SPRAY DRIED MICROPARTICLES OF VALSARTAN BY DRYING TECHNIQUE

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Abstract: Valsartan, an Antihypertensive agent drug, exhibits poor water solubility, dissolution and flow properties. Thus, the aim of the present study was to improve the solubility and dissolution rate of Valsartan by preparing crystals by spray drying technique. Valsartan crystals were prepared by spray drying using Ethanol and water (70:30) as solvents system to enhance solubility and dissolution rate. The prepared crystals containing Valsartan were evaluated for In-vitro dissolution and solubility. The prepared formulations were characterized by scanning electron microscopy, differential scanning calorimeter, X-ray diffraction and Fourier transform infrared spectroscopy. Dissolution profile of the spray dried crystals was compared with its recrystallized sample and pure sample. The samples were stored in stability chamber to investigate their physical stability Spray dried crystals exhibited decreased crystallinity and the solubility and dissolution of the Valsartan crystals were significant improved compared with its recrystallized and pure sample of Valsartan. In stability test, the release profile of the Spray dried crystals was almost unchanged as compared with initial results stored at 40°C and 75% relative humidity for 6 month. Hence this technique can be used for formulation of tablets of Valsartan by direct compression with directly compressible tablet excipients.

Keywords: Spray drying, Valsartan, Solubility, dissolution, crystallinity and Stability.

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INTRODUCTION

Valsartan ((2S)-3-Methyl-2-[pentanoyl- [4-[2-(2H-tetrazol-5yl) phenyl]phenyl] methyl]amino] butanoic acid) is a non-peptide, orally active and specific angiotensin II antagonist acting on the AT1 receptor subtype used in treatment of Hypertension as an Antihypertensive agent. Valsartan lowers the blood pressure by antagonizing the rennin angiotensin- aldosterone system (RAAS) (1, 2). Valsartan is a white fine crystalline powder, soluble in ethanol, acetone, and methanol. It is slightly soluble in water and belongs to BCS class II. Absorption of drug from gastrointestinal tract is limited by dissolution (rate limiting step) (3,4). Therefore enhancement of solubility and dissolution property of Valsartan is necessary to achieve its complete pharmacological benefits.

Formulation and manufacture of solid oral dosage forms, and tablets in particular, have undergone rapid change and development over the last several decades. One of the most revolutionary technologies is that of direct compression. Direct compression is economical, facilitates processing without the need of moisture, heat and involves small number of processing steps. In direct tableting method, it is necessary to increase flowability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tableting machine and sufficient mechanical strength of the compacted tablets. In addition to increasing efficiency of the manufacturing process it is also important to increase bioavailability of the drug by improving the solubility of the bulk drug powder. Spray dried (5) microparticles is one of such techniques to improve the micromeritic properties and dissolution of drug.

Consequently, many hydrophobic drugs show erratic and incomplete absorption from the gastrointestinal tract of animals and humans, which may lead to therapeutic failure. Thus, one of the major challenges to drug development today is poor solubility, as an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water (6,7). As a result, much research has been conducted into methods of improving drug solubility and dissolution rates to increase the oral bioavailability of hydrophobic drugs. Various techniques such as melt adsorption, supercritical fluid processes, using different composition of solvents to prepared the microparticles to improve the dissolution rate of poorly water soluble drugs (8). Manipulation of the solid state by decreasing crystallinity of drug substances through formation of solid dispersion is one of the methods used for promoting drug dissolution (9). The solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly water soluble active pharmaceutical ingredients because it is simple, economic, and advantageous technique. The concept of solid dispersion covers a wide range of systems. The enhancement in the dissolution rate is obtained by one or a combination of the following mechanisms: eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, improved wettability, drug precipitation as a metastable crystalline form or a decrease in substance crystallinity. The type
of solid dispersion formed depends on both the carrier-drug combination and the method of manufacture (9,10). Microwaves irradiation was used recently for the preparation of solvent-free solid dispersions and for enhancement of release of the poorly soluble drug, Spray drying is one such technique of preparing solid dispersion and is widely used as an alternative to milling to reduce particle size.

The objective of the present study was to prepare Spray dried crystals of Valsartan using Spray drying technique and was evaluated for solvents residual and DSC, FT-IR, XRD, and SEM analysis were performed to determine the physicochemical properties of the Spray dried crystals and compare with recrystallized sample and pure drug and determined the solubility and dissolution characteristics of the Valsartan Spray dried crystals and investigate their physical stability in a climate chamber at 40°C and 75% relative humidity (RH) for 6 month.

MATERIALS AND METHODS

Valsartan was obtained as a gift sample from Wockhardt Pvt. Ltd., Aurangabad, Maharashtra, India. All chemicals and buffers used were of analytical grade.

Preparation of Spray dried microparticle of Valsartan:

Spray dried particles consisted of Valsartan was prepared by dissolving the 5 gm drug in the mixture of Ethanol/water (70:30 v/v) solution. The solution was spray dried using Mini Spray Dryer LSD-48; (Jay instrument & systems Pvt. Ltd. Mumbai) at a Feed rate of 10%, an vacuum in the system -65 MM WC, Atomization pressure rate 1 kg/cm², Aspirator level at 30%, inlet temperature at 105 ±2°C and outlet temperature at 40 ±1°C. The formed microparticles were separated using cyclone separator, collected and stored in a desiccator at ambient temperature until ready to be used.

Recrystallization of Valsartan (RS)

Valsartan (5 gm) was dissolved in 100 ml Ethanol and water (70:30) heated at 45°C and cooled down to room temperature with occasional stirring. The crystals of Valsartan were collected by filtration and were dried at 45°C for 12 hours.

