



FORMULATION AND DEVELOPMENT STRATEGIES FOR DRUGS INSOLUBLE IN GASTRIC FLUID

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Article Received on: 18/11/11 Revised on: 20/12/11 Approved for publication: 10/01/12

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ABSTRACT

A success of formulation depends on how efficiently it makes the drug available at the site of action. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules especially in the gastric fluid for oral delivery of the drug molecules. But most of the time it becomes challenging to formulate poorly water soluble drugs. Therefore it is necessary to improve solubility of drug by various ways like solid dispersions, hot-melt extrusion, spray freezing into liquid, super critical fluid technology, micellar technology, spray drying, liquisolid technology, salt formation, co-solvency, and addition of solubilizing agent, micronization, and complexation. Although these techniques have commonly been used to increase dissolution rate of the drug, there are practical limitations with these techniques, the desired bioavailability enhancement may not always be achieved. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate/prepare solid dispersions. The purpose of this review article is to describe the techniques of solubilization for the attainment of effective absorption and improved bioavailability.

Key words: Solid dispersion, Liquisolid, Spray drying, Inclusion complex, dissolution enhancement, solubility enhancement

INTRODUCTION

Almost More than 90% drugs are orally administered. Drug absorption, sufficient & reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on Solubility of that compound in aqueous medium¹.

More than 90% of drugs are approved since 1995 have poor solubility. It is estimated that 40% of active new chemical entities (NCEs) identified in combinatorial screening programs employed by many pharmaceutical companies are poorly water soluble. Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances. Orally administered drugs on the Model list of Essential Medicines of the World Health Organization (WHO) are assigned BCS classifications on the basis of data available in the public domain². Of the 130 orally administered drugs on the WHO list, could be classified with certainty. 84% of these belong to class I (highly soluble, highly permeable), 17% to class II (poorly soluble, highly permeable), 24 (39%) to class III (highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble, poorly permeable). The rate and extent of absorption of class II & class IV compounds is highly dependent on the bioavailability which ultimately depends on solubility³.

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction.

Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. The drug solubility in saturated solution in a static property where as the drug

dissolution rate is a dynamic property that relates more closely to the bioavailability rate.

The pharmacopoeia lists solubility in terms of number of milliliters of solvent required to dissolve 1g of solute. If exact solubilities are not known, the Pharmacopoeia provides general terms to describe a given range. These descriptive terms are listed in (Table1)¹.

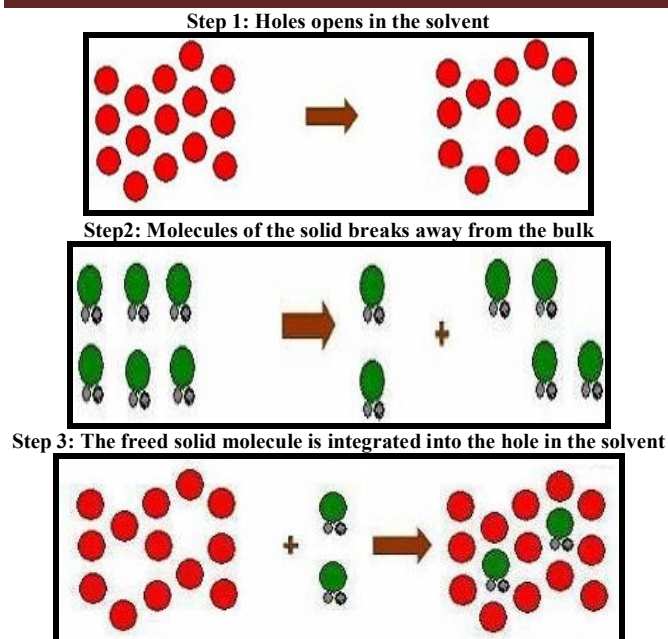
Need Of Solubility

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8% of new drug candidates have both high solubility and permeability⁴.

