University of Basra
College of Pharmacy

''Enhancement the dissolution characteristics of meloxicam by solid dispersion approach: theoretical proposal''

A graduation project submitted as part of the requirements for obtaining a Bachelor degree in Pharmacy.

Prepared by:

وفاء اكرم لطيف
سما صباح عبد الرزاق
فاطمة الزهراء يعرب داود

Supervised by:

Assist. Prof. Dr Muqdad Alhijjaj
Dr.Suhair Ashor

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Abstract

Solubility, is an important physicochemical factor affecting absorption of a drug and its therapeutic effectiveness. Poor water solubility can lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to low bioavailability. One of the most effective strategies for improving the solubility is the formulation of solid dispersion which is prepared by solvent evaporation method, melting method, melt solvent method, kneading method, co-grinding method, co-precipitation method, modified solvent. It is classified as first, second and third generation solid dispersions. In this paper, an attempt is made to clarify the method of improving solubility of meloxicam which is a poorly water-soluble drug (about 12 microg/ml, a class II BCS) by solid dispersion method. The final formulation can be characterized for solubility parameters, dissolution enhancement, drug content, drug-carrier miscibility and drug-carrier interactions by using Isothermal Calorimetry, NMR, FTIR, UV spectrophotometry and DSC.

Introduction

Solubility, is defined as the capacity of a substance to dissolve in a particular solvent at a certain temperature. It is important in the pharmaceutical industry because it impacts the absorption of drugs taken orally, and thus their bioavailability and pharmacokinetic profile.it is necessary for the drugs to have pharmacological activity as well as adequate water solubility for rapid dissolution at the site of administration particularly gastrointestinal tract.[1]

Poor water solubility of a drug is a difficult problem during the formulation and development of dosage forms. Therefore, many important products cannot reach the market due to their low solubility. [2]

Poorly water-soluble drugs often require high doses in order to reach therapeutic concentrations after oral administration. Enhancement of the dissolution rate is very important for such compounds, because it can lead to higher and reproducible oral bioavailability and hence dose reduction and high therapeutic efficacy as dissolution is the rate limiting step in process of drug absorption. To improve solubility and dissolution, there are many approaches available such as pH adjustment, inclusion complexation, particle size reduction, liquid solid methods, supercritical fluid processes etc. Among these several methods, solid dispersion has attracted attention because it enhances the solubility of drug particles thus enhancing dissolution characteristics and oral bioavailability. [3]

Meloxicam, is a nonsteroidal anti-inflammatory drug (NSAID) commonly used to treat pain or inflammation caused by rheumatoid arthritis and osteoarthritis .It is a pastel yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient (log P)= 0.1 in n-octanol/buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2 .The solubility of meloxicam can be improved by solid dispersion method.[4]

Proposed Objective:

Preparation of solid dispersion to enhance the solubility of Meloxicam.

Various techniques for solubility enhancement of poor water-soluble drug

More than one method can be used to improve the solubilization of poor water-soluble drugs and hence improve their bioavailability :

Particle size reduction

There is a relationship between the solubility of a drug and the particle size. Drug particle size can be reduced by various means such as jet mill, rotor stator colloidal mill, ball mill, etc. This reduction can increase in surface area and then enhances the drug dissolution. However, many limitations may be associated with this technique such as thermal and physical stress on the drug that may cause degradation, limited opportunity to control important characteristics of final product such as shape, size, morphology, surface properties, and electrostatic charges. In addition, thermodynamic instability of amorphous region are susceptible to recrystallization in hot and humid condition.[5،6]

Nanosuspension technology

Nanosuspension is sub-micron colloidal dispersion of pure particles of drugs, which is stabilized by surfactants. It can be used for topical ,oral use ,parenteral or pulmonary administration. In nanosuspension, particle size is usually less than one micron ranging between 200 and 600 nm.[6،7] Media milling, high pressure homogenization in water, high pressure homogenization in non-aqueous media and combination of precipitation and high pressure homogenization are the various methods preparation of nanosuspension. Nanosuspension approaches have been employed for various drugs including tarazepide, atovaquone, amphotericin B, etc.[8]

Salt formation

Dissolution rate of particular salt is usually different from that of parent compound. Sodium and potassium salts of week acid dissolve more rapidly than that of pure salt. The limitation of salt formation are epigastric distress due to high alkalinity, reactivity with atmospheric water and carbon dioxide leads to precipitation.[9]

