Utilization of Solid Dispersion Technique to Improve Solubility and Flowability of Acyclovir

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Abstract: Background and Purpose; Acyclovir is the most common drug used for treatment of herpes viruses. Challenges face acyclovir use, include; very poor aqueous solubility leads to low oral bioavailability (15-30%), and poor powder flowability which cause problems during the manufacture. The main objective of this research is to utilize different grades of natural and synthetic cyclodextrin to prepare acyclovir in the form of solid dispersion to overcome all the previously mentioned drawbacks. **Methods:** Solid dispersions were prepared by kneading and coevaporation methods using different grades of natural and synthetic cyclodextrins and evaluated for drug content, solubility study, flowability parameters (Hausner ratio, Carr's index, and angle of repose) determination. **Results:** Solid dispersions were successfully developed and enhanced the solubility of drug by more than 16 folds in case of β-cyclodextrin and 13-folds in case of hydroxypropyl-α-cyclodextrin (HP-α-CD). Angle of repose decrease from 55^{o} to 24^{o}, Hausner ratio decreased from 1.75 to 1.067, and Carr's index decreased from 42.8% to 16.3% which indicated the enhancement in acyclovir flowability when prepared as solid dispersion by using HP-α-CD. **Conclusion:** It can be concluded that HP-α-CD is an efficient polymer to prepare acyclovir solid dispersion. The prepared SD increased the solubility by more than 13-folds and in the same time enhanced the flowability of acyclovir. In spite of β-cyclodextrin enhanced the solubility to more extent (16-folds) but it not enhanced the flowability of acyclovir.

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1. Introduction

Acyclovir is a drug use to treat infections caused by certain types of viruses (Kimberlin DW, 2001). It is active against herpes viruses due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV (American Academy of Pediatrics, 2003). It treats cold sores caused by herpes simplex appear around the mouth, shingles caused by herpes zoster (Kimberlin DW, 2003). It is available as oral capsules, tablets, and suspension, and topical as cream. Acyclovir is a white, crystalline powder with the molecular formula C8H11N5O3 and a molecular weight of 225 (American Hospital Formulary Service, 1997). It is poorly water soluble (1.3 mg/ml) at 25°C and not exceed 2 mg/ml at physiologic pH and 37°C, it is very slightly soluble in ethanol (0.2 mg/mL); soluble in mineral acids and in dimethyl sulfoxide (Stone KM, 2004). Due to its poor aqueous solubility, after oral administration the absorption is slow, variable and incomplete, with Tmax about 2 hours and Cmax following oral dose of 600mg less than 6 µmol/L, leads to very low oral bioavailability (15–30%) (Stone KM, 2004). Another problem in acyclovir powder is a poor flowability, knowledge of the flow properties of a powder or a bulk solid is necessary to prevent the occurrence of several problems (flow obstructions, segregation, Irregular flow, etc.) during the manufacturing of different dosage forms. Several parameters as particle size, shape, and distribution, and chemical composition of the particles, moisture, and temperature usually control the flow properties of powders. Thus it is necessary to determine the flow properties in appropriate testing methods. Most common methods for measuring the flowability of powders are measurement of angle of repose, bulk and tap densities, carr's index, and calculation of hausner ratio. All these parameters give good indication about powder flowability (Thalberg, K, 2004). Bulk density was 0.59±0.01to 0.64±0.01 and Tapped density was 0.65±0.01 to 0.72±0.03, and also this result show poor flowability (Behera S., 2002).

Cyclodextrins have recently been recognized as useful excipients, they are a group of cyclic oligosaccharides which have approximates a truncated cone or torus structure, it can incorporate several types of lipophilic within its cavity and enhance their solubility due to it has exterior hydrophilic surface and interior nonpolar cavity (Marek R., 2013). Typical natural cyclodextrins contain a number of glucose monomers ranging from 6 unit as α –cyclodextrin (α-CD), 7 units as in case of β –cyclodextrin (β-CD), to 8 units as in γ –cyclodextrin (γ-CD) (Chao, L., 2010). Recently several grades of synthetic cyclodextrins become available as hydroxylpropyl (HP- α, β, or γ-CD) and hydroxylbutyl (HB–α, β, or γ–CD).

Cyclodextrins are mainly used to increase solubility of lipophilic compounds, to increase both chemical and physical stability, to enhance taste, and to enhance bioavailability. In some cases special grades of synthetic cyclodextrin may use to decrease the solubility and control the release of some hydrophilic drugs.

In order to improve the oral bioavailability, several techniques were used in research and during the manufacturing. One of most common one is the utilization of solid dispersion technology through formation of inclusion complex between the drug and some of soluble carriers leads to improve the solubility and enhance the dissolution rate (Astray, G., 2009). Therefore this technology is promising for improving the bioavailability of BCS Class II drugs as acyclovir.

