Solid dispersion system in drug delivery

The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids. The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. 1

Currently, approximately 40% of the marketed immediate release (IR) oral drugs are categorized as practically insoluble (<100 g/ml) (Takagi et al., 2006). So, there is an urgent need to develop strategies that can overcome the problem of less aqueous solubility. To generally describe " solubility" the Pharmacopoeia (USP) uses seven different solubility expressions as shown in Table 1. The European Pharmacopoeia uses similar solubility definitions except the 'practically insoluble' characteristic, which is not specified.4

1. 1 Biopharmaceutics classification system

The Biopharmaceutical Classification System (BCS) was introduced in the mid-1990s to classify the drug substances with respect to their aqueous solubility and membrane permeability. BCS is a useful tool for decision-making in formulation development from a biopharmaceutical point of view.

Solubility improvement strategies are required for Class II and Class IV drugs.

1. 2 Approaches to improve the solubility or to increase the available surface area for dissolution

Physical modifications

- Particle size
- Micronization

- Nanosuspensions
- Modifications of the crystal habit
- Polymorphs
- Pseudopolymorphs (including solvates)
- Complexation/solubilization
- Use of surfactants
- Use of cyclodextrins
- Drug dispersion in carriers
- Eutectic mixtures
- Solid dispersions (non-molecular)
- Solid solutions

Chemical modifications

- Soluble prodrugs
- Salts

1. 3 Solid Dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. 7

Much of the research that has been reported on solid dispersion technologies involves drugs that are poorly water-soluble and highly permeable to biological membranes as with these drugs dissolution is the rate limiting step to absorption. Hence, the hypothesis has been that the rate of absorption in-vivo will be concurrently accelerated with an increase in the rate of drug

dissolution. Therefore, solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs.

1. 3. 1 Types of solid dispersions

On the basis of release mechanisms and molecular arrangement in the matrix, solid dispersions are distinguished into following types9:

A. Simple eutectic mixture: Eutectic mixture is prepared by rapid solidification of fused melts of two components that show a complete liquid miscibility with negligible solid-solid solubility. It involves loose atomic or molecular interaction and not on the formation of chemical bonds. When the eutectic mixture is exposed to gastrointestinal fluids, both the poorly soluble drug and the carrier may simultaneously crystallize out as a very small particles result in an increased the surface area and improved dissolution and absorption of the drug.

B. Solid solution: A solid solution represents a homogenous one phase system, where the solid solution is dissolved in a solid solvent and the two components crystallize together. The solid solution achieves faster dissolution than a eutectic mixture because the drug particles in a solid solution are reduced to molecular size and dissolution of the drug takes place in the solid state prior to the exposure to the liquid medium.

C. Glass solution: It is a homogenous glassy system in which a solute dissolves on glassy solvent results in increased dissolution and absorption of the drug. It is characterized by a transparency and brittleness below the glass forming temperature. Glass solution is a metastable and the strength

of the chemical bonding is much less as compared to solid solution. Therefore, the release of the drug was found to be faster than a solid solution.

D. Amorphous precipitations in crystalline carrier: An amorphous form of a drug produces faster dissolution rate. The drug may precipitate out in an amorphous form in a crystalline carrier from solid dispersions prepared by melting or solvent method. A strong interaction between the drug and carrier resulting in the formation of channels within the matrix seems to be a possible mechanism for improved dissolution of the drug.

E. Compound or complex formation: The formation of a complex between the drug and the carrier may either decrease of increase the dissolution and the absorption rate of the drug. The formation of soluble complex with low association constant resulted in increased rate of dissolution and absorption.

The enhancement in dissolution rate of the drug can be ascribed to

An increasing solubility of the drug because of its amorphous state or small particle size (Kelvin's law)9, 10

An increased surface area available for drug dissolution because of the small size of the drug particles11, 12

An improvement in wetting of the drug caused by the hydrophilic carrier13, 14

1. 3. 2 Advantageous properties of solid dispersions

Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particle properties. Parameters such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability. 16

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

b. Particles with improved wettability: Strong contribution to the enhancement of drug solubility is related to the drug wettability improvement in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

c. Particles with higher porosity: Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties, for instance, solid dispersions containing

linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

d. Drugs in amorphous state: Poorly water soluble crystalline drugs, when in the amorphous state tends to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process.

