Solid dispersions using Mechanochemical Activation: An Approach to Enhance Solubility of Poorly Water Soluble Drugs

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Abstract-Mechanochemical activation is a practical co grinding operation used to obtain a solid dispersion of a poorly water soluble drug through changes in the solid state molecular aggregation of drug-carrier mixtures and the formation of non covalent interactions (hydrogen bonds) between two crystalline solids such as a soluble carrier, like Dextrose, Mannitol, Lactose etc and poorly soluble drug, aspirin, in order to improve its solubility and dissolution rate. Physical mixture of aspirin and different carrier were grounded in different ratios using a ball mill. The ground mixture produced a solid dispersion after 30 min of grinding while the drug solubility of aspirin with dextrose within the solid dispersion increased by 1.44 fold as compared to the pure drug. Drug activation due to hydrogen bonds between the carboxylic group of the drug and the hydroxyl group of dextrose as well as the decrease in crystallinity of the solid dispersion and the reduction of the particle size led to a better water solubility of aspirin. Solubility studies at different condition of temperature were performed. All the preparations were found to be in limit.

Keywords -Solid Dispersion, Mechanochemical Activation, Aspirin, Co-grinding, Non covalent Interactions.

I. INTRODUCTION

A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, PH adjustment, solid dispersion, complexation, co-solvency, miceller solubilization of poorly water soluble drug is a frequently encountered challenged in screening studies of new chemical entities as well as in formulation design and development.[1]

Currently, solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs and they can be prepared by different methods and used to design amorphous or crystalline multicomponent systems. With solid dispersions it is possible to choose a suitable carrier to modify the molecular mobility, relaxation times and intermolecular interaction. Some of the first substances employed in solid dispersions were crystalline carriers such as urea and sugars. These kinds of carriers produce crystalline or partially crystalline solid molecular dispersions, which are more thermodynamically stable than amorphous ones. For these reasons, more studies are necessary in order to obtain solid dispersions systems where drug and carrier particle size are reduced to a minimum and new non covalent molecular interactions are formed. Hence, it is possible to improve drug wettability and optimal stability. [2]

Actually, concepts of super molecular chemistry and crystal engineering broaden the knowledge about specific intermolecular non covalent interactions between molecules, such as hydrogen bonds, ionic, dipole-dipole or van der Waals and π-π interactions.[2]These are responsible for molecular assemblies in multicomponent systems, comprised of a drug substance and a complementary neutral or charged molecule carrier. These kinds of intermolecular interactions can be used in the design of amorphous or crystalline multicomponent systems and in the explanation of their structures. Etter, set up a series of rules and guidelines for hydrogen bonding in crystals that apply to the design of molecular assemblies. The simplest of these rules states that all available proton donor and acceptor groups will be used in the hydrogen bond, non-covalent intermolecular patterns of most organic molecules in the crystalline state. For instance, the carboxylic acid group of aspirin forms a strong hydrogen bond with the more basic amide carbonyl group of dextrose, and stabilizing effects are explained through the hydrogen bonding patterns of the dextrose carrier on amorphous organic substances such as aspirin in molecular dispersions.

Aspirin was selected as a model drug because it is poorly soluble in water, a crystalline non-steroidal, anti-inflammatory, analgesic, anti-platelet and antipyretic drug. Aspirin at low doses, to help prevent heart attacks, strokes, and blood clot formation in people at high risk of developing blood clots. Aspirin has also frequently shown to have low bioavailability when administered orally. In the last few years, additional uses have been found for aspirin as an effective agent for decreasing the risk of several types of cancer, particularly colorectal cancer. [3]

Meanwhile, dextrose is a widely used excipient in the manufacture of solid dosage forms because of its suitable properties, including hydrophilicity, low hygroscopicity, good compression and ease of purchase at a high quality. Therefore, dextrose was selected in order to design dispersion with aspirin, using a mechanochemical activation to obtain a

minimum particle size and to increase the number of hydrogen bonds. [4] Mannitol is relatively nonhygroscopic and can be used in vitamin formulation. It has negative heat of solution. [4] Lactose is an excipient that has low cost.[4] The term "mechanochemical activation" is defined as the accumulation of defects (amorphisation or crystalline loss) in solids, and occurs using different ground media. In this process the mechanical energy is transferred to solid material surfaces, resulting in sufficient intensity to produce a local energy accumulation in submicroscopic zones. This creates a metastable structure that must release part of the accumulated energy to reach a more stable thermodynamic stage resulting in processes such as the propagation and interaction of dislocations, phase transformations and mechanochemical reactions such as the rupturing of chemical bonds. The main part of the supplied energy is converted into heat but the concentration of the strain at particular crystal sites produces crystal crushing and the formation of new surfaces. Furthermore, the energy supplied yields an accumulation of defects into the crystal and finally leads to complete amorphisation. The experimental verification of mechanochemical activation falls under the broad field of solid state characterization and there are many techniques that are useful for this purpose (X-ray, infrared, Raman spectroscopy, differential scanning calorimetry (DSC) and electron microscopy). The purpose of the present study was to obtain a multicomponent solid dispersion using a ball mill over a crystalline bicomponent system of aspirin and dextrose whose main effect is to enhance drug solubility in water and thus, drug bioavailability. [2] The changes were examined using UV spectrometer. [5]

II. MATERIALS AND METHODS [2][4]

Aspirin with an average particle size of 50 µm, dextrose US (Merck limited), Lactose (Merck limited) and Mannitol (Merck limited) were used for this method. The entire chemicals used were of analytical grade.