Solid dispersion frequently prepare by the kneading method, melting (fusion) method, and solvent evaporation method (Zheng, Y., 2010). The drug usually convert from crystalline to amorphous state which has higher solubility But the main disadvantages of solid dispersion is that some of used carriers may have bad effects on some of powder characters as flowability (Sheth NS., 2011). Others may form solid dispersions which absorb moisture leads to phase separation, decrease flowability, and conversion from the amorphous to the crystalline state during storage.

The main aim of this research was to improve the solubility and flowability of acyclovir by utilization of solid dispersion technique through use of several grades of natural and synthetic cyclodextrins. Then the prepared solid dispersion were evaluated for their solubility and flowability in order to select the best carrier and best method of preparation which causes improvement in both solubility and flowability.

2. Material and Methods

Materials

Acyclovir was kindly supplied as a gift sample from SPIMACO ADDWAEIH (Riyadh, Saudi Arabia), Cyclodextrin (α- Cyclodextrin, β- Cyclodextrin, γ- Cyclodextrin, HP-α- Cyclodextrin, HP-β- Cyclodextrin, HP-γ- Cyclodextrin, HB-α- Cyclodextrin, HB-β- Cyclodextrin, HB-γ- Cyclodextrin) were kindly provided as a gift from Nihon Shokuhin Kako Co., LTD., Japan), All other chemicals and solvents were of analytical purity.

Methods:

1. Preparation of Solid dispersion

Solid dispersion of acyclovir were prepared in 1:1 ratio (acyclovir: polymer) by two different techniques (kneading, and coevaporation) with various natural and synthetic cyclodextrins (α- Cyclodextrin, β- Cyclodextrin, γ- Cyclodextrin, HP-α- Cyclodextrin, HP-β- Cyclodextrin, HP-γ- Cyclodextrin, HB-α- Cyclodextrin, HB-β- Cyclodextrin, HB-γ- Cyclodextrin) were used.

In the kneading method, mix the required amounts of polymers and distilled water in a mortar till a homogeneous paste is obtained. Then, acyclovir was added portion wise while trituration with addition of small amount of methanol and appropriate amount of water. The obtained pastes were dried in an oven at 45–50°C for 24 hr. The dried complexes were crushed and then sieved through 60-mesh and stored in dry place until used (Chaulang G, 2008).

In the coevaporation method, methanol was used as a solvent. The required quantities of acyclovir and polymers were dissolved in minimum quantities of methanol, and the solvent was evaporated by controlled heating at 45–50°C for 24 hr (Okonogi S, 2006).

2. Evaluation of the prepared solid dispersion:

The prepared complexes were evaluated for their drug content and to what extent improve the solubility of acyclovir. The SD were ranked from higher to lower regarding to its optimum drug content and maximum solubility then subjected for flowability measurement tests as following.

2.1. Drug content

Known amount of the prepared complexes theatrically equivalent to 200 mg of acyclovir was dissolved in methanol, and the concentrations of acyclovir were measured spectrophotometrically at 254.5 nm.

2.2. Saturation solubility studies of the Solid dispersions:

Excess amounts of the prepared solid dispersions were dispersed in 5 ml distilled water in 10 ml glass tubes to get a supersaturated solution. These tubes were shaken continuously for 72 hours at 25oC then centrifuged at 3500 rpm for 10 minutes. 1 ml of each filtrate was diluted with methanol and measured at 254.5 nm. Solubility study of pure acyclovir was also carried out.

3- Determination of flow properties:

The flow properties of pure acyclovir and its solid dispersions were described through the following methods:

3.1. Bulk and tapped densities method:

5 gm of tested powder was weighed and poured into 10 ml graduated cylinder, then the cylinder dropped for three times at 3 seconds interval from a height of 2.5 cm. The volume of the powder (Bulk volume) was recorded which used for calculation of bulk density according to the following equation (Cain J., 2002).

Bulk density (ρb) = weight in(g)/bulk volume (cm3)

The tapped density of the drug was determined after tapping the cylindrical measure several times until a constant volume was achieved (tapped volume), and used to calculate the tapped density of the drug according to the following equation (Cain J., 2002).

Tapped density(ρt)=weight in(g)/tapped volume(cm^3).

After the calculation of bulk and tapped density two parameters indicating the flowability were determined named Hausner ratio and Carr's index.

Hausner ratio is the ratio between tapped density and bulk density and Carr's index can be estimated from the following equation (Cain J., 2002).

Carr's index = (ρt - ρb / ρt) × 100.

The obtained value gives an idea about the flow characters of powder particles.

3.2. Angle of repose method:

By using fixed-base funnel method, the angle of repose was measured as following; powder sample either acyclovir alone or different solid dispersion was allowed to fall through funnel hanged at 2 cm distance above the surface until the apex of the pile reach the lower tip of the hanged funnel (Cain J., 2002). Then the diameter and the height of the pile were measured and used for calculation of angle of repose according to the following equation.

Tan θ = h / r

Where θ is angle of repose, h is the pile height, and r is the radius of the formed pile Each experiment was carried out in triplicate (n = 3).