As a matter of fact, more than one-third of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. It was reported a couple of decades ago that more than 41% of the failures in new drug development have been attributed to poor biopharmaceutical properties, including water insolubility, while it was still indicated recently that about 50% failure of drug candidates was due to poor “drug-like” properties. It is commonly recognized in the pharmaceutical industry that on average more than 40% of newly discovered drug candidates are poorly water-soluble. Poor “drug like” properties of lead compounds led to ineffective absorption from the site of administration, which has been designated as an important part of the high clinical failure due to poor pharmacokinetics. The basic aim of the further formulation & development section is to make that drug available at proper site of action within optimum dose.

Process Of Solubilisation¹

The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.



A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further 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, hydrotropism etc. Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development⁵. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. As Solubility & permeability is the deciding factor for the in-vivo absorption of the drug, these can be altered or modified by enhancement techniques like. The term 'solubility' is defined as maximum amount of solute that can be dissolved in a given amount of solvent. It can also be defined quantitatively as well as qualitatively. Quantitatively it is defined as the concentration of the solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug is represented through various concentration expressions such as parts, percentage, molarity, molality, volume fraction, and mole fraction⁶.

Biopharmaceutical Classification system categorizes every drug compounds in to four following categories

Solubility is Predetermine and rate limiting step for permeation hence it is require improving solubility of BCS Class-II compounds.

Dissolution Enhancement Techniques^{4,8}

Conventionally and most economical techniques used for enhancing dissolution rate and thereby bioavailability of insoluble drugs include

- Solid dispersion
- Inclusion complexation

Newer techniques used for dissolution enhancement include

- **Precipitation technologies**

1. Evaporative precipitation into aqueous solution
2. Controlled precipitation

- **Size reduction technologies**

1. Nanosizing technologies
2. Media milling
3. Homogenization in water
4. Homogenization in non-aqueous media
5. Supercritical fluid technology

- **Lipid based delivery systems**

1. Lipid emulsion technology
2. Microemulsion technology
3. Self dispersing lipid formulations
4. Liposomal systems
5. Inulin Glasses

- **Micellar solubilization technology (mixed micelles)**

- **Functional polymer technology**

- **Spray drying microparticle technology**

- **Liquisolid technology**

Solid Dispersions

Solid dispersion, a concept firstly introduced by Sekiguchi & Obi. The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method. However, the definition can now be broadened to include certain nanoparticles, microcapsules, microspheres and other dispersion of the drug in polymers prepared by using any one of the process. Sekiguchi and Obi suggested that the drug was present in a eutectic mixture in a microcrystalline state, after few years Goldberg et.al. Reported that all drug in solid dispersion might not necessarily be presented in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution.^{9, 10, 11, 12, 13}

Methods of preparation

A. Melt/Cool Method

- a. Melting Solvent Method
- b. Hot stage extrusion

B. Solvent Evaporation

- a. Hot Plate Drying
- b. Vacuum drying
- c. Slow evaporation at low temperature
- d. Rotary evaporation
- e. Spray drying
- f. Freeze drying
- g. Spin drying
- h. Fluid bed coating

C. Co-precipitation

- a. Addition of an anti-solvent

D. Dropping method

Inclusion Complex

Cyclodextrins are bucket-shaped oligosaccharides produced from starch. As a result of their molecular structure and shape, they possess a unique ability to act as molecular containers by entrapping guest molecules in their internal cavity. The resulting inclusion complexes offer a number of potential advantages in pharmaceutical formulations.^{17, 18}

Cyclodextrins increase the water solubility of poorly soluble drugs to improve their bioavailability. Light, thermal and oxidative stability of actives can be improved through the formation of Cyclodextrins complexes. Cyclodextrins have also been used to reduce dermal, gastrointestinal or ocular irritation, mask unpleasant tastes or odors, prevent adverse drug-ingredient interactions and convert oils/liquids into powders to improve handling²².