1. 3. 3. Carriers used in solid dispersions

Many carriers of natural, semi-synthetic and synthetic types are being used which include natural carbohydrates, semi-synthetic and synthetic hydrophilic polymers.

S. No: 1

Nature of carrier: Sugars

Name of the carrier: Dextrose, sorbitol, sucrose, fructose, maltose, galactose, xylitol, mannitol

S. No: 2

Nature of carrier: Acids

Name of the carrier: Citric acid, tartaric acid and succinic acid

S. No: 3

Nature of carrier: Polymorphic materials

Name of the carrier: Polyvinyl pyrrolidone (PVP), polyethylene glycols, hydroxyl propylmethylcellulose (HPMC), guargum, xanthan gum, sodium alginate, methyl cellulose, pectin, hydroxyl ethyl cellulose (HEC), hydroxyl propyl cellulose (HPC) and dextrins.

S. No: 4

Insoluble or enteric

Nature of carrier: polymer

Name of the carrier: Hydroxy propyl methyl cellulosepthalate, eudragit RL, eudragit L 100, eudragit S100, eudragit RS.

S. No: 5

Nature of carrier: Surfactants

Name of the carrier: Polyethylene stearate, poloxamer 188, tweens and spans.

S. No: 6

Nature of carrier: Miscellaneous

Name of the carrier: Nicotinic acid, succinamide, dextrans, gelatin, poly vinyl alcohol, urea, cyclodextrins, skimmed milk etc.,

Table 1. 2 Various carriers used in solid dispersions

1. 3. 4. Preparation techniques of solid dispersions

The following are the major processes for the preparation of solid dispersions.

A. Solvent evaporation method: In this method, the physical mixture of two components is dissolved in a common solvent and followed by the evaporation of solvent. The advantages of this method are low temperature requirements for the preparation of dispersion and thermal decomposition of drugs and carriers can be prevented. The higher cost of production, incomplete removal of solvent, adverse effects of solvent on the chemical stability of the drug and selection of common solvent are the drawbacks of this method.

B. Melting method (Fusion method): The physical mixture of drug and water-soluble carrier was heated to melt and the molten mixture was then cooled and solidified mass was crushed, pulverized and sieved. The melting point of a binary system depends on its composition and proper manipulation of drug carrier ratios. Decomposition should be avoided due to fusion time and the rate of cooling.

C. Kneading method: The physical mixture of drug and carrier were triturated using small quantity of organic solvent and water mixture, usually alcohol and water (1: 1v/v). The slurry is kneaded for 45 minutes and dried at 45°C. The dried mass is pulverized and sieved through sieve no. 60 and the fraction was collected. The advantages of this method are low temperature requirements for solid dispersion preparation and usage of organic solvent is

less. This method of preparation avoids thermal degradation of drug and employs less quantity of organic solvents.

D. Melting solvent method: This method involves dissolving the drug in a suitable solvent and the incorporation of the solution directly into the molten carrier. This method possesses the advantages of both solvent and melting methods.

E. Supercritical fluid methods: Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used as either a solvent for drug and matrix or as an antisolvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. This technique does not require the use of organic solvent and since CO2 is considered environmentally friendly, this technique is referred to as 'solvent free'. This technique is known as Rapid Expansion of Supercritical Solution (RESS).

F. Lyophilization/ Freeze Drying: This technique is an alternative to the solvent evaporation method. Here the drug and carrier are dissolved in common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

G. Melt agglomeration process: This technique is used to prepare solid dispersion where a binder acts as a carrier. The solid dispersion is prepared by heating binder, drug and excipient to a temperature above the melting

point or spraying the dispersion of drug in the molten binder on the heated excipients using a high shear mixer. The effect of binder type, method preparation and particle size are the critical factors influencing the solid dispersion preparation by this method. These parameters results in various dissolution rates, mechanism of agglomerate formation and growth, agglomerate size and distribution.

1. 3. 5. Limitations of solid dispersion systems:

- Problems limiting the commercial application of solid dispersions are:
- Laborious and expensive method of preparation.
- Reproducibility of physico-chemical characteristics.
- Difficulty in incorporating into the formulation of dosage forms.
- Crystallization of the amorphous drug in the dispersion.
- Poor scale up of manufacturing process and physical and chemical stability of drug and the vehicle.

