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Review Article

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A Consensus Review on Fast Disintegrating Tablets

Akanksha Sharma[1], Vishal Garg[2], Manish Kumar Gupta[1], Vijay Sharma[1]

[1]Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, Rajasthan, India
[2]Jaipur School of Pharmacy, Maharaj Vinayak Global University, Jaipur Rajasthan, India

Abstract Oral route is the most preferred route for administration of various drugs because it is regarded as safest, most convenient and economical route. Recently researcher developed the fast disintegrating tablets with improved patient compliance and convenience. Fast disintegrating tablets are solid dosage forms which dissolve rapidly in saliva without chewing and additional water. Fast disintegrating tablets overcome the disadvantages of conventional dosage form especially dysphagia (difficulty in swallowing) in pediatric and geriatric patients. Fast disintegrating tablets have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Upon introduction into the mouth, these tablets dissolve or disintegrate in the mouth in the absence of additional water for easy administration of active pharmaceutical ingredients. The popularity and usefulness of the formulation resulted in development of several fast disintegrating tablets technologies. This review includes requirements for fast disintegrating tablets, salient features, advantages, limitations, challenges in formulation, various technologies developed for fast disintegrating tablets, patented technologies, evaluation methods and various marketed products.

Keywords Fast disintegrating tablets, Superdisintegrants, Direct compression, wetting time

Introduction

Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of their ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are tablets and capsules. But an important drawback of these dosage forms are that for some patients these are difficult to swallow. Dysphagia or difficulty in swallowing is common among all age groups. Dysphagia is common in about 35% of the general population, well as an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities. Common complaints about the difficulty in swallowing tablets in the order of frequency of complaints are size, surface, form, and taste of tablets. Geriatric and pediatric patients and travelling patients who may not have ready access to water are most in need of easy swallowing dosage forms. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablets when water is not available, in motion sickness and sudden episodes of coughing during the common cold, allergic conditions and bronchitis. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Fast disintegrating tablets are not only preferable for people who have swallowing difficulties, but also are ideal for active people [1].

Fast Disintegrating Tablets

Fast disintegrating drug delivery systems (FDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and at the same time, offer added advantages over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation. FDDDS offer the luxury of much more accurate dosing than the primary alternative oral liquids. This segment of formulation is especially designed for dysphasic, geriatric, pediatric, bed-ridden, travelling and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations [2].

The FDT is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and/or quick disintegrating tablet. All FDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term oro-dispersible tablet for a tablet that disperses or disintegrates in less than 3 min in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good FDTs varies from several seconds to about a minute [3].

Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, anti-allergics and drugs for erectile dysfunction. Such a tablet disintegrates instantaneously when placed on tongue, releases the drug that dissolves or disperses in the saliva. This result to a rapid onset of action and greater bioavailability of the drug than those observed from conventional tablet dosage form.

Requirements of fast disintegrating tablets

- It should require no water for oral administration, yet dissolve/disintegrate/ disperse in mouth in a matter of seconds.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Should be harder and friable.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature [4]

Need to formulate fast disintegrating tablets

The need for non-invasive drug delivery systems continues due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses coupled with cost of disease management. FDT is one such dosage form which is useful for

- Geriatric patients mainly suffering from conditions like tremors and dysphasia.
- Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Travelling patients suffering from motion sickness and diarrhea that do not have easy access to water.
- Patients with persistent nausea for a long period of time are unable to swallow. Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H_2 blockers, which are prescribed in order to avoid gastric ulceration.
- Mentally challenged patients, bedridden patients and psychiatric patients [5-6].

Advantages of fast disintegrating tablets

- Administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- Rapid drug therapy intervention.

- Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.

Limitations of fast disintegrating tablets

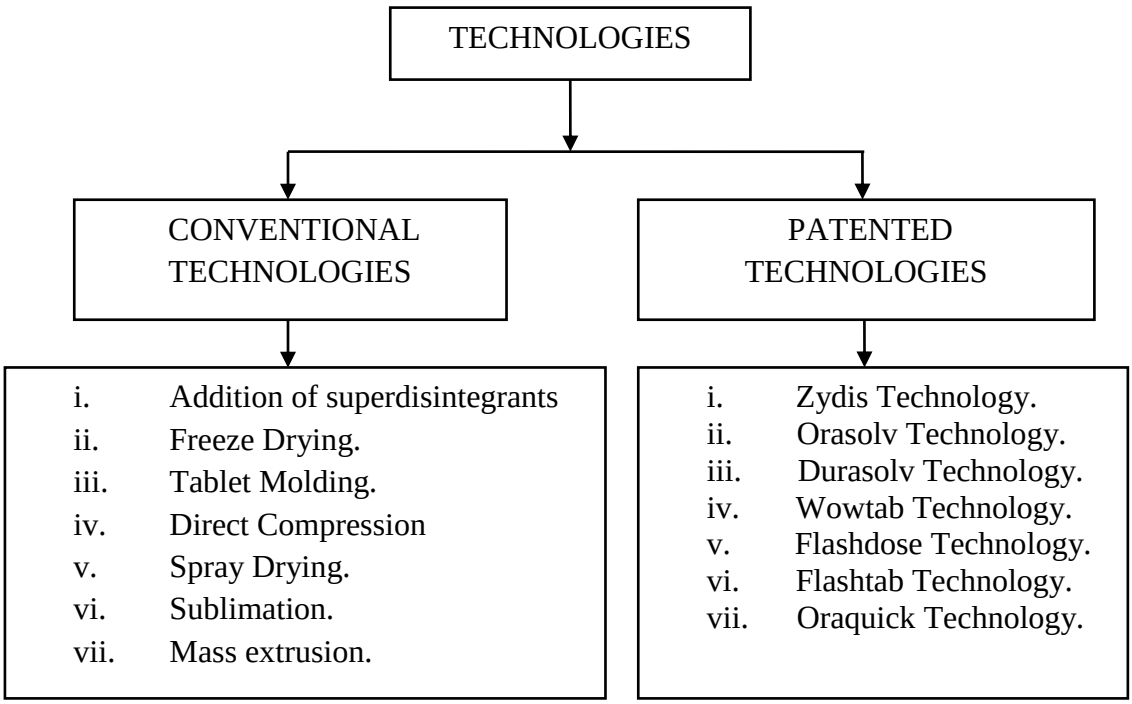
- The tablets usually have insufficient mechanical strength. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

Challenges in formulating fast disintegrating tablets

- **Palatability:** As most drugs are unpalatable, fast disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.
- **Mechanical strength:** In order to allow FDTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wow tab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs.
- **Hygroscopicity:** Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.
- **Amount of drug:** The application of technologies used for FDTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.
- **Aqueous solubility:** Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.
- **Size of tablet:** The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve [2].