Techniques used to form complexes²³⁻²⁷

Co-precipitation
Damp mixing
Extrusion
Dry mixing
Spray drying or freeze drying
Slurry Method
Kneading method
Neutralization method

Hot-Melt Extrusion

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. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. Solubility parameters are investigated to predict the solid-state miscibility and to select matrices suitable for melt extrusion.^{28, 29} High shear forces resulting in high local temperatures in the extruder are a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, 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.³⁰

Melting-Solvent Mix Method

In this method liquid component could be incorporate in high molecular weight PEG without significant loss of its solid property. Hence, it's possible to prepare solid dispersion by first dissolving drug in a suitable solvent and then the solution in incorporated directly in to the melted PEG without removing liquid solvent^{31, 32, 33}.

Example –

Spironolactone-PEG 6000,
Griseofulvin-PEG 6000

Advantages: Combine advantage of both fusion and solvent method.

Disadvantages

It is possible that selected solvent or dissolved drug may not be miscible with melted PEG.

The liquid solvent used may affect the polymorphic form of the drug precipitated in the solid dispersion.

The Use Of Surfactant

The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.^{34, 35, 36, 37}

PRECIPITATION TECHNOLOGIES**Evaporative precipitation into aqueous solution**

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent. The solution is pumped through a tube where it is

heated under pressure to a temperature above the solvent's boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution on the aqueous solution to optimize particle formation and stabilization³⁸.

Use of precipitation inhibitors

A significant increase in free drug concentration above equilibrium solubility results in supersaturation, which can lead to drug precipitation or crystallization. This can be prevented by use of inert polymers such HPMC, PVP, PVA, PEG etc.^{39, 40}

Supercritical Fluid Process

Supercritical fluids (e.g. carbon dioxide) are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are highly compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drugs are solubilised within SCF, they may be recrystallization at greatly reduced particle sizes⁴¹.

Supercritical fluid CO₂ is a good solvent for water-insoluble as well as water-soluble compounds under suitable conditions of temperature and pressure. Therefore, supercritical CO₂ has potential as an alternative for conventional organic solvent used in solvent-based processes for forming solid dispersion due its favourable properties of being non-toxic and inexpensive. Supercritical Fluid Process consists of following steps^{42, 43}:

- charging the bioactive material and suitable polymer into autoclave
- addition of supercritical CO₂ under precise conditions of temperature and pressure, that causes polymer to swell
- mechanical stirring in the autoclave
- Rapid depressurization of the autoclave vessel through a orifice to obtained desired particle size.

Advantage: The temperature condition used in this process are fairly mild (35-75 °C), which allows handling of heat sensitive bio molecules, such as enzyme and proteins.

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. Not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Nowadays Particle size reduction can be achieved by micronisation and nanosuspension. Each technique utilizes different equipments for reduction of the particle size^{44, 45}. In micronization the solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug⁴⁶. Nanosuspension is another technique which is sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. The nanosuspension approach has been employed for drugs including tarazepide, atovaquone, amphotericin B, paclitaxel and bupravaquon. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while

absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor. Nanosuspensions are produced by homogenization and wet milling process ⁴⁷.

Advantages

- Liquid forms can be rapidly developed for early stage testing (pre-clinical) that can be converted into solids for later clinical development.
- Typically, low excipient to drug ratios is required.
- Formulations are generally well tolerated provided that strong surfactants are not required for stabilisation.
- Generally, crystal forms are chemically and physically more stable than amorphous particles.
- A method to consider for stubborn compounds that defeat previous attempts to increase solubility.

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 payload without encouraging agglomeration may be technically challenging. Technically, development of sterile intravenous formulations is even more challenging.

Spray Freezing Into Liquid And Lyophilization

This technique involves atomizing an aqueous, organic, aqueous-organic cosolvent solution, aqueous organic emulsion or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. CO₂, helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon or hydrofluoroethers). The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders. Use of acetonitrile as the solvent increases drug loading and decreases the drying time for lyophilization. The dissolution rate is remarkably enhanced from the SFL powder containing amorphous nanostructured aggregates with surface area and excellent wettability ^{48, 49, 50}.

