(Review Article)

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A Review on Solid Dispersion

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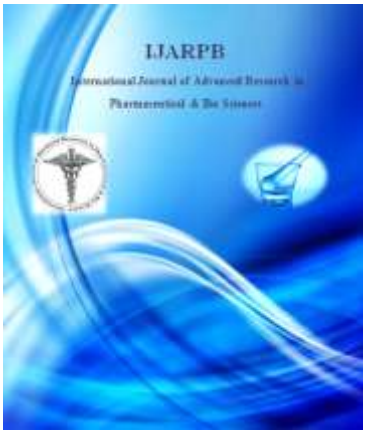

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ABSTRACT

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. 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. 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.

KEY WORDS: pH adjustment, solid dispersion, complexation, hydrotropy.

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INTRODUCTION

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. 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. 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 drugs weakly acidic and weakly basic with poor aqueous solubility. Hence, various techniques are used for the improvement of the solubility of poorly water-soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc[1].

Techniques of Solubility Enhancement

There are various methods to improve solubilization of poorly water soluble drug and to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc.

pH Adjustment

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4.

Advantages

- Simple to formulate and analyze.
- Simple to produce and fast track.
- Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages

- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble.
- Tolerability and toxicity (local and systemic) related with the use of a non physiological pH and extreme pHs.
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

Co-Solvency

The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as co-solvents.

Advantages

- Simple and rapid to formulate and produce.

Disadvantages

- As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered.
- Uncontrolled precipitation occurs upon dilution with aqueous media.
- As with all solubilized forms, the chemical stability of the insoluble drug is worse than in a crystalline state.

Co-solvent products

Nimodipine Intravenous Injection (Nimotop, Bayer) and Digoxin Elixir Pediatric (Lanoxin, GSK) are examples of co-solvent formulations.

Particle Size Reduction

The bioavailability intrinsically related to drug particle size. By reducing particle size, increased surface area improves the dissolution properties. Particle size reduction, it is done by milling techniques using jet mill, rotor stator colloid mills etc.

Advantages

- Liquid forms can be rapidly developed for early stage testing (pre-clinical) that can be converted into solids for later clinical development.
- Low excipient to drug ratios is required.
- Formulations are generally well toleratedprovided that strong surfactants are not required for stabilisation.
- Crystal forms are chemically and physically more stable than amorphous particles.

Disadvantages

- Due to the high surface charge on discrete small particles, there is a strong tendency for particle agglomeration.
- Developing a solid dosage form with a high pay load without encouraging agglomeration may be technically challenging.
- Development of sterile intravenous formulations is more challenging.

Ball milled products

This process is widely used in non-pharmaceutical applications particularly in cosmetics to obtain ultra fine particles for sun block. Examples of pharmaceutical products include rapamycin (Rapamune, 1 mg and 2 mg tablets, Wyeth).

Microemulsions

Microemulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous / transdermal use. A microemulsion is an optically clear pre-concentrate containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent which dissolves a poorly water soluble drug[2].

Advantages

- The pre-concentrates are relatively easy to manufacture.
- Well developed microemulsion pre-concentrates are not normally dependent upon digestion for drug release.

Disadvantages

- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
- The tolerability of formulations with high levels of synthetic surfactants may be poor in cases where long term chronic administration is intended.
- Formulations containing several components become more challenging to validate.

Microemulsion products

Examples of poorly soluble compounds that use micro-emulsion pre-concentrates are the HIV protease inhibitor tipranavir (Aptivus capsules, Boehringer Ingelheim GmBH) and the category defining immunosuppressant cyclosporine A, USP modified (Neoral capsules, Novartis AG).

Micellar Solublization

The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium. They can also be used to stabilise drug suspensions.

Examples of poorly soluble compounds that use Micellar solubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone and rosiglitazone.

Complexation

Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α, β, γ-cyclodextrin) bound in a 1, 4-configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form noncovalent inclusion complexes resulting in increased aqueous solubility and chemical stability. Derivatives of β-cyclodextrin with increased water solubility (e.g. hydroxypropyl-β-cyclodextrin HP-β-CD) are most commonly used in pharmaceutical formulation.

