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REVIEW ARTICLE

A review on oral dispersible tablet

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ABSTRACT

It has been reported that about 40% of the compounds being developed by the pharmaceutical industries are poorly water soluble. The limiting factor to the *in vivo* performance of poorly water soluble drugs after oral administration their inadequate ability to be wetted by and dissolved into the fluid in the gastrointestinal (GI) tract. Therefore, increasing the dissolution rate of poorly water soluble drugs is an important and significant challenge to pharmaceutical scientists in order to maximize absorption. Commercially used processes are spray drying, mechanical milling, formation of solid dispersion, and freeze drying. Aceclofenac is a nonsteroidal anti-inflamatory drug (NSAID), used for rheumatoid arthritis, osteoarthritis and other joint pains. Aceclofenac is often used orally. The oral bioavailability of aceclofenac was found to be very poor likely due to the very poor dissolution in aqueous fluids especially in acidic mediums. The studyi utilized of the solvent evaporation method for preparation of stable amorphous solid dispersions of Aceclofenac by adsorbing it on porous carrier (Florite).

INTRODUCTION:

In case of pharmaceutical materials, the importance of amorphous solid system form:

(a) Useful properties: amorphous solid have higher dissolution rate higher solubility.

(b) Instability: amorphous solid are generally less stable physically and chemically than corresponding crystals.[1,2,3]

Amorphous substances form a separate class of solids, distinct from the more common and well-known crystalline solids. The three-dimensional long-range order that normally exists in a crystalline material does not exist in the amorphous state and the position of the molecules relative to one another is more random. Pharmaceutical materials that are processed by high-energy processes such as jet milling, melt extrusion, freeze drying, spray drying and so forth, are often rendered at least partially amorphous.[4,5]

This occurs by the virtue of the fact that these processes create conditions that can prevent crystallization or mechanically disrupt the structure of an existing crystalline material. The specific volume of the amorphous state and high internal energy relative to the crystalline state can lead to enhanced dissolution and bioavailability, but can also create a possibility that it may spontaneously convert back to the more stable crystalline state during processing or storage. As stated earlier, the application of spray drying technique to obtain amorphous form of the drug substance, either alone or in combination with a hydrophilic polymer is now well known.[6]

Key words:

Solid dispersion technique

Fast dissolving tablets

Solubility and Its Significance:

The aqueous solubility of drug substances plays an important role in the formulation of drug dosage form. For the oral (entric) route of administration it is well stated that, unless the substance has an aqueous solubility above 10 mg/ml over the pH range 1to7, then potential absorption problems may occur. Solubility less than 1 mg/ml is likely to give dissolution-rate limited absorption because solubility and dissolution rate are interrelated.[7,8]

Solubility of many newly developed high potential drugs are a severe obstacle in formulation development, especially when they express minimum solubility simultaneously in aqueous and organic media, which leads to poor and/or varying bioavailability after oral administration.

According to Biopharmaceutics Classification System, for class II and class IV drugs the dissolution rate is the limiting factor for the absorption rate. An enhancement of dissolution rate is thus important.

The US Food and Drug Administration (FDA) to assess oral drug products introduced the ***Biopharmaceutics Classification System***[9,10,11]**.** In this system, drugs are

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classified into four groups based on the ability of a given drug substance to permeate biological membranes and aqueous solubility. Given drug substance is considered 'highly soluble 'when the highest dose strength is soluble in 250ml water or less over a pH range 1 to 7.5, and is considered 'highly permeable' when the extent of absorption in humans is determined to be 90% of an administered dose (in solution), related to an intravenous reference dose or based on mass balance. For a rapidly dissolving tablet, 85% of the labeled amount of drug substance must dissolve within 30 minutes. Compounds for which improvement in bioavailability has been most dramatic and most easily recognize as being due to lipid excipients have been those possessing high membrane permeability and low aqueous solubility as well as good solubility into digestible lipids. The BCS can serve as a useful preliminary guide for the selection of candidates for lipid-based delivery. As per biopharmaceutical classification system (BCS) which is based on solubility as related to dose and permeability of drug substances.

BCS Classification:

Class I consists of highly water-soluble drugs that are well absorbed from the G.I.T and have the preferred physicochemical properties. Drugs in Class I have high bioavailability after oral administration.