Technologies Used To Manufacture Fast Disintegrating Tablets

The technologies used to manufacture fast disintegrating tablets can be classified as:



Conventional methods used for the preparation of fast disintegrating tablets

- **Addition of superdisintegrants:** A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Superdisintegrants are used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Examples of superdisintegrants are croscarmellose, crospovidone and sodium starch glycolate, which are a cross linked cellulose, cross linked polymer and a cross linked starch respectively. The proper choice of disintegrant and its consistency of performance are critical to formulation development of such tablets. Microcrystalline cellulose and low substituted hydroxypropylcellulose were used as disintegrating agents in the range of 8:2–9:1 to prepare fast dissolving tablet. Agar powder is used as disintegrant for the development of rapidly disintegration tablets by enhancing the porosity of agar by water treatment. Sodium starch gycolate, crospovidone and crosscarmellose are some of the popular superdisintegrants.

Table 1: Various commercially available superdisintegrants along with their properties

S. No.	Name	Type	Properties
1.	Crospovidone	Polyvinyl-pyrrolidone	Crossed linked Polyvinlypyrrolidone Rapidly disperses and swells in water
2.	Croscarmellose Sodium.	Modified cellulose	Cross linked sodium carboxy methylcellulose. Excellent swelling and water wicking properties.
3.	Sodium starch Glycolate	Modified Starch	Sodium salt of carboxy methyl ether of starch. High swelling capacity and rapid water uptake

- **Freeze drying or Lyophilization:** It is one of the first generation techniques of preparing FDT, in which water sublimes from the product after freezing. The product obtained by freeze-drying process dissolves more rapidly than other available solid products. The enhanced dissolution characteristic of the formulations is because of the appearance of glossy amorphous structure to bulking agents and sometimes to drug also by freeze drying process. The ideal drug characteristics for this process are relative water insolubility with fine particle size and good aqueous stability in suspensions. Primary problems associated with water-soluble drugs are formation of eutectic mixture, because of freeze point depression and formation of glassy solid on freezing which might

collapse on sublimation. The addition of cryprotectants like mannitol, crystal forming materials induces crystallinity and imparts rigidity to amorphous material and can prevent collapse of structure and mask the bitter taste. The advantage of using freeze-drying process is that pharmaceutical substances can be processed at non elevated temperature, thereby eliminating adverse thermal effects. However high cost of equipment and processing, limits the use of this process. Other disadvantages include lack of resistance necessary for standard blister packs of the final dosage forms [7-8].

- **Tablet Molding:** In this method, tablets are produced by molding of solid dispersion usually consisting of water soluble additives, drug and other excipients. Initially the dry blend of all the ingredients is wetted with a hydro-alcoholic solvent and then compressed into tablets using low compression forces. Porous tablets are formed as the solvent present inside the tablet is removed by air drying. Different mold techniques employed are:
  - **a) Compression molding:** Here the powdered mixture previously moistened with a solvent like ethanol/water which is then compressed into mould plate to form a wetted mass
  - **b) Heat molding:** The molded forms can be obtained from a molten matrix in which the drug is dispersed
  - **c) No vacuum lyophilization:** In this process the solvent from the drug solution or suspension is evaporated at standard temperature.

  Tablets produced by molding are like solid dispersion. Physical form of the drug depends whether and to what extent, it dissolves in the molten/wetted mass.

  Tablets prepared by this method offer rapid dissolution as the dispersion is made from water-soluble excipients. However the mechanical strength of molded tablets is a major concern. To improve the mechanical strength, various binding agent like sucrose, Polyvinylpyrrolidone, cellulose polymers may be added to solvent system. The scope of taste masking in molded tablets is however very limited [9].
- **Direct compression:** Conventional methods in formulating tablets such as dry granulation [10] wet granulation [11] and direct compression have been adapted to produce FDTs. of all these techniques, easiest way to manufacture tablets is direct compression. Low manufacturing cost, conventional equipment, commonly available excipients and a limited number of processing steps lead this technique to be a preferred one. High doses can also be accommodated and final weight of tablet can easily exceed that of other production methods [12]. Directly compressed tablets disintegration and solubilization, depends on single or combined action of disintegrants, water soluble excipients and effervescent agent. Superdisintegrants play a major role in the disintegration and dissolution of Fast Disintegrating Tablets made by direct compression. To ensure a high disintegration rate along with good mouth feel, choice of suitable type and an optimal amount of disintegrant is important.
- **Spray-Drying:** Highly porous, fine powders are obtained by this method. Allen *et al*. utilized this process for preparing Fast dissolving tablets. The Fast dissolving tablet formulations consisted of hydrolyzed/unhydrolyzed gelatin as supporting agents for matrix, mannitol as bulking agent, and sodium starch glycolate or croscarmellose sodium as disintegrating agent. Disintegration and dissolution were further improved by adding effervescent components, i.e. citric acid (an acid) and sodium bicarbonate (an alkali). The formulation was spray dried to yield a porous powder. The fast dissolving tablets made from this method disintegrated within a minute [13-14].
- **Sublimation** The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of fast dissolving tablets [15]. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tabletting process, which sublimated from the formed tablets [16]. Koizumi et al. developed fast dissolving tablet (FDT) utilizing camphor; a subliming material that is removed from compressed tablets prepared using a mixture of mannitol and camphor. Camphor was sublimated in vacuum at 80 °C for 30 minutes after preparation of tablets.