3. Results

Drug content and solubility study for different complexes:

The drug content for all solid dispersions were ranged from 96.1 to 99.6%, which match the amount of acyclovir incorporated in these dispersions and evident for the applicability of all used methods for preparations.

Figure 1 shows the results of saturation solubility studies, which revealed that the aqueous solubility of acyclovir was 1.84 ± 0.23 mg/mL and increased with its dispersion in the investigated polymers with variable extent. acyclovir reaches its highest solubility by its dispersion with β-CD > HP-β-CD > HP-α-CD > HB-β-CD > α-CD > HB-α-CD > HP-γ-CD > HB-γ-CD>γ-CD, in all the employed techniques.

Flow Properties

The flow properties of the acyclovir in its pure state and different solid dispersions are shown in Figure 2. This result was confirmed by the values of Hausner ratio, Carr's index, and angle of repose.

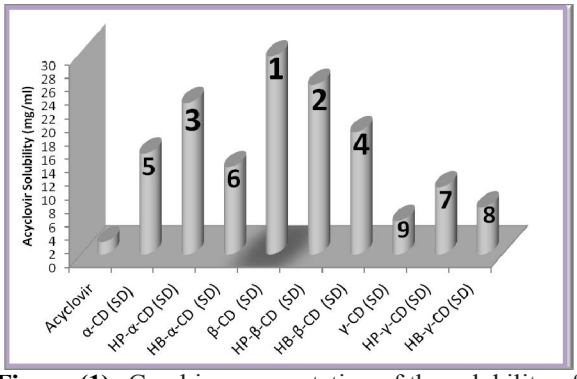

Figure (1): Graphic representation of the solubility of acyclovir from different solid dispersions in comparison to pure acyclovir powder.

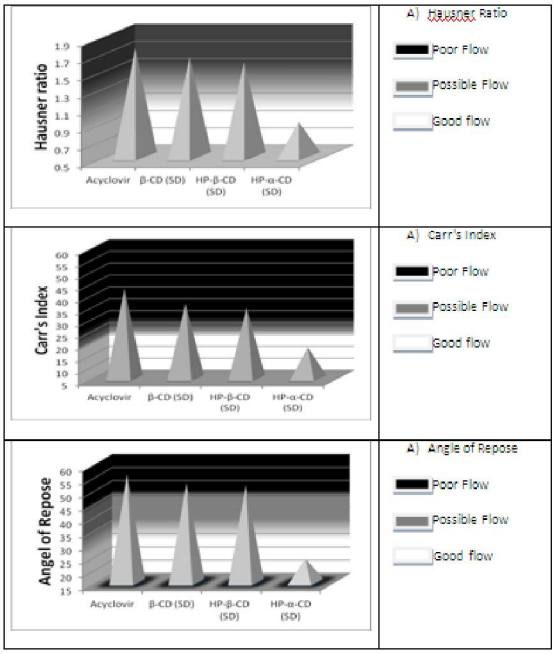

Figure 2. Flow properties of acyclovir pure drug and its different prepared solid dispersion

4. Discussions

Preparation of cyclovir solid dispersion with coevaporation technique was more efficient where the solubility of acyclovir increased approximately to 16-folds its solubility in pure state owing to its higher affinity to inclusion in the hydrophobic cavity of CD which is also aided by heating and stirring as in case of coevaporation which give the molecule the appropriate energy to collide in the correct orientation. In contrast to kneading method that showed inefficiency to produce a true inclusion complex which may be due to the hindrance of drug–CD interactions in a semisolid medium and the solubility increased only 4-folds its solubility in pure state.

Regarding acyclovir flowability, Hausner ratio was 1.75, Carr's index was 42.8 %, and the angle of repose was 55° for pure acyclovir powder. According

to USP 29-NF24, possible to flow materials have Hausner ratio ranged from 1.26 – 1.34; Carr's index from 21 – 25 and angle of repose from 31 – 45°. This mean that acyclovir powder has bad flowability. On the other hand, the flow parameters of solid dispersion prepared by β-CD which was gave highest solubility were 1.4 for Hausner ratio, 28.6 % for Carr's index, and 49° for the angle of repose. These results indicated that β-CD solid dispersion enhanced the solubility but not enhanced the flowability. Same results were obtained for the solid dispersion prepared with HP-β-CD which was the second one in the results of solubility study. But in case of solid dispersion prepared with HP-α-CD which was the third one in the rank of enhancing the solubility, the flowability parameters were 1.067 for Hausner ratio, 16.36 % for Carr's index, and 24.5° for the angle of repose, which indicate the enhancement in all flowability parametes and the solid dispersion has good flowability and can be incorporated during the manufacturing without need for the addition of glidant which usually has deleterious effect on the solubility and bioavailability of some drugs.

5. Conclusion

Depending on the results of the study it can be concluded that; HP-α-CD is an efficient polymer to prepare acyclovir solid dispersion. The prepared SD increased the solubility by more than 13-folds and in the same time it enhanced the flowability of acyclovir. In spite of β-cyclodextrin enhanced the solubility to more extent (16-folds) but it not enhanced the flowability.

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