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Research Article

DEVELOPMENT OF PARTICLE ENGINEERED ACYCLOVIR SPHERICAL AGGLOMERATES FOR ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE

Rashmi Bhosale, Pallavi Dhekale, Omkar Bhandwalkar *, Adhikrao Yadav

Gourishankar Institute of Pharmaceutical Education & Research, Limb, Satara, Maharashtra, India

*Corresponding Author Email: omkargurav4442@gmail.com

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ABSTRACT

Present study related to the fabrication and characterization of particle engineered spherical agglomerates of acyclovir by using dichloromethane and methanol. Engineered particles were prepared by spherical crystallization technique using a two solvent system comprising methanol and dichloromethane. The effect of speed of rotation and amount of bridging solvent on spherical agglomeration were studied. Prepared spherical crystals were subjected to various physicochemical evaluations such as practical yield, drug content, solubility, dissolution studies. Spherical crystals also characterized by scanning electron microscopy, FTIR spectroscopy, Differential scanning calorimetry, X-ray powder diffraction studies. The spherical crystals prepared by incorporation of bridging solvent showed improved aqueous solubility as well as dissolution rate as compared to pure drug. Spherical crystallization is a simple and cost effective process, which can be modify the morphology for particle design of all majority of drugs and combinations.

Keywords: Acyclovir, Spherical agglomerates, Solubility, In vitro dissolution study, Scanning electron microscopy.

INTRODUCTION

Bioavailability of drug depends on its solubility and permeability in a given medium. At present, about 40% of drugs in the development phase and approximately 70% of drugs coming from synthesis or high throughput screening are poorly water soluble, and also lots of drugs are not soluble in organic solvents[1]. Limited aqueous solubility of drugs is becoming increasingly prevalent in the drug product development scenario. According to the Biopharmaceutical Classification System (BCS) aqueous solubility and permeability are the most significant parameters affecting drug bioavailability[2]. The enhancing prevalence of low aqueous soluble drugs in development gives notable risk of new products demonstrating low and erratic bioavailability with consequences for safety and efficacy, particularly for drugs delivered by the oral route of administration. Although various strategies exist for improving the bioavailability of drugs with low aqueous solubility, the achievement of these approaches is not yet able to be guaranteed and is greatly dependent on the physical and chemical nature of the molecules being developed. Crystal engineering offers a number of methods to enhanced solubility and dissolution rate, which can be adopted through an in-depth knowledge of crystallization processes and the molecular properties of drugs[3, 4, 5]. Spherical agglomeration is the novel method of particle engineering that can directly shift the fine crystals produced in the crystallization into a spherical shape. It is the versatile procedure that enables to control the type and the size of the crystals. Spherical crystallization was defined by Kawashima as "an agglomeration method that move crystals directly to compact spherical forms during the crystallization process." It also enables coprecipitation of the drug and the encapsulating polymer in the form of a spherical particle[6].It had been described as a very effective system in improving the dissolution behavior of some drugs that are characterized by low water solubility and a slow dissolution profile. It has also been applied to improve the flowability and the compressibility of some powders. Moreover, critical steps involved in wet granulation can be avoided. Quasi-emulsion solvent diffusion system (QESDS) is most commonly used. Using this method,spherical crystallization can be carried out by using a mixed system of three partially miscible solvents i.e. good solvent bridging liquid–poor solvent[7].

Acyclovir [9-(2-hydroxyethoxylmethyl) guanine], a synthetic purine nucleoside analog derived from guanine, is the most widely used antiviral agent. It is effective in the treatment of herpes simplex virus (HSV), mainly HSV-1 and HSV-2, and varicella-zoster virus[8]. The conventional routes and therapies accessible for the management of Herpes, keratitis, includes orally administered tablet but are linked with it is extremely low bioavailability ranging from 15-30%. Frequently administration of high doses results in irregular nausea, diarrhoea, rash and headache. This trouble can be resolved by improving the solubility and hence dissolution of low aqueous soluble drug acyclovir[9]. Consequently, in present investigation an attempt has been made to improve the physicochemical properties of acyclovir through enhancing its solubility and dissolution rate by spherical crystallization technique. In the present study we tried to prepare spherical crystals using a two solvent system comprising methanol and dichloromethane to improve solubility and dissolution rate of acyclovir which would help to improve bioavailability.

MATERIALS AND METHODS

Materials

Acycolvir was obtained as a gift sample from Lupin Ltd. Boiser, Mumbai, India. Analytical chemicals were obtained from Loba Chemie, Mumbai, India.