PH adjustment

Poor water soluble drug may potentially dissolve in water by changing the pH. The buffer capacity and tolerability of the selected pH are important to consider. Solubilized excipients that increase environmental pH within the dosage form to a range higher than pKa of weekly acidic

drugs can increase the solubility of that drug, those excipients that act as alkalizing agents may increase the solubility of weekly basic drugs.[10]

Hydrotrophy

Hydrotrophy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water soluble drugs.[11]

Nanotechnology approaches

Nanotechnology can be used to improve drugs that currently have poor solubility. Nanotechnology refers broadly to the study and use of materials and structures at the nanoscale level of approximately 100 nanometers.[12]

For many new chemical entities with very low solubility, oral bioavailability enhancement by micronisation is not sufficient because micronized product has the tendency of agglomeration, which leads to decrease the effective surface area for dissolution .[13،14]

Surfactant

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small polar molecules are added, they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may decrease the surface tension and increase the solubility of the drug within an organic solvent .[15،16]

Solid dispersion

solid dispersion is 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 molecularly dispersed in amorphous particles or in crystalline particles. Solid dispersion can also be referred as the dispersion of one or more active ingredients in an inert matrix at solid state prepared by the melting, solvent, and melting solvent method. [18][17]

Mechanisms by which Solid dispersions can increase the dissolution rate of poorly water soluble drugs

- Reduction in particle size.
  The carrier in solid dispersion is dissolved and the drug release as fine colloidal particles in an aqueous media so the surface area will increase lead to dissolution enhancement.

- Improvement in wettability.
  Drug wettability improvement has very important effect on increasing solubility. Carriers for instance cholic acid and bile salt can significantly increase the wettability property of drug results in dissolution and solubility enhancement.

- Changing crystalline form of drug to amorphous form.
  As no energy is required to break crystal lattice in amorphous state during dissolution so poor water soluble crystalline drugs in amorphous state will have higher solubility.

- Particles with high porosity.
  The increased porosity of solid dispersion particles which depends on carrier properties accelerates the drug release profile. [19]

Classification of Solid Dispersion

-Carrier-Based Class of Solid Dispersion

First Class of SD

In this class using of urea and sugars as a hydrophilic carrier with high water solubility and low toxicity .The use of urea as a hydrophilic carrier can increase the absorption of sulfathiazole and - chloramphenicol in the eutectic mixture compared to that of the conventional formulations.

-Urea and sugars were firstly used as crystalline carriers for production of SD. These formulations were thermodynamically unstable, resulting in slow drug release.[20]

Second Class of SD

Because of thermodynamic instability of first class SD , second class SDs were introduced by using amorphous polymeric carriers instead of urea or sugars result in formulations have smaller particle sizes which can enhance wettability thereby increasing the aqueous solubility of drugs.[21]

The third class of SD

In this class, surfactant can be used alone or in the combination with other hydrophilic carriers for the preparation of SD. Surfactants are widely used to improve the solubility and bioavailability of poorly water-soluble drugs and can play a crucial role in the pharmaceutical industry. Adsorption of a surfactant on a solid surface can modify the hydrophobicity of the drug, thereby reducing surface tension between two liquids or between a liquid and a solid. As example for surfactants are Inulin inutec , poloxamer ,Gelucire 44/14 and Compritol 888 ATO.[22] [23]

-Structure-Based Class of Solid Dispersion

Eutectic Mixtures

A eutectic mixture is a mixture of two components that melt at a single temperature. Where the melting point of the mixture was lower than that of component A or B[24]

Glass Solution/Glass Suspension

A glass solution is a homogeneous system in which the drug molecule is dissolved in a glassy solvent [25][26] .Glass suspension is a homogeneous system in which the drug molecule is suspended in a glassy solvent .The glassy state is characterized by transparency and brittleness below the glass transition temperature for both glass solutions and glass suspensions.[27]

Solid Solution

Solid solution is categorized on the basis of miscibility and molecular size of the components into continuous and discontinuous solid solutions. In continuous solid solutions, the two components can be mixed in all proportions at which the bonding strength between the two components is greater than that of the individual components. [28]

In discontinuous solid solutions, the solubility of each component is limited in solid solvent[25] .Solid solutions are classified into substitutional and interstitial based on molecular size. In substitutional solid solutions, solute molecules substitute for solvent molecules in the crystal lattice. In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice.[26]

Preparation Methods of Solid Dispersion

-Kneading technique

In this method ,thick paste is formed by adding water to the carrier and drug then the paste is kneaded for particular time.