Examples of poorly soluble compounds that use complexation are

- α-cyclodextrin- PGE_1 (Controlled hypotension during surgery), Cefotiam-hexetil (Antibiotics)
- β-cyclodextrin- PGE_2 (Induction of labour), Piroxicam (Antiinflammatory, Analgesic)
- γ-cyclodextrin- OP-1206 (Buerger's disease)
- HPβ-cyclodextrin- Hydrocortisone (Mouth wash against gingivitis, etc.), Itraconazole (Esophageal candidiosis)
- HPγ-cyclodextrin- Diclofenac Na (Non-steroid anti-inflammatory)
- Methyl β-cyclodextrin- Chloramphenicol (Eye drop, Antibiotic agent).

Supercritical Fluid (SCF) Process

Supercritical fluids can dissolve nonvolatile solvents, with the critical point of carbon dioxide; the most widely used supercritical fluid. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research. A SCF exists as a single phase above its critical temperature (TC) and pressure (PC)[3].

Solid Dispersions

SCF techniques can be applied to the preparation of solvent-free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Traditional methods suffer from the use of mechanical forces and excess organic solvents. In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Solid dispersion techniques can yield eutectic (non molecular level mixing) or solid solution (molecular level mixing) products.

Hydrotrophy

Hydrotrophy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to “salt in” the solute and those salts that decrease solubility “salt out” the solute. Several salts with large anions or cations that are themselves very soluble in water result in “salting in” of non electrolytes called “hydrotropic salts” a phenomenon known as “hydrotropism”. Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea and the poorly soluble drugs.

Advantages

- Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, cosolvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.
- It only requires mixing the drug with the hydrotrope in water.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.

Definition of Solid Dispersions

Solid dispersions is an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly soluble drugs. 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. The drug can be

dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

Table 1: Based on their molecular arrangement, 6 different types of solid dispersions can be distinguished

Sr. No.	Solid dispersion type	Matrix *	Drug **	Remarks	No. of phases
I	Eutectics	C	C	The first type of solid dispersion prepared	2
II	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
III	Solid solutions				
	Continuous solid solutions	C	M	Miscible at all composition, never prepared	1
	Discontinuous solid solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed.	2
	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinuous: 2 phases even though drug is molecularly dispersed.	1or 2
	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug inhelical interstitial spaces of PEG.	2
IV	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/ evaporation rate. Obtained after crystallization of drug in	2

				amorphous matrix	
V	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate. Many solid dispersions are of this type.	2
VI	Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or upon fast cooling OR evaporation during preparation, many examples especially with PVP.	1

*A: matrix in the amorphous state, C: matrix in the crystalline state.
**A: drug dispersed as amorphous clusters in the matrix.
C: drug dispersed as crystalline particles in the matrix.
M: drug molecularly dispersed throughout the matrix.

Advantages of Solid Dispersion

Particles with Reduced Particle Size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.

Particles with Improved Wettability

Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly increase the wettability property of drug. Even carriers without any surface activity, such as urea, improved drug wettability. Carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

Particles with Higher Porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

Drugs in Amorphous State

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its

amorphous state, because no energy is required to break up the crystal lattice during the dissolution process.

For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

Preparation of Solid Dispersions

There are various methods for preparation of solid dispersions. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are poorly miscible. During many of the preparation techniques, de-mixing (partially or complete), and formation of different phases is observed. Phase separation can be prevented by

1. Maintaining a low molecular mobility of matrix and drug during preparation and
2. Maintaining the driving force for phase separation low, for example, by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

Fusion Method

The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. This procedure resulted in solid dispersions of type I. Poly ethylene glycol (PEG) is a hydrophilic polymer used to prepare solid dispersions with the fusion method. Another polymer frequently applied as a matrix in the fusion method is poly vinyl pyrollidone (PVP).

Disadvantages

1. The method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible, two liquid phases or a suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants.
2. A problem can arise during cooling when the drug-matrix miscibility changes. In this case phase separation can occur. It was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions.
3. Degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug. For example, to melt a sugar matrix of galactose a temperature of 169°C was required and in order to get the glassy PVP in the rubbery state a temperature of about 170°C is required. Poly ethylene glycols melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method.

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Hot Melt Extrusion Method

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar, but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms.