Preparation of Acyclovir Spherical agglomerates (10, 11)

Acyclovir spherical crystals were prepared by QESDS crystallization technique. 5 gm of Acyclovir was dissolved in the mixture of 20 ml methanol (good solvent) and 5 ml dichloromethane (bridging liquid), thermally controlled at 25°C. The solution was poured into 200 ml of purified water (poor solvent) with a stirring rate of 750 ± 50 rpm using a propeller type of agitator at room temperature. After agitating the system for 10 min, the prepared spherical crystals were collected by filtration through filter paper under vacuum. The spherical crystals were washed with distilled water and placed at 45°C for drying in a hot air oven for 24 hrs and then stored in desiccator for further use.

Evaluation of prepared spherical crystals
Detection of drug content (11)

Acyclovir spherical crystals equivalent to 10 mg of Acyclovir were accurately weighed, crushed and transferred to a 100 ml volumetric flask. To this, 50 ml of methanol was added and sample was sonicated for 20 min so as to dissolve the drug and the polymer. The volume was made up to 100 ml with methanol and filtered through a 0.45 µm filters. The filtrate was diluted with methanol and analyzed at 277 nm by UV Visible spectrophotometer (Shimadzu 1800, Japan).

Solubility study

Solubility studies were carried out using distilled water as a solvent. Excessive quantity of acyclovir and its spherical crystals were taken in a series of screw-capped test tubes with a fixed volume (10 ml) of distilled water. The resulting suspension was treated at room temperature with 100 rpm in an incubator shaker. After 24 hrs, the samples were withdrawn and filtered through 0.45 µm filters. The filtrate was diluted with deionized water and analyzed at 277 nm by UV Visible spectrophotometer.

In vitro Dissolution study of spherical agglomerates

In-vitro dissolution studies were carried out of acyclovir spherical crystals. Each test was carried out in USP dissolution apparatus II (Paddle) consisted of 900 ml of 0.1N HCl maintained at 37.0 ± 0.5°C and stirring at 50 rpm. An accurately weighed quantity of each sample equivalent to 10 mg of acyclovir was subjected to the test. Samples 5 ml were withdrawn at predetermined time interval (5, 10, 15, 20, 30, 45 and 60 minutes) and immediately replace with the equal volumes of dissolution medium. Samples were filtered and were analyzed at 277 nm by UV Visible spectrophotometer (Shimadzu 1800, Japan).

Characterization of spherically agglomerated crystals
Scanning Electron Microscopy (SEM)

The morphology of powdered samples of selected for formulation was studied by SEM using the JEOL (JEOL 5400 JAPAN). The powders were previously fixed on brass stub using double sided adhesive tape and then were made electrically conductive by coating in vacuum with a thin layer of gold (100-300^{0}A) for 240s photographs were taken 5-10 Kv voltage and appropriate magnification.

Fourier transform infrared spectroscopy (FTIR)

The infrared spectra of ACV and ACVSP were obtained using FTIR spectrophotometer (Shimadzu, IR Affinity, Japan). The samples to be analyzed were transferred to the compartment. The spectra were obtained for the range of 600–4000 cm−1at an average of 25 scans and resolution of 4 cm−1.

X-ray powder diffraction (XRD)

X-ray diffraction pattern of plain Acycovir and its spherical crystals were recorded using Philips X-ray diffractometer (Model: PW 1710) with copper target at 30 kV voltage and 30 mA current. The scanning speed was 1° per minute.

RESULTS AND DISCUSSION
Drug content

The drug content was found to be 97.98 %.

Solubility study

Aqueous solubility of drug was improved by spherical crystallization method. The aqueous solubility study was carried out in distilled water. ACVSP showed improved aqueous solubility (1.2 ± 0.01 mg/ml) as compared with aqueous solubility of plain ACV (0.8 ± 0.02 mg/ml). This may be due to changes in the crystal forms because of different habit, structure, and surface modification. In some instances, solvents included into the crystal forms solvets or clathrates that change the surface properties and the reactivity of the drug particles and the internal energy of the molecules, playing an important role in increasing solubility. Aqueous solubility of drug was also significantly improved in all spherical crystals prepared by incorporation of hydrophilic polymers because hydrophilic polymers were increased wettability of spherical crystals and resulting improved aqueous solubility.

In vitro Dissolution study of spherical agglomerates

In vitro dissolution study of ACV and its spherical crystals showed faster drug release profile in ACVSP spherical crystals as shown in Figure 1. The reason for this faster drug dissolution was linked to the increase in surface area occurred due to spherical crystallization, better wettability of the spherical crystals due to incorporation of the hydrophilic polymers into the poorly water soluble ACV and also because of spherical crystals has a more porous internal structure exhibit a faster drug release rate than those of the less-porous plain drug.

FTIR Spectroscopy study

The ACV of identification and spherical crystals of have been evaluated by FTIR. Pure ACV showed prominent peak of 3441 cm-1, 3275 cm-1,1710 cm-1 because of hydroxyl, aromatic amine and carboxylic acid c=o stretching respectively. The IR spectroscopy revealed that the absence of chemical interaction of the drug with additives during spherical crystallization process.