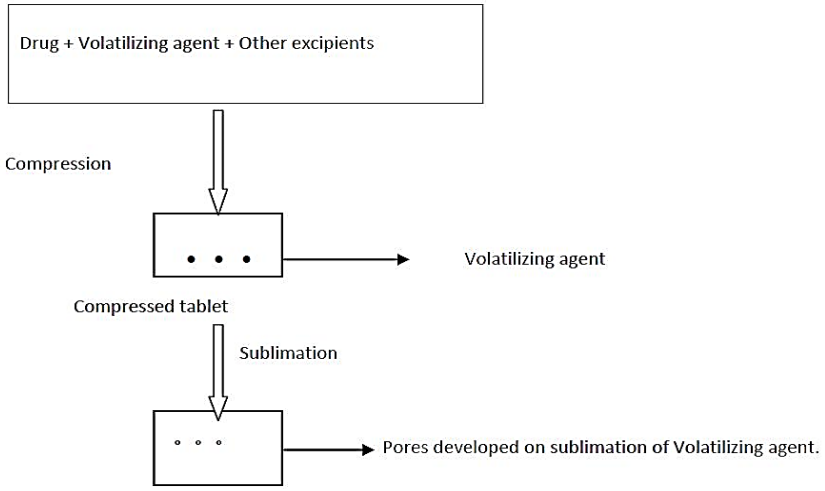


Figure 1: Steps involved in sublimation

- **Mass extrusion**

This technique includes softening of the active blend using solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through extruder or syringe to get a cylinder of the products into segments using heated blade to form tablets. The dried cylinder can also be used to coat granules having bitter taste for taste masking [17].

Patented technologies for fast disintegrating tablets

- **Zydis technology:** This technology includes physical trapping of the drug in a matrix composed of a saccharide and a polymers [18]. Polymers generally employed are partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginates, polyvinyl alcohol, polyvinyl pyrrolidine, acacia and mixture of these. The methodology involves solution or dispersion of components is prepared and filled in to blister cavities, which are frozen in a liquid nitrogen environment. The frozen solvent is removed or sublimed to produce porous wafers. Peelable backing foil is used to pack Zydis units. Zydis formulation is sensitive to moisture and may degrade at humidity greater than 65% RH [19].
- **OraSolv:** OraSolv was Cima's first fast-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste-masking associated with the OraSolv formulation is two-fold. The unpleasant flavor of a drug is not merely counteracted by sweeteners or flavours [20-21]. Both coating the drug powder and effervescence are means of taste-masking in OraSolv. The major disadvantage of the OraSolv formulations is its mechanical strength. The OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets.
- **Durasolv technology:** DuraSolv is Cima's second-generation fast-dissolving/ disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a faster and more cost-effective manner. DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials. One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike OraSolv, the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in DuraSolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound [22].

- **WOW tab technology:** WOW tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water". Wowtab is an intra-buccally soluble compressed tablet formulated by combination of low mouldability saccharides (for rapid dissolution) and high mouldability saccharides (for good binding property) to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet using a conventional manufacturing process. Low mouldability saccharides employed are lactose mannitol, glucose, sucrose, and xylitol while high-moldability saccharides used are maltose, maltitol, sorbitol, and oligosaccharides. The active ingredients may constitute up to 50% w/w of the tablet weight [23].
- **Flashdose technology:** Flashdose [24-25] technology has been patented by Fuisz. Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self- binding shearform matrix termed as "floss". This technology utilizes a unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy. Shearform matrices are prepared by flash heat processing in which the sugar is simultaneously subjected to centrifugal force and to temperature gradient, which raises the temperature of the mass to create an internal flow condition. The flowing mass exits through the spinning head that flings the floss. The floss so produced is amorphous in nature so it is further recrystallized. This crystalline sugar can then incorporate the active drug and be compressed into a tablet. This dosage form can accommodate the drug upto 600 mg. The major drawbacks of these dosage forms are that the tablets are highly friable, soft and moisture sensitive.
- **Flashtab technology:** Prographarm laboratories have patented the Flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcystals. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion-spheronization, simple pan coating methods and microencapsulation. The microcrystals of microgranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation, and compressed into tablets. All the process utilized is same as that of conventional tabletting technology, and the tablets produced are reported to have good mechanical strength and disintegration time less than one minute.
- **Oraquick technology:** The Oraquick mouth-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. The taste masking process does not utilize solvents of any kind, and therefore leads to mouther and more efficient production. Also, lower heat of production than alternative mouth-dissolving/disintegrating technologies makes Oraquick appropriate for heat-sensitive drugs. KV Pharmaceutical claims that the matrix that surrounds and protects the drug powder in microencapsulated particles is more pliable (tablets can be compressed to achieve significant mechanical strength without disrupting taste masking) Oraquick claims quick dissolution in a matter of seconds, with good taste-masking.

Solubility Enhancement: An Overview

Solubility

The maximum amount of solute is dissolved in a given solvent under standard conditions of temperature, pressure & pH. The important parameter of the solubility is to achieve the desired drug concentration in the systemic circulation and dissolution rate of the drug is the determining step for oral absorption of the poorly water soluble drugs and at the site of absorption the drug must be present in the form of aqueous solution. In **"quantitative terms"** solubility is defined as concentration of solute in a saturated solution at a certain temperature. In **"qualitative terms"** solubility is defined as spontaneous interaction of two or more substances to form a homogenous molecular dispersion [26-29].

According to the European Pharmacopeia, "Solubility can also be defined as the parts of the solvent required for one part of the solute.

