolol, metoprolol
Class II	High	Low	Nifedipine, carbamazepine, azilsartan, naproxen
Class III	Low	High	Insulin, metformin, cimetidine
Class IV	Low	Low	Taxol, chlorthiazide, furosemide

combination of precipitation and high pressure homogenization are the various method of preparation of nanosuspension [13,14]. Nanosuspension approaches have been employed for various drugs including tarazepide, atovaquone, amphotericin B [15].

Surfactant: The use of surfactant in enhancement of solubility of poorly soluble drug has been employed successfully. Seedhar N et al., [16] studied solubility improvement of enrofloxacine using a series of co-solvents and surfactants with solubility increase up to 26 times. Commonly used non-ionic surfactants are lauroylmacroglycerides, castor oil, di-fatty acid ester of low molecular weight polyethylene glycol.

Salt formation: Dissolution rate of particular salt is usually different from that of parent compound. Sodium and potassium salt of week acid dissolve more rapidly than that of pure salt. Limitation of salt formation includes epigastric distress due to high alkalinity, reactivity with atmospheric water and carbon dioxide leads to precipitation, patient compliance [17].

PH adjustment: Poor water soluble drug may potentially dissolve in water by applying a pH change. To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs [18].

Hydrotrophy: Hydrotrophy is a solubilization phenomenon in which solubility of poorly water soluble drug is enhanced to many folds by using sodium benzoate, urea, sodium citrate, and sodium salicylate [19]. Rasool AA et al., [20] improve solubility of many drugs, i.e., diazepam, griseofulvin, testosterone, progesterone, and 17-estradiol in presence of nicotinamide and related compounds.

Solid dispersion: In 1961, Sekiguchi and Obi first introduce the solid dispersions to increase the dissolution and oral absorption of poorly water-soluble drugs. In this method, the poorly soluble drug and carrier are dissolved in organic solvent and then it is subjected to evaporation to get solid powder. Various polymers such as water soluble as well as water insoluble polymers are use such as soluplus, polaxamer, HPMCAS, HPMC, PVP K30.

Solid dispersion

Mechanism responsible for solubility enhancement from solid dispersion: A number of methodologies can be adapted to improve solubilisation of poor water soluble drug and further to improve its bioavailability.

- **Reduced particle size**

When the solid dispersion is exposed to aqueous media, the

carrier dissolve and the drug release as fine colloidal particles. The resulting enhanced surface area results in higher dissolution rate of poor water soluble drugs [21].

- **Drug in amorphous state**

Poor water soluble crystalline drugs in amorphous state tend to have higher solubility [22]. This is because no energy is required to break crystal lattice in amorphous state during dissolution.

- **Particles with high porosity**

Particles in solid dispersion have been found to have high porosity [23]. The increased porosity of solid dispersion particles hastens the drug release profile. Increase in porosity depends on carrier properties, i.e., linear polymers results in larger and more porous particles than that of reticular particles.

- **Particles with improved wettability**

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement has been verified in solid dispersion [24]. Carrier with surface activity, i.e., cholic acid and bile salt can significantly increase the wettability property of drug results in enhanced dissolution profile.

Classification of solid dispersion: Solid dispersion classified in 3 groups;

- **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 [25].

- **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 [26].

- **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 dispersion [28]: There are three types of solid dispersion which is as follows,

- **Binary Solid Dispersion**

In this type, there are two phases namely drug and polymer.

- **Ternary Solid Dispersion**

In this type, there are three phases such as drug, polymer and surfactant. Mostly Polysorbate 80 is used as a surfactant.

- **Solid Surface Dispersion**

In this type, drug is deposited on surface of polymer, resulting decreasing the particle size of drug and increased its solubility.

Methods of Solid Dispersion: Various method of solid dispersion used for enhancing the solubility of poorly soluble drug which is as follows,

Solvent Evaporation Technique [29,30]: In this method, drug which have poor solubility problem and the polymer dissolved in appropriate organic solvent such as dichloromethane, acetone and chloroform to form homogenous liquid. Then, it is subjected to evaporation of organic solvent to get dried mass which is then pulverised in mortar and pestle to get dried fine powder.

Hot Melt Extrusion Technique [31]: In this technique, drug and polymer are mixed with each other and then feed into single screw hot melt extruder. Due to the heat, the mixture is melt and to produce extrudes. Then it is triturate to form powder.

By using Spray drying [32,33]: In this method, drug and polymer are dissolved in organic solvent and sprayed through the nozzle into the heated chamber. Due to the high temperature, solvent is evaporate and to get finest size particles of powder.

By using lyophilization technique [34]: Lyophilization is work on a simple principle of physics known as sublimation. In sublimation, first the sample is dried (solid form) and then it is subjected to the vapour state without passing through liquid state. Due to vaporization, solvent is removed and to get finest particles of powder.

Kneading Method [35]: In this method, drug and polymer are wetted with solvent and then kneaded in a glass mortar to form paste. Then paste is dried, and passed through sieve to get fine particles of powder.

Electrostatic spinning method [36,37]: Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. In this process, electrostatic field involved over a conductive capillary attaching to a reservoir containing a polymeric solution and a conductive collective screen. Itraconazole/HPMC has been prepared using this technique.