After that, drying and sieving are performed to obtain uniform size of solid dispersion . [29]

-Co-precipitation method

In this method, an anti-solvent is added to cause precipitation to the mixture of the solution of carrier and the added drug which has been kept under magnetic stirring. [30].Then the precipitate is removed, filtered and dried.

- Co-grinding method

In this method, the drug and carrier are mixed together at a particular speed using a blender and then subjected to grinding in the chamber of a vibration ball .The latter may cause deformation of crystal lattice by increasing the activation that result from strong grinding forces. This leads to reduction in crystallinity of drug and consequent increase in dissolution rate and bioavailability . [31]

-Melting method

In this method, mortar and pestle can be used to mix the drug and carrier to form homogenous dispersion. Then the mixture can be heated above the melting point of both the drug and carrier.

-Uniform dispersion is obtained by crushing and sieving a film mass that is formed by cooling the mixture. [32]

-Gel entrapment technique

Transparent gel is formed by dissolving HPMC in organic solvent . The drug is dissolved in gel by sonication for minutes then organic solvent is evaporated under vacuum .Mortar can be used to reduce the size of solid dispersions and then SD should be sieved. [33]

-Spray-Drying Method

The carrier is dissolved in water and the drug is dissolved in a suitable solvent . A clear solution will be produced by mixing the solutions using a suitable method such as sonication then spray dryer will be used to make the solution spray dried . [34]

-Lyophilization Technique

Lyophilization is a molecular mixing technique where a lyophilized molecular dispersion is obtained when the drug and carrier are co dissolved in a common solvent, frozen and sublimed . This technique was suggested as an alternative method to solvent evaporation. [35]

-Electrospinning Method

In this procedure, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overwhelm the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters will be produced. As the solvent gets evaporated, the formed fibers can be collected on a spinning mandrel or can be collected by screen to give a non-woven fabric. The method is cheap, simple and has great potential for the preparation of nanofibers and control drug release. [36] [37]

- Melt Extrusion Method

In this method, solid dispersion is prepared by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is 40% (w/w) .Solid dispersions is affected by the speed of screw and water content. This technique is used in the preparation of different dosage forms such as sustained-release pellets.[38] [39]

-Melt Agglomeration Process

In this method ,solid dispersion is prepared either by heating the binder(which is the carrier), drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in

molten binder on the heated excipient by using a high shear mixer . [40]Due to better control of the temperature and higher binder content to be incorporated in the agglomerates, rotary processor may be an alternative equipment for melt agglomeration. [41]

-Supercritical fluid process

Is a new method for reduction of drug Particles and this technique involves dissolving drug and carrier in a common solvent that is introduced into a vessel by a nozzle at the same time with carbon dioxide. The supercritical fluid carbon dioxide (SC-CO2) will extract the solvent rapidly when the solution is sprayed, and this result in the precipitation of solid dispersion particles on the bottom and walls of the vessel. [42] The resulting particles will be stable, small ,with higher flowability and low residual of organic solvent. [43]

-Dropping method solution

This method can involve the pipetting a solid dispersion of a melted drug-carrier mixture and then drop it onto a plate to solidify into round particles .This occurs by the aid of carriers that solidify at room temperature. The dropping method will make the manufacturing more simple and also will increase the dissolution rate and doesn't have problems of solvent evaporation as it doesn't use organic solvents. [44]

-Solvent evaporation method

In this method, the drug and carrier are both dissolved in organic solvent then the solvent is evaporated until a clear solvent is obtained. After that, grinding the solid mass , sieving and drying will be performed. The main advantage is preventing the thermal decomposition of the drug and carrier as the organic solvent requires a low temperature to be evaporated. [45]

Carriers used in solid dispersion:

1- Polyethylene glycol (PEG) :

Are polymers of ethylene oxide, with a molecular weight (MW) usually falling in the range 200-300000. For the manufacture of solid dispersions and solutions, PEGs with molecular weights of 1500-20 000 are usually employed. [46]

2- Polyvinylpyrrolidone (PVP)

Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3000. In general, the glass transition temperature (Tg) is high; for example, PVP K25 has a Tg of 1558C. For this reason, PVPs have only restricted application for the preparation of solid dispersions by the hot melt method . The disadvantage of the high molecular weight PVPs is their much higher viscosity at a given concentration.[47][48]

3- Cellulose Derivatives

1. Hydroxypropylmethylcellulose (HMPC) : HPMCs are mixed ethers of cellulose, they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane. [49]