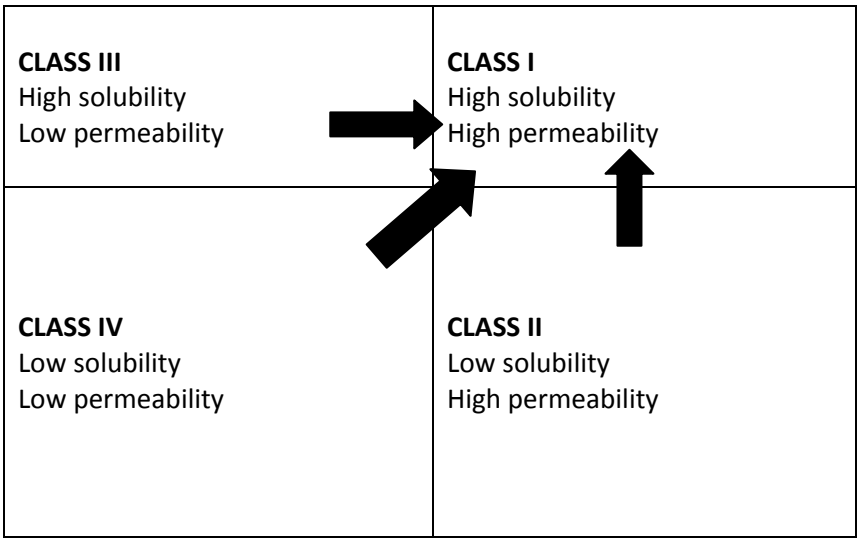

Figure: BCS Classification of Drugs

Class II consists of water-unsolvable drugs that, when dissolved, are well absorbed from the G.I.T. The dissolution rate *in vivo* is generally the rate-limiting step in drug absorption. Commonly, drugs in this class have irregular absorption due to the numerous formulation effects and *in vivo* variables that can affect their dissolution profile.

Class III exists of water-soluble drugs that do not permeate bio-membranes readily.

Class IV consists of water-insoluble drugs that, when solubilised, do not penetrate bio-membranes readily. Unsuccessfully, most new chemical entities are water-insoluble lipophilic compounds.

Methods for Enhancing Solubility:

A wide range of principles and methods is available for the purpose of enhancing dissolution and/or dissolution rate of 'low-solubility' substances, for example[12,13,14]

- Preparation of solid dispersions
- Selection of salt form for weak acids and bases
- Reduction of particle size and, thereby, increased specific surface area
- Use of surfactants for increased wettability
- Complex formation with excipients, e.g. hydrophilic polymers
- Change of crystal form by precipitation with hydrophilic polymers
- Use of metastable polymorphs
- Lipophilic formulations, i.e. emulsions, microemulsions etc.

Methods for Improvement of Bioavailability:

As the definition of bioavailability is concerned a drug with poor bioavailability is the one with-

1. Poor aqueous solubility and/ or slow dissolution rate in the biological fluids.
2. Poor stability of the dissolved drug at the physiologic pH.
3. Inadequate partition coefficient and thus poor permeation through the biomembrane.
4. Extensive presystemic metabolism.

There are several ways in which the dissolution of the drug can be enhanced. Some of the widely used methods, are aimed at increasing the effective surface area of the drug.[10] Salt formation, micronization, use of surfactant and cosolvent in the formulation are the commonly adopted technique for solubility improvement of poorly water soluble drugs[15].

Formulation of Amorphous Solid Dispersions:

The term solid dispersion can be defined as homogeneous system in which one or more drugs are dispersed molecularly but irregularly within a matrix of inert carriers. The carrier used for this purpose is often polymers, adsorbent which are intrinsically amorphous in the nature.[16,17,18]

The Ideal Characteristics for Carrier Materials are as Follows

- It should be freely water soluble with intrinsic rapid dissolution properties.
- It should ideally increase the water solubility of the drug.
- Carrier and drug should be miscible in the solvent used for processing to avoid irregular crystallization and subsequent variability in dissolution rate.
- It should not form stable complexes with drug that would retard dissolution.
- It should be chemically, physically and thermally stable.
- The carrier should be pharmacologically inert.
- It should not be toxic.

Commonly used carriers are the hydrophilic, organic polymers like polyvinylpyrolidone (PVP), polyethylene glycol (PEG), polyvinyl alcohol (PVA), Crospovidone, Polivinylpyrolidone-ethylacetate copolymer (PVP-PVA), copolymer of acrylates and polymathacrylates and various cellulose derivative like, hydroxypropylmethylcellulose (HPMC),hydroxypropylcellulose (HPC), HPMC-acetate , succinate etc., hydrophilic adsorbent like colloidal silicon dioxide (Aerosil, Cabosil, Sylysia ,Syloid), magnesium aluminometasilicate (Neusilin),porous calcium silicate (Florite) etc.

The Advantage of Solid Dispersions:

Pharmaceutical glasses or amorphous solids present an attractive approach to drug delivery because of their improved bioavailability compared to their crystalline counterparts. Amorphous solids lack the three-dimensional long-range molecular order characteristic of crystals, but may exhibit short-range order. Amorphous materials are higher energy states, and as expected have faster dissolution rates relative to corresponding crystals. The drug substance is often obtained in the amorphous state meaning that crystal lattice forces have already been overcome.[19]

- Solid dispersion has reduced particle size that helps in enhanced dissolution of molecule.
- Based on the drug and carrier, wettability & dissolution is increased and that conductive to dissolution is generated.