1. 4 FDT's:

Fast-disintegrating and fast-dissolving tablets are becoming popular as novel delivery systems for drug administration. They are more convenient for children, elderly patients, patients with swallowing difficulties, and in the absence of potable liquids. The most desirable formulation for use by the elderly is one that is easy to swallow easy to handle. Taking these requirements into consideration, attempts have been made to develop a fast-disintegrating tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at anytime by anyone who do not have easy access to water. It is also easy to

dose the aged, bedridden patients, or infants who have problems swallowing tablets and capsules. Recently, many companies have researched and developed various types of fast-disintegrating dosage forms. 18

These tablets display a fast and spontaneous de-aggregation in the mouth, soon after the contact with saliva, though they can be handled or extracted from the package without alteration. The active agent can thus rapidly dissolve in the saliva and be absorbed through whatever membrane it encounters, during deglutition, unless it is protected from pre-gastric absorption. To fulfill these requirements, tablets must be highly porous, incorporating hydrophilic excipients, able to rapidly absorb water for a rapid deaggregation of the matrix. Different technological techniques, such as freeze drying or molding or direct compression are currently employed to prepare the formulations of this type present on the pharmaceutical market.

1. 4. 1 Advantages of Fast Disintegrating Drug Delivery System (FDDS) 19, 20

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients, mentally ill, disabled and uncooperative.
- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Good mouth feel property of FDDS helps to change the basic view of medication as " bitter pill", particularly for pediatric patients.

- Ability to provide the advantages of liquid medication in the form of solid preparation.
- Rapid dissolution of drug and absorption, which may produce rapid onset of action.
- Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

1. 4. 2 Approaches for fast disintegrating tablets

A. Patented technologies

Currently, four fast-dissolving/disintegrating technologies have reached the U. S. market:

- Zydis (R. P. Scherer, Inc.)
- WOWTAB (Yamanouchi Pharma Technologies, Inc.)
- OraSolv (Cima Labs, Inc.)
- DuraSolv (Cima Labs, Inc.)

B. Three others are available outside the U. S.

- Flash Dose (Fuisz Technologies, Ltd.),
- Flash tab (Prographarm Group),
- OraQuick (KV Pharmaceutical Co., Inc.)
- Nanocrystal Technology

C. Conventional technologies

- Freeze -drying or lyophilization
- Tablet Molding
- Direct compression
- Spray drying
- Sublimation
- Mass extrusion
- Direct compression

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of the tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilization depends on the single or combined action of disintegrates, water soluble excipients and effervescent agent. Disintegrate efficacy is strongly affected by tablet size and hardness. Large and hard tablets have a disintegration time more than that usually required. As consequences, products with optimal disintegration properties often have medium to small size and /or high friability and low hardness. Breakage of tablet edges during handling and tablet rupture during the opening of blister, all results from insufficient physical resistance.

Disintegrants have a major role in the disintegration and dissolution process of mouth dissolving Tablets made by direct compression. To ensure a high disintegration rate, choice of suitable type and an optimal amount of disintegrant is important. Other formulation components such as water soluble excipients or effervescent agents can further enhance dissolution or

disintegration properties. But the main drawback of using effervescent excipients is their highly hygroscopic nature.

The understanding of disintegrant properties and their effect on formulation has advanced during the last few years, particularly regarding so called superdisintegrants. Disintegration efficiency is based on a force equivalent concept, which is the combined measurement of swelling force development and amount of water absorption. Force equivalent expresses the capability of disintegrant to transform absorbed water into swelling force. The optimization of tablet disintegration was defined by means of disintegrant critical concentration. Below this concentration, the tablet disintegration time is inversely proportional to disintegrate concentration and above that disintegration time remains approximately constant or even increases.

The simultaneous presence of disintegrate with a high swelling force called disintegrating agent and substances with low swelling force (starch, cellulose and direct compression sugar) defined as, " swelling agent" was claimed to be a key factor for the rapid disintegration of the tablet, which also offers physical resistance.