2. Hydroxypropylcellulose (HPC): HPC exhibits good solubility in a range of solvents, including water, ethanol, methanol and chloroform. The release rate can be enhanced when the ratio of HPC is amplified and when lower MW HPCs are used as the carrier. [50]

3. Carboxymethylethylcellulose (CMEC): CMEC also belongs to the cellulose ethers, but unlike many of the others, it resists dissolution under acidic conditions but it dissolves readily at pH values above 5-6. [50]

4.Hydroxypropylmethylcellulose phthalate (HPMCP): HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 or pH 5.5. [51]

4- Urea

Urea is the end product of human protein metabolism. It has a light diuretic effect and is regarded as non-toxic. Its solubility in water is greater than 1 and it also reveals good solubility in several common organic solvents.[50]

5- Polyacrylates and polymethacrylates

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic, they are mainly used as coatings to change the release of the drug from the dosage form. Commonly they are referred to by the trade name Eudragit drug.

Among the Eudragits, Eudragit E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pHs, while Eudragit L can be used when it is desirable to avoid release in the stomach. [52]

6- Sugar, polyols and their polymers

Although sugars and related compounds are highly water soluble ,they are less suitable than other carriers for the manufacture of solid dispersions. The melting point of most sugars is high, making preparation by the hot melt method problematic, and their solubility in most organic solvents is poor, making it difficult to prepare co-evaporates . [53]

ADVANTAGES OF SOLID DISPERSIONS

- The rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug.
- A reduction in presystemic metabolism. This advantage may occur due to saturation of the enzyme responsible for biotransformation of the drug, as in the case of 17-bestradiol or inhibition of the enzyme by the carrier, as in the case of morphine-tristearin dispersion.
- Transformation of the drug liquid form into a solid form .For example, clofibrate and benzoyl benzoate can be incorporated into PEG-6000 to give a solid.
- Solid dispersions can be used as formulation vehicle to facilitate the preclinical safety and early clinical studies on new chemical entities with very low aqueous solubility. It provides a means to rapidly assess the safety and efficacy profile of the drug substance that may be otherwise difficult to obtain. [54,55]

DISADVANTAGES OF SOLID DISPERSIONS

- Change in crystallinity and a decrease in dissolution rate with aging. Crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage.
- Moisture and temperature have more deteriorating effect on solid dispersions than on physical mixtures. Most of the polymers that used in solid dispersions can absorb moisture, which may result in phase separation, the latter may result decrease in the solubility and dissolution rate.
- Difficulty in handling because of tackiness. [56,57]

Characterization methods of Solid Dispersion

Drug carrier interactions:

It is performed by FT-IR spectroscopy, Solid state NMR and Raman spectroscopy. [58]

Drug content

In this defined amount of solid dispersion is dissolved in suitable solvent then after appropriate dilution concentration is measured by UV spectrophotometry. HPLC is also an useful tool for drug content measurement. Calibration graph is constructed by peak area versus concentration of drug. [58]

Physical Structure

It is performed by following techniques:

- Surface area analysis.
- Surface properties.
- Scanning electron microscopy.
- Dynamic vapor sorption
- Raman microscopy.
- Inverse gas chromatography. [58]

Amorphous content:

It is performed by the DSC, Powder X-ray diffraction, polarized light optical microscopy and Hot stage microscopy. [58]

Drug -carrier miscibility

It is performed by DSC, X-ray diffraction and NMR. [59]

Dissolution enhancement

Solubility enhancement by the solid dispersion can be examined by help of the following parameters:

- Dissolution.
- Intrinsic dissolution.
- Dynamic solubility.
- Dissolution in bio-relevant media. [60]

Temperature Modulated Differential Scanning Calorimetry (TMDSC)

Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. [61]

Stability:

Stability of the solid dispersion can be evaluated by Isothermal Calorimetry, DSC (Tg, Temperature recrystallization) and Saturated solubility studies. [61]

Water vapour sorption

Water vapour sorption can be used to differentiate between amorphous and crystalline material when the hygroscopicity is different. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples. [62]

Isothermal Microcalorimetry

Isothermal microcalorimetry can measure the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg) . [63]

Conclusion

At the conclusion of this research paper, in which we mentioned solubility enhancement by various techniques specially solid dispersion method in terms of its concept, techniques for enhancement, its mechanisms, classifications, preparation methods, characterization , advantages and disadvantages, the solubility of meloxicam which belongs to class II Biopharmaceutical Classification System (low solubility, high permeability) can be enhanced by solid dispersion method.

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