X-ray powder diffraction pattern

The XRD scan of plain ACV showed intense peaks of crystallinity, whereas the XRD pattern of the ACV spherical crystals exhibited XRD pattern with less intense and denser peaks compared with plain ACV indicating the decrease in crystallinity or partial amorphization of the drug in its agglomerated form shown in Figure 3.

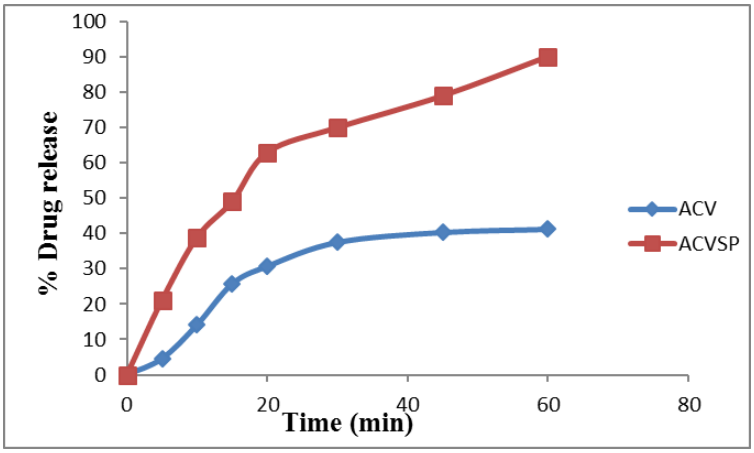

Figure 1: In vitro dissolution profile of Acyclovir and Acyclovir spherical crystals

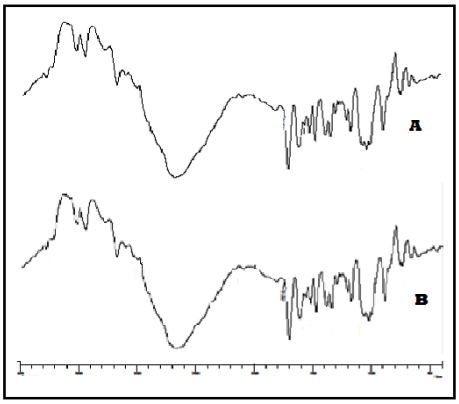

Figure 2: FTIR spectra of A) Acyclovir and B) Acyclovir spherical crystals

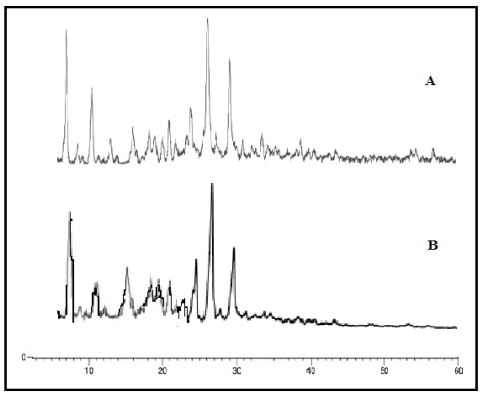

Figure 3: P-XRD of A) Acyclovir and B) Acyclovir spherical crystal

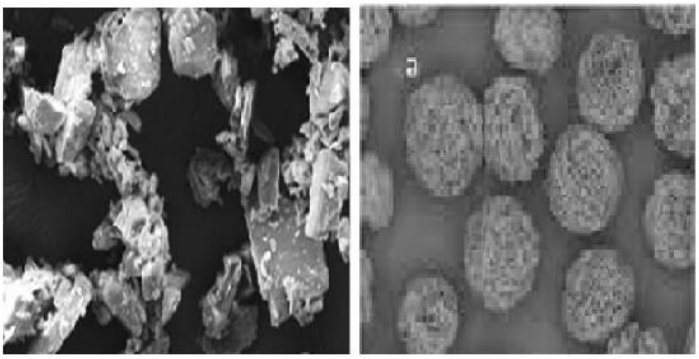

Figure 4: SEM of A) Acyclovir and B) Acyclovir spherical crystals

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) was performed for ACV and for ACVSP particles for investigating the morphology modification and are depicted in figure 4. This method does very conclusively confirm that the ACV spherical crystals agglomerates are formed. The SEM of ACV showed that square shaped large and irregular crystals. In contrast ACVSP showed small spherical particle with the tendency of aggregation suggesting the existence of crystals on the surface of spherical.

CONCLUSION

From the above observations, we can conclude that agglomerated crystals of ACV prepared by the crystallization technique showed an improvement in the solubility and dissolution rate as compared with pure ACV. Dichloromethane was found to be a better bridging solvent in dissolution enhancement of ACV. Instead of preparation of granules, agglomerates of BCS class II drugs to enhance bioavailability and tabletting properties are a better option for the pharmaceutical industries.

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