Table 2: Definition of solubility

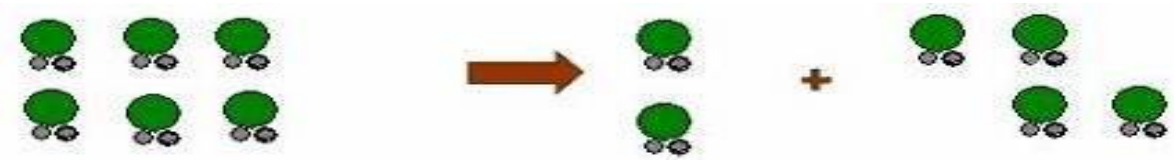
Definition	Parts of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very Slightly soluble	1000-10,000
Insoluble	>10,000

Processes of Solubilisation

The mechanism 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.

Step 1: Holes opens in the solvent.

Step2: Molecules of the solid breaks away from the bulk.



Step 3: The free solid molecule is integrated into the hole in the solvent.

Figure 2: Process of Solubilisation

Factors affecting solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system [30-32].

Particle size

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. The effect of particle size on solubility can be described by the below equation:

Eq.1.1

$$\log \frac{S}{S_0} = \frac{2 \gamma V}{2.303 R T r}$$

S_0 is the solubility of infinitely
S is the solubility of fine parti
V is molar volume
g is the surface tension of the
r is the radius of the fine particle

Temperature

Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased and the solution process releases energy then the solubility will decrease with increasing in temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute.

Pressure

For gaseous solutes, an increase in pressure increases solubility and decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

Nature of the solute and solvent

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubility's of these two substances is the result of differences in their natures.

Molecular size

Molecular size will affect the solubility. The larger molecule or higher its molecular weight less soluble the substance and larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since introduction more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

Polarity

Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will be dissolved in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules.

Polymorphs

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropic. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one another without undergoing a phase transition. Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubilities. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

Factors affecting on rate of solution

Size of the particles

When the total surface area of the solute particles is increased, the solute dissolves more rapidly because the action takes place only at the surface of each particle. Breaking a solute into smaller pieces increases its surface area and hence its rate of solution.

Temperature

For liquids and solid solutes, increasing the temperature not only increases the amount of solute that will dissolve but also increases the rate at which the solute will dissolve. For the gases, reverse is true.

Amount of solute dissolved

When there is little solute already in solution, dissolution takes place relatively rapidly. As the solution approaches the point where no solute can be dissolved, dissolution takes place more slowly.

Stirring

With liquid and solid solutes, stirring brings fresh portions of the solvent in contact with the solute, thereby increasing the rate of solution.

Dissolution

Dissolution is a process in which a solid substance solubilizes into a given solvent i.e. mass transfer from the solid surface to liquid phase. Therefore drug dissolution is the process by which drug molecules are liberated from a solid phase and enter into a solution phase. In the vast majority of circumstances, only drugs in solution can be absorbed, distributed, metabolized, excreted or even exert pharmacological action. The extent to which dissolution proceeds under a given set of experimental conditions is referred to as the solubility of the solute in the solvent. Thus, dissolution is an important process in the pharmaceutical sciences. The modified Noyes-Whitney equation considered as to improve the dissolution rate of water insoluble drugs and to minimize the limitations of oral bioavailability.

$$dC/dt = AD(Cs - C) / h \qquad \text{Eq. 1.2}$$

Where, dC/dt is the rate of dissolution

A is the surface area available for dissolution

D is the diffusion coefficient of the compound

Cs is the solubility of the compound in the dissolution medium

C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

Table 3: Parameters effecting on the dissolution rate of drug

Parameters	Symbol	Effect on drug dissolution rate
Diffusion coefficient of drug	D	Greater value then dissolution rate increases and diffusion decreases if the dissolution rate increases.
Surface area of solid	A	Greater surface area increases dissolution rate.
Water/oil partition coefficient of drug	Kw/o	Higher value then more lipophilicity and more dissolution rate in aqueous fluids.
Concentration gradient	(C_s-C_b)	Greater concentration gradient, faster diffusion and by increasing drug solubility and the volume of dissolution medium then the dissolution rate may also increased.
Thickness of stagnant layer.	H	More thickness less dissolution and drug diffusion and decreased by increasing agitation.

Approaches to increase the Dissolution rate

a) To increase the surface area available for dissolution by decreasing particle size of drug.
b) Optimizing the wetting characteristics of compound surface.
c) To decrease the boundary layer thickness.
d) Ensure sink conditions for dissolution.

Biopharmaceutics Classification System

Fundamental basis of the BCS established by **Dr. Gordon Amidon** who was presented with a Distinguished Science Award at the August 2006 International Pharmaceutical Federation (FIP) Congress in Salvador, Brazil. In the **Biopharmaceutics Classification System (BCS)** in a drug development tool that allows estimation of the contributions of three major important factors are dissolution, solubility, and intestinal permeability, that effect upon the oral drug absorption of the solid dosage form products. The absorption rate of a poorly water-soluble drug, from

the orally administered solid dosage form is controlled by its dissolution rate in the fluid present at the absorption site i.e. the dissolution rate is often the rate-determining step in drug absorption.

The classification is associated with a drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers [33]:

Absorption Number (A_n): It is defined as the ratio of the mean residence time to mean absorption time. It denotes the dimensionless dose/solubility ratio for the particular drug formulation.

$$An = Peff \times tres / R \qquad \text{Eq. 1.3}$$

Where,

Peff is the effective permeability

R is the radius of the intestinal segment.

Dissolution Number (D_n): Defined as the ratio of mean residence time to mean dissolution time.

$$Dn = tres / tDiss \qquad \text{Eq.1.4}$$

Where,

tres the mean residence time (≈180 min)

tDiss is the time required for a drug particle to dissolve

Dose Number (D_0): Defined as the mass divided by the product of uptake volume (250 mL.) and solubility of drug.

$$D_0 = M_0 / CsV_0 \qquad \text{Eq.1.5}$$

Where M_0 is the dose of drug administered

V_0 is the initial gastric volume (≈250 mL.)

Based on the classification of drug substances are divided into four classes and the classification system is called as **biopharmaceutical classification system**. In the BCS, theses are classified into four categories according to their permeability and solubility as shown in Figure 3.