Micellar Solubilization

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. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05-0.10% for most surfactants), micelle formation occurs, entrapping the drugs within the micelles. This process is known as micellisation and generally results in enhanced solubility of poorly soluble drugs [51]. Commonly used non-ionic surfactants include polysorbates, polyoxy ethylated castor oil, polyoxyethylated glycerides, lauroyl macroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved. Micellar solubilization is a widely used alternative for the dissolution of poorly soluble drugs ⁵².

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. Upon contact with water, the formulations spontaneously disperse (or 'self emulsifies') to form a very

clear emulsion of exceedingly small and uniform oil droplets containing the solubilized poorly soluble drug. Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 20-200 nm. These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity. A self microemulsifying drug delivery system (SMEDDS) is an anhydrous system of microemulsions ⁵³. It has also been referred to as microemulsion pre-concentrate by some researchers. It is composed of oil, surfactant and cosurfactant and has the ability to form o/w microemulsion when dispersed in aqueous phase under gentle agitation. The agitation required for the self-emulsification comes

from stomach and intestinal motility. The surfactant can be non-ionic like polyoxyethylene surfactants e.g. Brij or sugar esters like sorbitan monooleate (Span 80), cationic, or anionic like alkyltrimethylammonium bromide and sodium dodecyl sulphate, or zwitterionic such as phospholipids like lecithin (phosphatidylcholine) commercially available from soybean and eggs. Lecithin is very popular because it exhibits excellent biocompatibility. Combinations of ionic and non-ionic surfactants are also found to be effective. The major disadvantage of microemulsions is their high concentration of surfactant/cosurfactant, making them unsuitable for IV administration. Dilution of microemulsions below the critical micelle concentration of the surfactants could cause precipitation of the drug; however, the fine particle size of the resulting precipitate would still enhance absorption. Compared to macroemulsion pre-concentrates, microemulsion pre-concentrates remain optically clear after dilution and usually contain a higher amount of water soluble surfactant and a higher content of a hydrophilic solvent. These formulations are only administered orally due to the nature of the excipients. Solubilization using microemulsion pre-concentrates is suited to poorly soluble lipophilic compounds that have high solubility in the oil and surfactants mixtures. Most self-emulsifying systems are limited to administration in lipid-filled soft or hard-shelled gelatin capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hygroscopic contents from dehydrating or migrating into the capsule shell. Emulsion droplet size is a major factor influencing bioavailability of drugs from emulsion formulations, with small droplet radii enhancing the plasma levels of drugs, in part due to direct lymphatic uptake. ⁵⁴ Since SMEDDS contain high concentration of surfactants, they should be limited to oral applications and may not be advisable for long-term use due to the potential of causing diarrhoea.

Advantages

- The pre-concentrates are relatively easy to manufacture.
- Well developed microemulsion pre-concentrates are not normally dependent upon digestion for drug release. Therefore, optimal bioavailability and reproducibility can be also being expected without co-administration of food (i.e. the fasted state)

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 microemulsion 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).

Liquisolid Technology

A more recent technique, “powdered solution technology” or “Liquisolid technology”, has been applied to prepare water-insoluble drugs into rapid release solid dosage forms. Powdered solutions are designed to formulate liquid medications in powdered form. The concept of powdered solutions enables one to convert a liquid drug or poorly water-soluble solid drug dissolved in a suitable non-volatile solvent into a dry, non-adherent, free flowing and readily compressible powder by its simple admixture with selected carrier and coating materials. In spite of formulating the drug in a tableted or a encapsulated dosage form, it is held in solution thus enhancing its release.⁵⁵

Liquid medication includes liquid lipophilic drugs and drug suspensions or solutions of solid water insoluble drugs in suitable non-volatile solvent systems.