2.1 Preparation of the physical mixtures

The Physical mixtures of 30 gm were prepared by mixing equal weights of the drug and carrier and tumbling in a plastic receptacle for 10 min to assure a homogeneous mixture. Later, two more mixtures were prepared in ratio 1:2 and 1:3 of drug andcarrier.

2.2 Grinding of the physical mixture

The prepared sample of aspirin and carrier were grounded into ball mill in ratio of 1:1, 1:2 and 1:3 ratios (60 rpm) for about 30 min each. The properties assessed were bulk density, flow property and apparent solubility.

III.CHARACTERIZATION

3.1 Determination of solubility

Solubility was evaluated from the dissolution of 10 mg of each sample in 100 ml of water at 37±0.5°, stirring at 60 rpm for a 2 h period, then filtering and measuring absorbance at a wavelength of 276 nm. Measurements were carried out in triplicate. By monitoring the dissolution for a period of 6 h, it was noticed that after the first 2 h, the value of the absorbance became constant; therefore, all other tests were carried out in 2 h period.

3.2 Determination of Flow properties

Flow properties were determined by determining by bulk density, tapped density, compressibility index and packing factor.

The Bulk Density was determined by pouring presieved (40 mesh) bulk drug into a graduated cylinder via a large funnel and measuring the volume and weight "as is" (g/cm^3).

Bulk Density = W/VB

Where W=weight of sample; VB= volume of sample

The Tapped density was determined by placing a graduated cylinder containing a known mass of drug or formulation and tapped for fixed number of taps (~1000) until the powder bed volume has reached a minimum (g/cm^3).

Tapped density =W/V_f

Where W= weight of sample; V_f = tapped volume

The compressibility index was determined as

% compressibility = [(Tapped density-Bulk density)/Tapped density] X 100

Packing factor was determined as the ratio of tapped density to the bulk density.

Packing factor = Tapped density / Bulk density.

IV. RESULTS

4.1 Solubility

The data contained in [Table II] show that the apparent solubility of aspirin improves in the physical mixture, when compared to that of the pure drug sample aspirin.

[Table II] also shows that the increase in solubility is greater with Dextrose as compare to Mannitol and Lactose. There was further increase in solubility when mixture of 1:2 and 1:3 with dextrose [Table III] were also ground for an equivalent period of 30 min.

Table I: Solubility of Aspirin in distilled water

S. N.	Drug	Saturated Solubility (µg/ml)			Mean saturated solubility ±SD (µg/ml)
		S_1	S_2	S_3	
1	Aspirin	269.05	273.28	266.78	269.70 ±3.29

Table II: Solubility of solid dispersion of drug with different carrier in 1:1 ratio

S. N.	Drug: Carrier Mixture	Saturated Solubility (µg/ml)			Mean Saturated Solubility ± SD (µg/ml)
		S_1	S_2	S_3	
1	Drug +Mannitol	285.42	294.06	281.11	286.86 ±6.59
2	Drug +Lactose	307.26	315.64	311.40	311.43 ±4.19
3	Drug +Dextrose	328.11	336.34	320.09	328.18 ±8.12

Table III: Solubility of solid dispersion of drug with Dextrose in different ratio

S. N.	Drug: Dextrose Ratio	Saturated Solubility(µg/ml)			Mean Saturated Solubility ± SD (µg/ml)
		S_1	S_2	S_3	
1	1:1	328.11	336.34	329.09	331.18 ±4.49
2	1:2	347.98	356.65	349.11	351.24 ±4.71
3	1:3	388.28	386.12	393.54	389.31 ±3.81

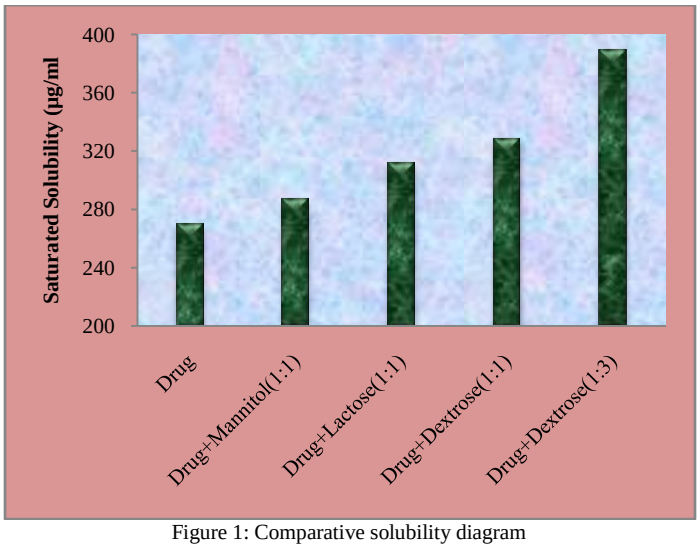

Figure 1: Comparative solubility diagram

Table IV: Flow properties of solid dispersion of drug with Dextrose in 1:3 ratio

S. N.	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility index	Packing Factor
1	0.75	0.95	0.21	1.26

Table V: Solubility studies of solid dispersion with dextrose in 1:1 ratio after 60 days

S. N.	Saturated Solubility		
	In Room Temperature	In Oven maintained at 40^0C	In refrigerator
1	324.89 µg/ml	315.04µg/ml	317.27µg/ml

V. CONCLUSION

The apparent solubility of the ground solid dispersion of Aspirin and dextrose increased, as compared to that of the pure Aspirin. Therefore formation of solid dispersion using mechanochemical activation method was found to be good alternative while enhancing solubility of poorly soluble drugs.

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