1. 4. 3 Mechanism of tablet disintegration and water absorption

When mouth dissolving tablets placed in the mouth, upon contact with saliva the tablet disintegrates or dissolve instantaneously. The mechanisms involved in the tablet disintegration mechanisms are

- Swelling
- Wicking (capillary)
- Deformation

- Particle repulsive forces
- Chemical reaction (acid base reaction)

a. Swelling

Not all disintegrates swell in contact with water swelling is believed to be a mechanism in which; certain disintegrating agents (like starch) impart their disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to disintegrate.

b. Wicking (porosity and capillary action)

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablets porosity provides a way for the penetration of fluid into tablets. The disintegrants particles (with cohesiveness and compressibility) themselves act to enhance porosity and provide these capillaries into the tablets. Liquid is drawn up or wicked into these ways by capillary action and rupture the inter-particulate bonds causing the tablet to break into small parts.

c. Deformation

Starch grains are generally thought to be " elastic" in nature that is the grains that are deformed under pressure will return to their original shape when that pressure is removed. But, with the compression forces involved in tabletting, these grains are permanently deformed and are said to be " energy rich" with these energies being released upon exposure to water, that is the ability for starch to swell is higher in " energy rich" starch grains than in starch grains that have not been deformed under pressure. It is believed that no single mechanism is responsible for the action of most

disintegrants. But rather, it is more likely the results of interrelationships between these major mechanisms.

d. Due to disintegrating particle/particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablets made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also causes disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

e. Chemical reaction (acid base reaction)

Disintegration of tablet included with citric acid and tartaric acid along with the sodium bicarbonate, sodium carbonate, potassium carbonate; these react in contact with water to liberate carbon dioxide that disrupts the tablet.

Name of the Product: Imodium Lingual

Active Ingredients: Loperamide hydrochloride

Dose: 2 mg

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Name of the Product: Pepcidin Rapitab

Active Ingredients: Famotidine

Dose: 20mg and 40 mg

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Name of the Product: Mosid - MT

Active Ingredients: Mosapride citrate.

Dose: 2. 5mg and 5mg

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Name of the Product: Calritin Reditabs

Active Ingredients: Loratadine

Dose: 10 mg

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Name of the Product: Nimulid - MD

Active Ingredients: Nimesulide

Dose: 50mg and 100mg

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Name of the Product: Zyrof Meltab

Active Ingredients: Rofecoxib

Dose: 50 mg

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Name of the Product: Feldene Melt

Active Ingredients: Piroxicam

Dose: 10mg and 20 mg

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Name of the Product: Maxalt-MLT

Active Ingredients: Rizatriptan

Dose: 5mg and 10 mg

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Name of the Product: Pepcid RPD

Active Ingredients: Famotidine

Dose: 20mg and 40 mg

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Name of the Product: Zyprexa Zydis

Active Ingredients: Olanzapine

Dose: 5mg, 10mg, 15mg and 20 mg

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Name of the Product: Zofran ODT

Active Ingredients: Ondansetron

Dose: 4 mg and 8 mg

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Name of the Product: Remeron Soltab

Active Ingredients: Mirtazepine

Dose: 15mg, 30mg and 45 mg

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Name of the Product: NuLev

Active Ingredients: Hyoscyamine sulfate

Dose: 0. 125 mg

Table 1. 3 Marketed fast disintegrating tablets

Piroxicam, a non-steroidal anti inflammatory agent, belonging to BCS class II is widely used as a first - line drug in the symptomatic relief of rheumatoid arthritis and osteoarthritis. It's low aqueous solubility has to be overcome through formulation strategies.

Skimmed milk can be used as a drug carrier as it is inexpensive, easily available, biodegradable, and does not exhibit toxicity problems as experienced with PEG and PVP. 24-26

Polymers as carriers also have limitations in enhancing the solubility of poorly soluble drugs due to their high viscosity. So the use of skimmed milk

in the formulation of the SD of the drugs with limited aqueous solubility may be a potential and cost effective way to overcome the problem. 27

Skimmed milk is a colloidal suspension of casein micelles, globular proteins and lipoprotein particles. The principal casein fractions are a-s1, a-s2, b-casein and k-casein. b-casein is amphiphilic and acts as a detergent molecule with surfactant property. The milk also contains whey proteins with principle fractions of the b-lacto globulin, a-lactalbumin, bovine serum albumin and immunoglobulins. These molecules were found to be surface active with a superior solubility than caseins. 28

Aminoacids have been suggested either as additives in peroral application or in the form of aminoacid salts to reduce gastrointestinal disorders arising due to piroxicam like NSAID's. The surface active agents and amino acid content are expected to be the reason for increased permeation of the drug from the solid dispersion. 29, 30