Liquisolid systems refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials⁵⁶

Advantages of Liquisolid Compact

1. A great number of slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs such as Digitoxin, Prednisolone and Hydrocortisone etc. can be formulated into liquisolid systems using the new formulation-mathematical model.
2. Better availability of an orally administered water-insoluble drug is achieved when the drug is in solution form.
3. Though the drug is in a tableted or encapsulated dosage form it is held in a solubilized liquid state, which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution.
4. Production cost of liquisolid systems is lower than that of soft gelatin capsules.
5. Advantage of liquisolid systems, particularly for powdered liquid drugs, during dissolution of a liquisolid tablet, after the disintegration process is completed, the drug solution or liquid drug, carried on the suspended and thoroughly agitated primary particles, is dispersed throughout the volume of the dissolution medium; such a phenomenon does not extensively occur during the dissolution process of soft gelatin capsule preparations. Therefore, since more drug surface is exposed to the dissolving medium, liquisolid systems exhibit enhanced drug release.
6. Optimized rapid-release liquisolid tablets or capsules of water-insoluble drugs exhibit enhanced in-vitro and in vivo drug release as compared to their commercial counterparts.
7. Optimized sustained-release liquisolid tablets or capsules of water-insoluble drugs exhibit surprisingly constant

dissolution rates (zero-order-release) comparable only to expensive commercial preparations that combine osmotic pump technology and laser-drilled tablets.

Disadvantages of Liquisolid System

1. The liquisolid systems have low drug loading capacities and they require high solubility of drug in non-volatile liquid vehicles.
2. It requires more efficient excipients which have higher adsorption capacities which provide faster drug release with a smaller tablet size to improve liquisolid formulations.
3. To maintain acceptable flowability and compatibility for liquisolid powder formulation high levels of carrier and coating materials are required and that in turn will increase the weight of each tablet above 1 gm which is very difficult to swallow.

Spray Drying Technology

The production of particles from the process of spraying has gained much attention in recent years. These efforts have resulted in spray technology being applied to the manufacture of particles to generate products ranging from pharmaceutical direct compression excipients and / or granulations to microencapsulated flavours. The two main spray techniques are spray drying & spray congealing^{57, 59}. The action in spray drying is primarily that of evaporation, whereas in spray congealing it is that of a phase change from a liquid to a solid. The two processes are similar, except for energy flow. In the case of spray drying, energy is applied to the droplet, forcing evaporation of the medium resulting in both energy and mass transfer through the droplet. In spray congealing, energy only is removed from the droplet, forcing the melted to solidify^{60, 61}.

Recently, the process received great attention in the field of micro particles for the preparation of dried liposomes, amorphous drugs, mucoadhesive microspheres, drying of preformed microcapsules, Gastroresistant microspheres, and controlled-release systems. Comprehensive studies have been performed on the preparation of microspheres by spray drying techniques for different purposes, like modification of biopharmaceutical properties, formulation of dry emulsions, spray dried phospholipids, nanoparticle-loaded microspheres, for drug delivery, spray-dried powders formulated with hydrophilic polymers, biodegradable microspheres, and spray-dried silica gel microspheres. Eudragit RL microspheres containing vitamin C were prepared by Spray drying method. Spray-drying was useful for the preparation of Paracetamol encapsulating Eudragit RS/RL or Ethylcellulose microspheres. The spray drying technique has been widely applied to prepare micro-particles of drug with polymer. When a drug crystal suspension of a polymer solution is spray-dried, microcapsulated particles are prepared, whereas spray drying of solution of polymer containing dissolved drug leads to formation of drug-containing microspheres in which the drug can be dispersed in a molecular state or as micro crystals. In both cases, the particles tend to have a spherical shape and are free flowing. These properties are preferable pharmaceutical manufacturing process such as tableting and capsule filling. Controlling microsphere size is an important process variable that can affect product performance^{62, 63}. Scanning Electron microscope (SEM) is used to characterize the size of microspheres. The conventional method of sizing involves periodic sampling and subsequent analysis using off-line techniques, but these have limitations such as late feedback response times, sampling errors and lacks the sensitivity required for it to be