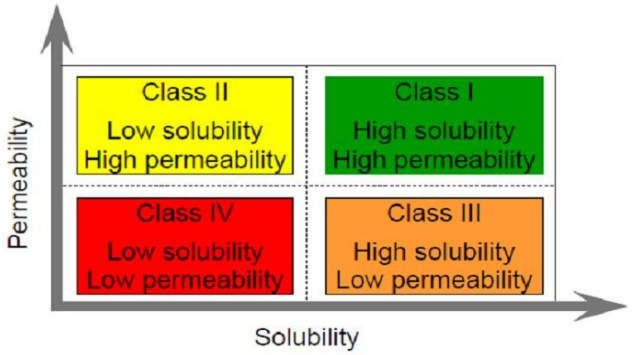


Figure 3: A typical representation of biopharmaceutical classification system

According to the Biopharmaceutics Classification System, the Drug substances can be classified as follow:

CLASS – 1: High permeability and high solubility (amiphiphic)

Example: Metaprolol, Dilitazem, Verapamil, Propanlol.

CLASS -2: Low Permeability and High solubility (liophilic)

Example: Ketoconazole, Atorvastatin, Simvastain, Atorvastatin.

CLASS-3: High permeability and Low solubility (hydrophilic)

Example: Acyclovir, Captopril, Cimetidine.

CLASS-4: Low Permeability and Low Solubility (problematic)

Example: Taxol and Hydrochlorothiazide.

Solid Dispersion

The term solid dispersion refers to a group of the solid products and consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug and matrix can be either crystalline or amorphous. It can be defined as the dispersion of one or more active ingredients in an inert matrix (carrier) where the active ingredients exist in finely crystalline, solublised or amorphous state and used to enhance the solubility & oral bioavailability.

This can be done by reducing the particle size of a drug to molecular level, to transform the drug from the crystalline to the amorphous state. Therefore, solid dispersion technologies are particularly promising for improving the aqueous solubility, dissolution rate and bioavailability of BCS Class II drugs as bioavailability of drugs depends on their solubility and permeability as shown in Figure 2.

Classification of Solid Dispersions

Three different generations of solid dispersions are as shown in Figure 4 [34].

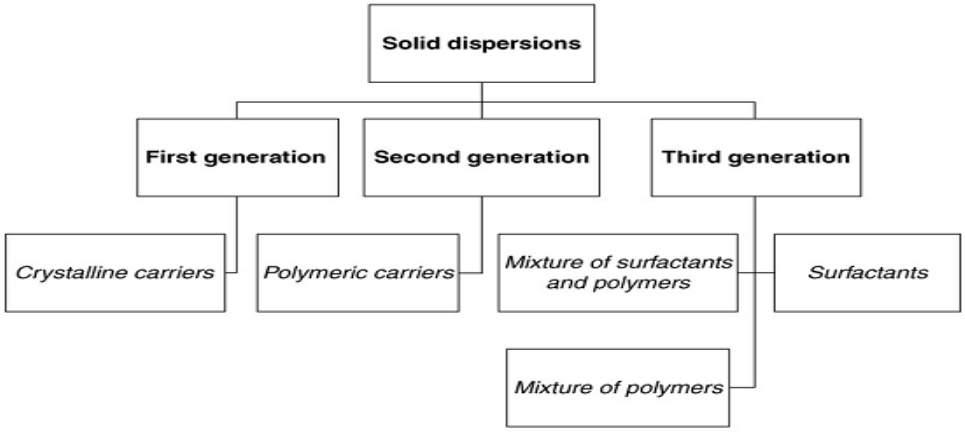


Figure 4: Different Generations of Solid Dispersions

Carrier and Solvent selection

Carrier and solvent selection should be influenced by the chemistry of the drug. It should be optimized the solubility of the drug in the carrier.

1st Generation: Crystalline carriers, Urea, sugar and organic acid.

2nd Generation: Amorphous carriers, PEG, PVA, Povidone and Cellulose derivatives.

3rd Generation: Surface active self emulsifying carriers, Poloxamer 407, tween 80, Gelucire 44/14 [35].

Table 4: Examples of different carriers

S No.	Chemical Class	Examples
1	Acids	Citric acid, Tartaric acid, Succinic acid
2	Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
3	Polymeric Materials	Polyvinylpyrrolidone, PEG-4000, PEG-6000, Carboxymethyl cellulose, Hydroxypropyl cellulose, Guar gum, Xanthan gum, Sodium alginate, Methyl cellulose, HPMC, Dextrin, Cyclodextrins, Galactomannan
4	Surfactants	Polyoxyethylene stearate, Poloxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamine E TPGS NF
5	Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxyalkyl xanthines

Ideal properties of carriers:

1. High water solubility improves wettability and enhances dissolution.
2. High glass transition point (Tg) and improve stability
3. Relatively low melting point (melting process).
4. Capable of forming a solid solution with the drug.

Ideal properties for Solvent selection

1. Dissolve both drug and carrier.
2. Use of surfactants to create carrier drug solutions but care should be taken as they can reduce the glass transition point [36].

Advantageous properties of Solid Dispersions

1. 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. A high surface area is formed, resulting in an increased dissolution rate and consequently improved bioavailability.

2. Improving the wettability of particles: Carriers with surface activity, such as cholic acid and bile salts. When used can significantly increase the wettability property of drug. Carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

3. Higher porosity of particle: 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.

4. Drug in amorphous state: Poorly water soluble crystalline drugs, when in the amorphous state that has higher solubility. 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 [37].

Disadvantages of solid dispersions

The effect of moisture on storage stability of amorphous pharmaceuticals is a significant concern, because it may increase drug mobility and promote drug crystallisation. Most of the polymers, used in solid dispersions can absorb moisture, which may result in Phase separation, crystal growth or conversion amorphous to crystalline or from metastable crystalline to more stable structure form during storage and may result in decreasing solubility and dissolution rate.