Advantages over fusion method

1. This technique offers the possibility of continuous production, which makes it suitable for large-scale production.
2. The product is easier to handle because at the outlet of the extruder the shape can be adapted

to the next processing step without grinding.

Solvent Method

This method involves two steps-

1. The preparation of a solution containing both matrix material and drug.
2. The removal of solvent(s) resulting in formation of a solid dispersion.

Using the solvent method, the pharmaceutical engineer faces two challenges

1. The first challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible preferably drug and matrix material are in the dissolved state in one solution.

2. The second challenge in the solvent method is to prevent phase separation, e.g. crystallization of either drug or matrix, during removal of the solvent(s). Drying at high temperatures speeds up the process and reduces the time available for phase separation. On the other hand, at high temperatures the molecular mobility of drug and matrix remains high, favoring phase separation (e.g., crystallization).

Table2: Some Organic Solvents

Sr. No.	Solvents	Melting Point (°C)	Boiling Point (°C)	Vapour Pressure at 25°C (kPa)
1.	Water	0	100	3.16
2.	Methanol	-93.9	65	16.9
3.	Ethanol	-117	78.5	5.79
4.	1-propanol	-85.8	97.4	2.27
5.	2-propanol	-127	82.4	5.85
6.	Chloroform	-63	62	26.1

7.	Dimethylsulphoxide (DMSO)	19	189	0.08
8.	Acetic acid	17	118	1.64
9.	1,4-dioxane	12	102	4.92
10.	2-methyl-2-propanol (TBA)	25	82	5.49

Supercritical Fluid Methods

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent. When supercritical CO_2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO_2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS).

Characterization of Solid Dispersion
Detection of Crystallinity in Solid Dispersions

Many techniques are available which detect the amount of crystalline material in the dispersion. The amount of amorphous material is never measured directly but is mostly derived from the amount of crystalline material in the sample.

The following techniques are available to detect the degree of crystallinity

1. Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material.
2. Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transform Infrared Spectroscopy (FTIR) was used to accurately detect crystallinities ranging from 1 to 99% in pure material.
3. Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different.
4. Isothermal Microcalorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg).
5. Dissolution Calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample.
6. Macroscopic techniques that measure mechanical properties that are different for amorphous and crystalline material can be indicative for the degree of crystallinity.
7. Differential Scanning Calorimetry (DSC) technique is used to detect the amount of crystalline material.

Detection of Molecular Structure in Amorphous Solid Dispersions

The properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix.

1. Confocal Raman Spectroscopy was used to measure the homogeneity of the solid mixture of ibuprofen in PVP.
2. Using IR or FTIR, the extent of interactions between drug and matrix can be measured.
3. Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug[4].

Electrostatic Spinning Method

This technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology. In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandril. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and non biodegradable) polymers are useful in controllable dissolution properties. Fabrics generated by water-soluble carriers could be used in oral dosage formulations by direct incorporation of the materials into a capsule. Itraconazole/HPMC nanofibers have been prepared using this technique.

Surface-Active Carriers

A surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs. Two of the important surface-active carriers are Gelucire 44/14 and Vitamin E R-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Gelucire 44/14 has commonly been used in solid dispersion for the bioavailability enhancement of drugs. A commonly used surfactant, Polysorbate 80, when mixed with solid PEG, has also been reported to be an alternative surface-active carrier. Polysorbate 80 is liquid at room temperature; it forms a solid matrix when it is mixed with a PEG because it incorporates within the amorphous regions of PEG solid structure.

REFERENCES

1. Dhirendra K. *et al*, “Solid dispersions: A review”, Pak. Journal of Pharmaceutical Sciences, 22(2), 2009, 234-46.
2. Brahmankar DM, *et al*, “Bio pharmaceutics and Pharmacokinetics”, 2009, 349-57.
3. Martin A, “Physical pharmacy”, Lippincott Williams & Wilkins, A. Walters Kluwer Co, Philadelphia, 2003, 5, 410-18.
4. Rajewski RA, and Stella VJ, “Pharmaceutical applications of cyclodextrins, *in vivo* drug delivery”, Journal of Pharmaceutical Sciences, 1996, 85, 1142-69.