used in the detection of fluctuations. Using PAT as an in-process monitor during spray drying could offer better process control and improved product quality resulting in products of greater value. Thus, PAT serves as a useful tool to provide real time information about process and product size. Micro particles of diltiazem hydrochloride with ethyl cellulose (EC) were prepared by using spray drying technique. Drug was dispersed in benzene solution of EC or dissolved in methanol solution of EC with 1:1-1:5 drug EC ratios, followed by spray drying. A microcapsule structure was obtained in the suspension system, while a microsphere structure, while the drug was in an amorphous state, was formed in the solution system.

Advantages of spray drying

1. Able to operate in applications that ranges from aseptic pharmaceutical processing to ceramic powder production.
2. It can be designed to virtually any capacity required. (Feed rates range from a few pounds per hour to over 100 tons per hour).
3. The actual spray drying process is very rapid, with the major portion of evaporation taking place in less than a few seconds.
4. Adaptable to fully automated control system that allows continuous monitoring and recording of very large number of process variables simultaneously.
5. Wide ranges of spray dryer designs are available to meet various product specifications.
6. It has few moving parts and careful selection of various components can result in a system having no moving parts in direct contact with the product, thereby reducing corrosion problems.
7. It can be used with both heat-resistant and heat sensitive products.
8. As long as they are can be pumped, the feedstock can be in solution, slurry, paste, gel, suspension or melt form.
9. Offers high precision control over Particle size, Bulk density, Degree of crystallinity, organic volatile impurities and residual solvents.
10. Powder quality remains constant during the entire run of the dryer. Nearly spherical particles can be produced, uniform in size and frequently hollow, thus reducing the bulk density of the product.

Disadvantages of spray drying

1. The equipment is very bulky and with the ancillary equipment is expensive.
2. The overall thermal efficiency is low, as the large volumes of heated air pass through the Chamber without contacting a particle, thus not contributing directly to the drying.

CONCLUSION

A drug administered in solution form is immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is also the basic requirement for the formulation and development of different dosage form of different drugs. The various techniques described above alone or in combination can be used to enhance the solubility of the drug. Solubility can be enhanced by many techniques and number of folds

increase in solubility. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary.

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Table 1: Expressions of Solubility

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

Table 2: BCS Classification ^{2, 19, 20}

BCS Class – I	High solubility and High Permeability
BCS Class – II	Low solubility and High Permeability
BCS Class – III	High solubility and Low Permeability
BCS Class – IV	Low solubility and Low Permeability

Table 3: Materials used as Carriers for Solid Dispersion ^{14, 15, 16}

Sugars	Dextrose, sucrose, Galactose, sorbitol, Maltose, Xylitol, Mannitol, Lactose
Acids	Citric acid succinic acid
Polymeric Materials	PVP, PEG, HPMC, Methyl cellulose, Hydroxyl, ethyl cellulose, Cyclodextrins. Hydroxyl propyl cellulose, Pectin, polyethylene oxide, MCC cellactose, Avicel, starch
Insoluble or Enteric polymer	Hydroxypropylmethylphalate, Eudragit RL, Eudragit RS, Eudragit L-100 Eudragit S-100
Surfactant	Polyethylene stearate, Renex Poloxamer 188, Texafor API, Tweens, Spans , Cholesterol esters, Lecithin, Cholic acid, deoxycholic acid, Bile salts.
Miscellaneous	Pentaerythritol, Urea Urethane, Hydroxyalkylxanthins.