Pharmaceutical Applications of Solid dispersion

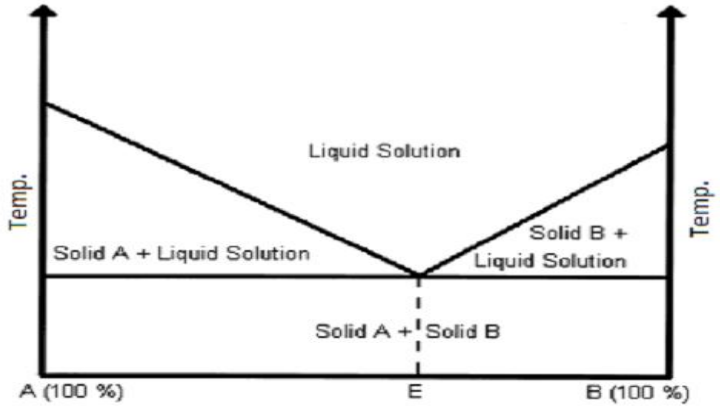


Figure 5: A typical phase diagram of a eutectic system

The pharmaceutical applications of solid dispersions technique are numerous. They may be employed:

1. To enhance the absorption of drug.
2. To obtain a homogeneous distribution of a small amount of drug in solid state.
3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemisation, photo oxidation etc.
4. To dispense liquid or gaseous compounds.

Types of Solid Dispersions

Simple eutectic mixtures: When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a comet of the two compounds in order to obtain a physical mixture of very fine crystals of the two components as shown in Figure 5.

Solid Solutions

Continuous solid solutions: In a continuous solid solution, the components are miscible in all proportions. Theoretically, it means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components.

Discontinuous solid solutions: The solubility of each of the components in the other component is limited and a typical phase diagram is shown in Figure 6 that shows the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component.

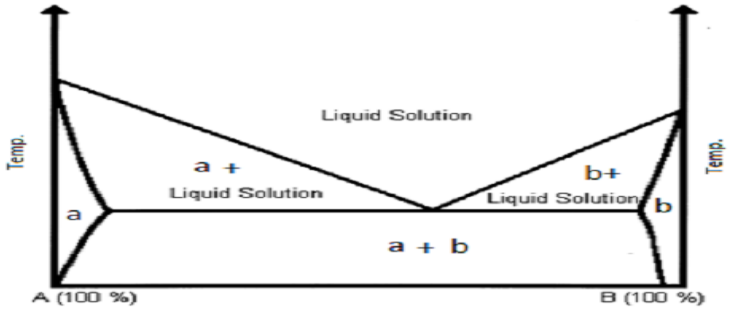


Figure 6: A typical phase diagram of discontinuous solid solution

Substitutional crystalline, interstitial crystalline and amorphous solid solutions Substitutional crystalline solid solutions: Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or into the interstices between the solvent molecules. A Substitutional crystalline solid dispersion is depicted in Figure 7.

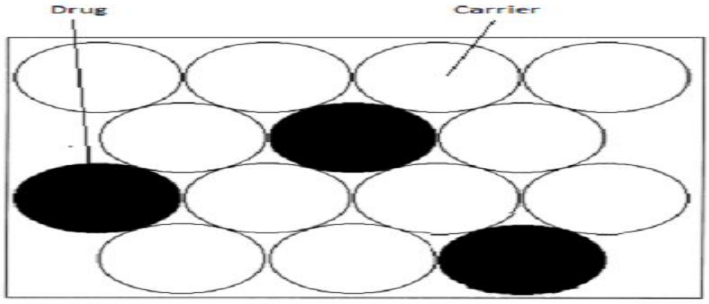


Figure 7: A typical phase diagram of Substitutional solid solution

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

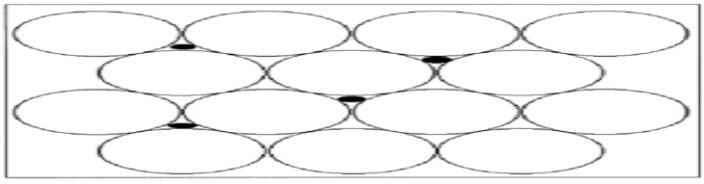


Figure 8: A typical phase diagram of interstitial solid solution

Amorphous solid solutions: The solute molecules are molecularly dispersed but irregularly within the amorphous solvent and using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improving drug's dissolution properties.

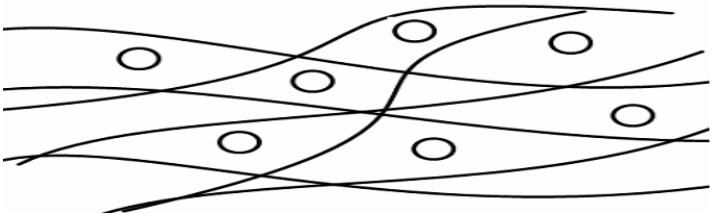


Figure 9: A typical diagram of amorphous solid solution

Glass solutions and glass suspensions: Chiou and Riegelman first introduced the concept of formation of a glass solution as another potential modification of dosage forms in increasing drug dissolution and absorption. A glass solution is a homogenous, glassy in which the solute system dissolves in a gaseous solvent [39-40].

Methods of Preparation of Solid Dispersions

There are various number of techniques used to prepared the solid dispersions and in which is used for the solubility and dissolution enhancement of poorly soluble drugs in which leads to production of drug particles with reduced size, increase wettability, high porosity or amorphous state with improved the bioavailability of poorly water insoluble drugs.

Solvent Evaporation Method

In the solvent method, first step is the preparation of a solution containing both matrix material and drug and second step involves the removal of solvent(s) resulting in the formation of a solid dispersion. When mixing becomes occur at the molecular level is preferred, because this may leads to optimal dissolution properties. The main advantage of the solvent evaporation method is that the thermal degradation of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents [41].

Certain Disadvantages of this method in which can be explained as below:

1. To mix both drug and matrix in one solution is the first challenge, in which is difficult when they differ significantly in polarity and 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 major challenge in this method is to prevent the phase separation, e.g. crystallization of either drug or matrix, during removal of the solvent(s). On the other hand, at high temperatures the molecular mobility of drug and matrix remains high, favouring phase separation (e.g. crystallization). This can be showed in Figure 10.