POROUS CARRIER:

Porous carriers are low density solids and have been widely used in last few decades for delivery of pharmaceutical active agents in novel and therapeutically effective manner. Porous pharmaceuticals can be developed using preformed porous excipients or these can be formulated using various techniques like freeze drying, gas entrapment, solvent diffusion, melt sonocrystallization etc[20,21]. Preformed porous carriers provide large surface area for active constituent loading. Drug loading over porous carriers can be performed by simple methods like physical mixing, solvent evaporation, melt adsorption etc or using complex modified procedures like supercritical fluid processes[22]. Pore size of these carriers can vary from macroporous to microporous. Porous carriers with a varied distribution of pore size like carriers containing pore size of both microporous and macroporous range have been produced by researchers. Microporous are usually indicated for pores less than 50 µm and macroporous are for pores in the 100-300 µm range . Carriers can have open or closed channel pores or both. The size of porous carriers is usually in the range of micrometers but carriers in millimeter range are also available. Porous carriers used in pharmaceuticals usually remain insoluble in aqueous fluids but their hydrophobicity varies from completely hydrophilic carriers, which immediately disperse in water, to completely hydrophobic ones which float on water for hours. Porous carriers can be divided into two groups based on their structural behavior towards aqueous fluids; one group includes plastic porous carriers which have fixed size and form which don't change on contact with aqueous fluids (e.g. silicates and synthetic polymers) and second group includes soft gel carriers such as superporous hydrogels, porous hydrogels, aerogels etc. which swells or dissolves slowly or rapidly on contact with aqueous fluids.[23]

Applications of Porous Carriers In Pharmaceuticals:

Porous carriers have shown wide applications in different delivery systems for active pharmaceutical agents.

a.Improvement of Dissolution:

Porous carriers due to their large exposed surface area have been used to improve dissolution of poorly

aqueous soluble drugs like many NSAIDs etc. The solubility and oral bioavailability of a poor water soluble drug, 3-bis(4-methoxyphenyl) methylene-2-indolinone (TAS-301) was improved by its melt adsorption on Florite RE.

b. Floating Drug Delivery System:

Porous pharmaceuticals have been widely used for development of floating drug delivery systems due to their inherent low density. Floating systems have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for a prolonged period. This results in an increase in the gastric residence time (GRT) and a better control of fluctuations in the plasma drug concentrations.

c. Controlled Drug Delivery Systems:

Porous carriers were used to provide release of drugs or macromolecules ranging from zero order to pulsed and controlling porosity of carriers drug release can be modified.

d.Pulmonary Drug Delivery Systems:

Porous pharmaceuticals are useful for delivery of active agents to nasal or pulmonary sites but especially useful to target lungs because of their low density. For inhalation drug delivery, it is advantageous to use particles of various porosities and densities to dictate where in the lung the particles will be delivered.

e. Enzyme Immobilization:

Many enzymes like lipase, bovine serum albumin etc have been immobilized on polymeric porous carriers like Accurel to improve their activity and bioavailability. Immobilization is a suitable approach that allows biocatalyst reuse, makes product recovery easier and is able to enhance resistance against inactivation by different denaturants.

f.Biotech Related Applications:

Porous carriers have been studied for purification of nucleic acid like Genomic DNA by selective calcium silicate or Accurel adsorption[24]

Aim and Objectives:

The aim of present work to evaluate the potential of the solid dispersion technique for the development of fast dissolving tablets of Aceclofenac using Florite as hydrophilic porous carrier. In order to achieve this aim following objectives were set:

1. To adsorb Aceclofenac over Florite resulting in microparticles and to evaluate them.
2. To improve the dissolution of Aceclfenac using porous calcium silicate (Florite RE).
3. To formulate and evaluate (in-vitro) immediate release of directly compressed tablets using above microparticles with improved drug dissolution.[25]
4. To formulate and evaluate (in-vitro) immediate release of dispersible tablets prepared by Direct compression method using above microparticles with improved drug dissolution.

CONCLUSION:

Porous carriers have been used to improve dissolution rate of the poorly water soluble drugs. Florite is porous calcium silicate that possesses many nterpartical, intrapartical pores, particularly of size 0.12 and 0.15 um respectively on its surface. It is hydrophilic and easily dispersible in water. Large surface area and hydrophilic surface of florite are useful for adsorption of drug and quick dispersion in to water, respectively. Secondly, the fineness of carrier makes it suitable to attain uniformity of dispersion. Therefore, florite was selected as adsorbent. Aceclofenac was dissolved in minimum amount of acetone that is sufficient to dissolve the drug and wet the carrier particles. Adsorbent was dispersed in drug solution and it was evaporated in vacuum rotary evaporator.

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