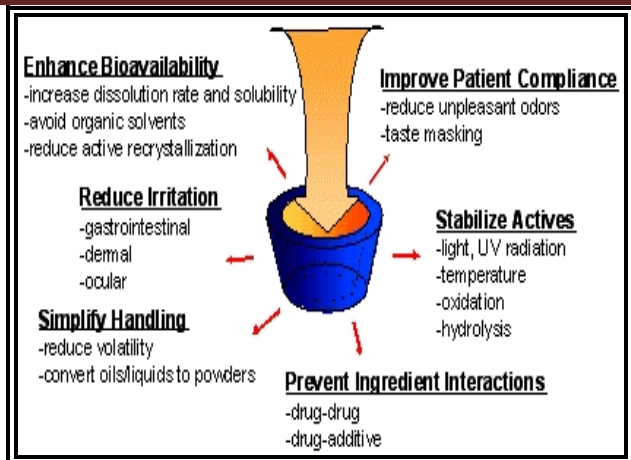


Figure 1: Multiple benefits exist for Cyclodextrins complexes in pharmaceutical formulations²¹

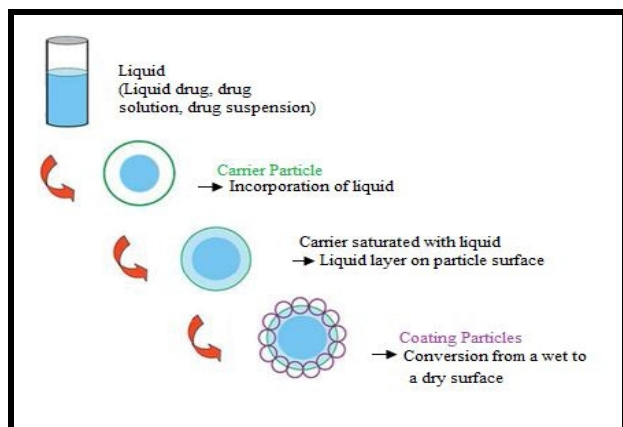


Figure 2: Steps in Formulation of Liquisolid⁵⁷.

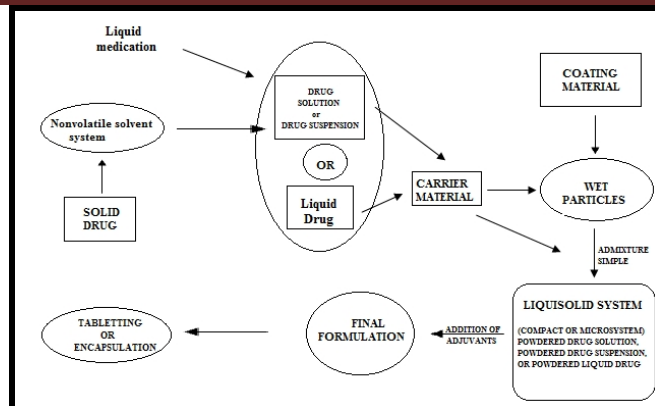


Figure 3: General method for formulation of liquisolid compact⁵⁸

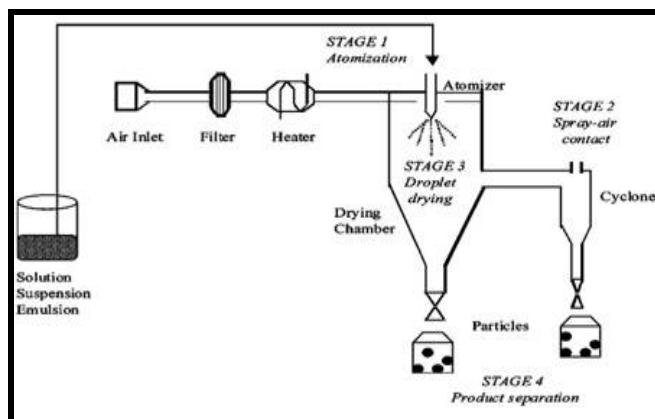


Figure 4: stages involved in Spray drying process⁵⁷