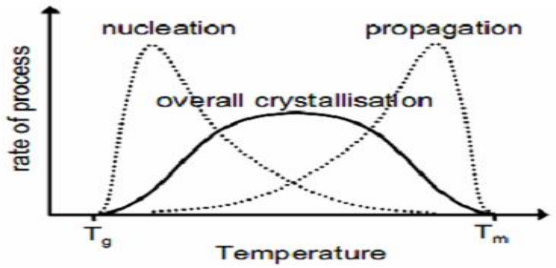


Figure 10: Overall crystallization rate as a function of temperature

Tg is the glass transition temperature and Tm is the melting temperature.

Fusion method

This method is also called as the **melt method**. Sekiguchi and Obi (1961) given about the dispersion that consisted of sulfathiazole and urea as a matrix which were becomes melted using a physical mixture at the eutectic composition and then followed by a cooling step. The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline.

Disadvantages

The fusion method have serious limitations:

1. In this method in which the drug and matrix can only be applied 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 may results in an in homogeneous solid dispersion. This can be prevented by using surfactants.

2. A problem may arise during cooling when both the drug-matrix miscibility changes may occur and phase separation can occur in this case and it was observed that when mixture was slowly cooled, drug in crystalline form may occurred, whereas on fast cooling and yield the formation of amorphous solid dispersions [42].

Matrix Method

It is a patented technology in which is used for the solid dispersions preparation on the basis of melt method. This technique includes the use of a special twin screw extruder and the presence of two independent hoppers in which the temperature can vary over a broad temperature range and also reduces the residence time of drug in extruder and also avoid thermal stress for both drug and excipients. A drug becomes protected from oxidation by the complete elimination of oxygen and also protects the mixture from moisture [38].

Hot melt extrusion method

This method is generally same as the fusion method except from the intense mixing of the components is induced by the extruder in a vessel, when compared to melting then the product stability and dissolution are similar and melt extrusion includes the potential to shape, heated the drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms, miscibility of drug and matrix can be a problem. Generally, the theoretical approach for the melt extrusion process is presented by dividing the process of flow into four following sections.

- Feeding of the extruder.
- Conveying of mass (mixing and reduction of particle size).
- Flow through the die.
- Exit from the die and down-stream processing.
- Inside a stationary cylindrical barrel the extruder consists of one or two rotating screw. The barrel is often manufactured in sections, which are bolted or clamped together. An end-plate die, connected to the end of the barrel, determines the shape of the extruded product.

  Certain advantages of hot melt extrusion method over the fusion method:
- This method also offers the possibility of continuous production, which makes it suitable for large-scale production.
- 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.

Melt agglomeration Method

In this method, prepared by heating the mixture of the drug, carrier and excipients to a temperature within or above the melting range of the carrier an possible to produce stable solid dispersions by melt agglomeration in a rotary process and 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.

Freeze Drying Method

In this process both the drug and carrier is dissolved in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Another important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. Larger the surface area and cooling the agent with direct contact and may result in faster vitrification and decreasing the risk of phase separation. In the glass apparatus the temperature of the sample should be below than the Tg of the freeze concentrated fraction. The condenser temperature was kept at 75^{o}C and dry the solution with Cyclohexanol used as a solvent in this method [43, 44].

Supercritical Fluid Technology

A supercritical fluid can defined as any substance at a temp. & pressure above its critical point where the liquid and gas phase can co exist and at this stage it is called Supercritical fluid, while this technique utilizing these fluids, then it is called as Supercritical fluid technology.

Table 5: Some common super critical solvents used

Solvent	Critical Pressure (Atm)	Critical temperature (K)	Density (mg/ml)
H_2O	218	647	320
CO_2	73	304	470
C_2H_5OH	63	517	280
C_6H_6	48	562	300
NH_3	113	406	240
C_2H_6	48	306	600
$CHCl_3$	28	209	340

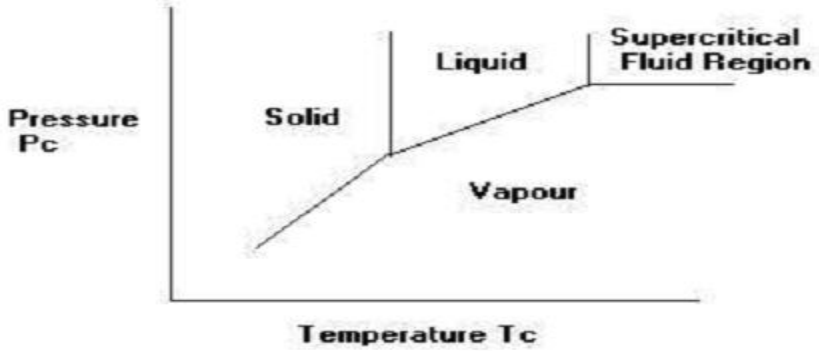


Figure 11: Typical diagram of supercritical region

SCF is used to enhance the solubility; dissolution rate of poorly soluble drugs in which becomes classified the processes in two groups as depending on the use of the supercritical fluid in the system:

A.) Solvent

B.) Antisolvent [45-47]**.**

RESS (Rapid expansion of a supercritical solution): When the solid is dissolved in the gas and then the solid is precipitated by reducing the pressure then it becomes brought as a **snow** in the gas. Firstly this concept is applied to produce fine particles with narrow range size distribution using SCF technology and this technique called as rapid expansion of a supercritical solution (RESS). The main advantage of RESS technique that produces the production of small particles with uniform size. **RESOLV (Rapid expansion of a supercritical solution into liquid solvent)**: Technologies using supercritical fluid technology using as an antisolvent. The supercritical fluid used as antisolvent that comes in contact with the solute dissolved in a suitable organic solvent. **GAS (Gas antisolvent)**. The main advantages of this technique are to be introduced the SCF through the bottom of the vessel when a mixing of good solvent and antisolvent can be obtained. It is a technique that involves the gradual introduction of carbon dioxide inside a vessel filled with the solute solution. The carbon dioxide is pumped into the vessel till the fixed pressure is attained.