Inclusion complexes: Inclusion complexes are formed by insertion of non -polar molecule (known as guest) into the cavity of another molecule or group of molecule (known as host). The most commonly used host molecules are cyclodextrins. Cyclodextrin are cyclic oligomers produced by enzymatic degradation of starch by Cyclodextrin Glucosyl Transferase (CGT). Naturally occurring cyclodextrin are α cyclodextrin, β cyclodextrin, and γ cyclodextrin [38]. The improvement of solubilization ability within water soluble polymer/drugincluded CD aggregates require less cyclodextrin to solubilizing the same amount of drug. Solid inclusion complexes are prepared by various methods such as kneading method coprecipitation, neutralization, co-grinding, spray drying method, and microwave irradiation method.

Table 3: Examples of different polymer used in solid dispersion.

Drug	Polymer	Preparation method	Reference
Terbinafine HCl	Polyethylene glycol 6000	Melting method	[40]
	polyvinyl pyrrolidone K 30	Solvent method	
Carbamazepine	Soluplus, Eudragit EPO, HPMC 100, Kollidon VA64 and Affinisol HPMC HME 4000	Hot melt extrusion method	[41]
Curcumin	Hydroxy Propyl Methyl Cellulose Acetate Succinate (HPMCAS), Carboxy Methyl Cellulose Acetate Butyrate (CMCAB) and Cellulose Acetate Adipate propionate (CAAdp)	Spray drying technique	[32]
Azilsartan Medoxomil	Affinisol 716G (HPMCAS)	Solvent evaporation method	[46]
Felodipine	Soluplus	Solvent evaporation method	[42]
Simvastatin	Sodium Starch Glycolate (SSG) and Croscarmellose Sodium (CCS)	Coevaporation	[43]
Eplerenone	Soluplus	Lyophilization technique	[34]
Fenofibrate	PEG 6000	Solvent evaporation Method	[44]
Indomethacin	Poly (2-Hydroethyl Methacrylate) (PHEMA)	Solvent evaporation Method	[45]
Telmisartan	Poloxamer 407, PEG 6000	Solvent evaporation Method	[29]
Valsartan	Sodium Starch Glycolate (SSG), Crosspovidone, Avicel PH 101, Pre-gelatinized starch, Avicel PH 102 and Aerosil 200	Solvent evaporation Method	[47]
Repaglinide	Eudragit E100, hydroxyl propyl cellulose Mw 80 000 and poly vinyl pyrollidone K30	Spray drying technique	[33]
Piroxicam	skimmed milk	Solvent evaporation technique	[48]
Felodipine	Modified β-Cyclodextrin (SBE- β-CD)	kneading technology and solvent evaporation technique.	[49]
Felodipine	Polyethylene Glycol (PEG 6000) and Polyvinyl Alcohol (PVA)	Solvent evaporation technique	[30]
Carbamazepine	HPMC (Methocel® E3 LV and Methocel® E5 LV)	Hot melt extrusion	[50]

Advantages and Disadvantages of solid dispersion [39]

a. **Advantages**

- Reduction in particle size: different carrier use in solid dispersion reduces particle size of drug particle which improve solubility and bioavailability.
- Improve wettability of particle: solid dispersion improves wettability of particle.
- 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.
- Improve dissolution which ultimately improves the solubility and bioavailability.

b. **Disadvantages**

- Instability due moisture content.
- Difficulty in incorporating into formulation of dosage forms.

Evaluation of physicochemical properties of solid dispersion [34,40-46]

- **Phase Solubility Study**

It is carried out in the presence of polymer (carrier) using shaking flask method. It is mostly conducted according to the Higuchi and Connors. In this method, drug is placed in a 25 ml containing 1%, 2%, 3%, 4% and 5% polymer solution. Then it is placed in orbital flask shaker for 48 hrs. at 37°C±0.5°C temperature. Then sample is filtered and analysed by UV spectrophotometer for determination concentration of drug.

- **Saturation Solubility Study**

Drug and solid dispersion batches are added in excess quantity in 25 ml distilled water up to its super saturation. Then it is placed in orbital flask shaker for 48 hrs. at 37 °C±0.5°C temperature. Then it is filtered through whatman filtered paper and analysed for determination of concentration of drug by UV spectrophotometer.

- **Drug content**

Known quantity of solid dispersion is dissolved in a solvent and then analysed by UV spectrophotometer for determination of drug content.% drug loading and % entrapment efficiency is calculated by following equation,

% Drug loading = (Weight of drug in solid dispersion powder)/ (Weight of solid dispersion powder) X 100 -----(1)

Characterization of Solid dispersions [34,46]

- **Fourier Transform Infrared Spectroscopy (FT-IR)**

FT-IR mostly used for to characterize drug- polymer (carrier) compatibility study. Its main application is to study the solid state interaction between drug and polymer.

- **Differential Scanning Calorimetry (DSC)**

It is a powerful technique used for to study amorphous content. It also detect endothermic and exothermic peak. It also studies whether the drug was incorporated into the polymer (carrier) or not on the basis of melting point.

- **Powder X-ray Diffraction (PXRD)**

It is mostly useful for to characterize whether the solid dispersion is amorphous or crystalline. Sharper peak indicate more crystalinity.

- **Scanning electron microscopy**

It is used for to characterize particle morphology.

Examples of different polymer used in solid dispersion

Table 3.

Conclusion

The solubility property of drugs remains one of the most challenging aspects in formulation development. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is the basic requirement for the absorption of the drug from GIT. The various techniques Solid dispersion described above can be used to enhance the solubility of the drugs.

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