Kneading Method

In this method the Physical mixtures of the drug and carrier were prepared by mixing and accurately weighted the drug:polymer of different ratios for 5 min using glass mortar and pestle and then the physical mixture was triturated using a small volume of ethanol-water solution to give a form of thick paste, which was kneaded for 30 min respectively, and then dried at 45^{o}C in an oven. The dried mass was pulverized, passed through 30 mesh sieve size, stored in a desiccator, and passed through 60 mesh sieve size, then weighed and transferred to airtight container and stored properly [48]**.**

Spray Drying Method

In this method it is mainly dissolving or suspending the drug and polymer in a common solvent and the solvent is removed by drying it into a stream of heated air flow and yielded the drugs in the amorphous state, but sometimes during processing the drug may be partially crystallized. Operating conditions and dryer design depends upon the drying characteristics of the product and require powder specifications. In this method drug & carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is evaporated at 400^{o}C under reduced pressure by using vacuum evaporator, obtained mass is dried in a desiccator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent. The product is crushed, pulverized & sieved through a suitable mesh number sieve. Solid Dispersions of glibenclamide with Geluride was successfully prepared using silicon dioxide as an adsorbent by spray drying technique with enhanced dissolution rate [49].

Fluidized bed coating system on sugar beads

This technique involves the drug-carrier solution becomes sprayed on the granular surface of excipients or sugar beads to produce the drug product in which the tableting or can be encapsulated can be formed. The use of water soluble polymer or insoluble polymer, we may produce immediate or controlled release solid dispersions. Both the drug (Itraconazole) and Hydroxypropylmethylcellulose (HPMC) used as polymer and coated on sugar spheres is formed and sprayed the solution of drug and Hydroxypropylmethylcellulose in both the organic solvent of dichloromethane and ethanol on the sugar beads and then encapsulated.

Direct Capsule Filling

It was first done in 1978, filling of semisolid materials into the hard gelatin capsules (melts), solidifies at room temperature. In the liquid melt of solid dispersions are prepared and filled into the hard gelatin capsules directly and avoid grinding-induced changes in the crystallinity of the drug. When a surfactant mixed with the carrier to avoid formation of a drug-rich surface layer (e.g.poly-sorbate80 with PEG, phosphatidyl choline with PEG).The temperature of the molten solution should not exceed ~70-^{o}C because it might compromise the hard-gelatin capsule shell.

Dropping Method

A solid dispersion of a melted drug carrier mixture is pipette out and then dropped onto a large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. The size and shape of the particles also influenced by certain factors as viscosity of the melted drug and size of pipette.

Characterization of Solid Dispersions

There are different parameters are available to determine the physical nature of the solid dispersions and these methods can be explained as below:

1. Infrared spectroscopy

Infrared spectroscopy (IR) is helpful in determining the solid state of the drug (molecular dispersion, amorphous, crystalline or a combination) in the carrier regardless of the state of the carrier. Crystallinities of under 5-10% cannot generally be detected. The absence of any significant change in the IR spectral pattern of drug & polymer physical mixture indicated the absence of any interaction between the drug and the polymer.

2. X- Ray diffraction studies

The analytical tools such as X-ray diffractometry are usually employed in the pharmaceutical field to characterize the solid drug substance. The powder X-ray diffraction is used for detection of crystalline phases in mixed system. The crystallinity parts give sharp narrow diffraction peaks and the amorphous component gives a very broad peak.

3. FT-Raman spectroscopy

Drugs containing aromatic moieties are frequently much better Raman scatters than are polymers, thus facilitating their detection in mixed systems.

4. Differential scanning calorimetry (DSC)

The measurement of heat flow into or out of a material as a function of time or temperature can be done by DSC technique. DSC can be used to determine crystallinity by quantifying the heat associated with fusion of the material.

By the increase of temperature of an amorphous solid Glass transition may occur. As the temperature increases, an amorphous solid will become less viscous. At some point the molecules may obtain enough freedom of motion to spontaneously arrange themselves into a crystalline form. This is known as the crystallization temperature (Tc). The transition from amorphous solid to crystalline solid results in an exothermic peak in the DSC signal. As the temperature increases the sample eventually reaches its melting temperature (Tm). The melting process results in an endothermic peak in the DSC curve.

5. Dissolution testing

Drugs having intrinsic dissolution rate < 0.1 mg/cm^2/min usually exhibit dissolution rate limited absorption. Comparison of dissolution profile of drug, physical mixtures of drug and carrier and solid dispersion may help to indicate the mechanism of improved release of drug in the formulation (solubilization / wetting / particle size reduction).

6. Hot stage microscopy

It gives indication of drug-carrier miscibility. It may also help to predict the homogeneity of the system prepared by the melt method.

7. Confocal Raman Spectroscopy

It is a newer approach for analytical assessment of solid dispersions which covers the physical state as well as the distribution of the drug via its spatial resolution. It is suitable tool for observing changes in a formulation caused by physicochemical processes. Confocal Raman spectroscopy was used to measure the homogeneity of the solid dispersions.

Development of Solid Dosage Forms

Solid dispersion must be developed into convenient dosage forms, such as capsules and tablets, for their clinical use and successful commercialization. Some investigators used situ dry granulation method for the preparation of tablet dosage forms for a chlorpropamide urea solid dispersion, where the drug, the carrier, and the excipients were mixed in a rotating flask on a water bath maintained at 100 ^{o}C. The properties of these formulations also changed with time, and the authors concluded that aging could "limit their usefulness as prospective dosage forms" [50].

Problems in Solid dispersions

Even better solubility enhancement of the drug can be obtained with solid dispersion technology but there are only some few products that have been marketed so far and certain examples of commercially prepared solid dispersions are as shown in Table 6.

Table 6: Examples of commercially available solid dispersion

Drug	Carrier	Brand Name	Manufactured
Griseofulvin	PEG	Gris-PEG	Pedinol Pharmacal Inc.
Itraconazole	HPMC	Sporanox	Janssen Pharmaceutica

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