Determination of residual solvents in Spray dried crystals by gas chromatography

GC studies were carried out on SHIMADZU model 2014 (Shimadzu Technologies, Japan) coupled with a split/split less injector, operated in a split-mode and FID. The computer with GC solutions software has been used to control the gas chromatograph. Rtx-5 capillary column (cross bond 5% diphenyl/95% dimethyl polysiloxane) with a length of 30 meters and an internal diameter of 0.25 mm was used throughout the study.

Differential scanning calorimetry (DSC)
A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

**Fourier transform infrared (FTIR) spectroscopy**

The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). About 2 mg of the pure drug, recrystallized and spray dried crystals were used separately. Pure drug, spray dried crystals and recrystallized samples were dispersed in KBr powder and the pellets were made by applying 6000 kg/cm² pressure.

**X-ray analysis**

X-Ray powder diffraction patterns were used to detect possible polymorphic transition during the crystallization process. X-Ray powder diffraction patterns were obtained at room temperature using a Philips X’ Pert MPD diffractometer, with Cu as anode material and graphite monochromator, operated at a voltage of 40 mA, 45 kV.

**Scanning electron microscopy (SEM)**

Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm spherical nature and morphological characters of the crystals.

**Mechanical Properties**

Tensile strength of spray dried crystals was determined by compressing 500 mg of crystals using hydraulic press at different kg/cm² for 1 min. The compacts stored in desiccator for overnight to allow elastic recovery. The thickness and diameter were measured for each compact. The hardness of each compact was then measured using Pfizer hardness tester. The tensile strength (σ) of the compact (kg/cm²) was calculated using following equation.

\[ \sigma = \frac{2F}{\pi Dt} \]

Where, F, D and t are hardness (kg/cm²), compact diameter (cm) and thickness (cm), respectively.

**Solubility studies of microcrystals**

The solubility of Valsartan Spray dried crystals in water and pH 7.2 Phosphate buffer was determined by taking excess quantity of Spray dried crystals and adding to screw capped 50 ml glass vials filled with water and pH 7.2 Phosphate buffer. The vials were shaken for 24 hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and the drug concentration was determined spectrophotometrically at 248 nm. Solubility study has been performed triplicate.
Dissolution studies of microcrystals

The dissolution of Valsartan pure sample, Spray dried crystals and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium (900ml) consisted of 7.2 Phosphate buffer was used and 10 ml of dissolution medium was withdrawn at every 10 min interval for 1 h. and replaced with fresh dissolution medium. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 248 nm. Dissolution study has been performed triplicate.

Determination of the physical stability

To determine the physical stability of Spray dried crystals, a stability study of prepared Microparticles was carried out at 40°C and 60% relative humidity for 6 months according to the ICH guidelines. The spray dried microparticles were packed in high density polyethylene (HDPE) container and placed in stability chamber. The samples were withdrawn at the interval of 0, 1, 3 and 6 months and evaluated for appearance, characterization by FT-IR and dissolution release and compared with initial results (11).

Result and discussion:

A solvent system involved an Ethanol and water for a drug. The selection of these solvent depends on the miscibility of the solvents and solubility of the drug in individual solvents. Ethanol is miscible in any proportion with water.

Recrystallization of Valsartan was done to find out the changes in crystal lattice, being induced by solvents, can influence the physicochemical properties of the substance. Hence the mechanical and dissolution properties of spray dried crystals were compared with pure sample and recrystallized sample. Recrystallization of Valsartan was carried out using same solvent composition as was used for Spray drying (12).

The spray dried formulations collected and powders were free-flowing and white in color. The percentage yield of spray dried Valsartan was found to be 83%.this small yield can be increase by adding of solid substance or in large scale production as it was small scale preparation. Drug content for the spray dried crystals was found to be 98.8±0.013.

Based upon high solubility of Valsartan in Ethanol, high viscosity and crystal morphology, chloroform determined to be suitable Spray drying medium for Valsartan because of its high solubility in Ethanol (1gm/14ml). The controlling of residual Ethanol was needed though. Ethanol a toxic organic solvent based on their concentration and has little detriment to human body. Therefore, the low level of Ethanol the Spray dried crystals should not be harmful to both animal and human.
Gas chromatography results confirmed that there were below detection level of chloroform in the Spray dried crystals against the ICH limit i.e. 5000 ppm (13). The low level of ethanol in the Spray dried crystals results from its ability to form high surface area crystals and from the fact that the intermolecular forces among both ethanol molecules is not as strong as those of water. This allows ethanol to sublime more completely and easily than water (14).

The DSC thermograms showed a sharp endothermic peak for all the Valsartan crystals. This one step melt might be due to only one crystal form of the Valsartan formed during the spray drying process, thus indicating that Valsartan did not undergo any crystal modification. The temperature range of the endothermic peak of all the Valsartan crystals lies in the range of 114.9 to 117.2 °C (Fig. 1). In DSC curve, pure Valsartan had a sharp endothermic peak at 117.2°C with enthalpy of 147.64 J/g that corresponded to the melting point of Valsartan. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The melting endotherm for spray dried Valsartan was 114.9°C with decreased enthalpy of (139.43J/g) indicating decreased crystallinity of Valsartan in Spray dried crystals (15).

![DSC Spectrum](image)

**Fig 1 Shows DSC Spectrum of different samples of Valsartan**

Infrared spectra of Valsartan commercial sample, recrystallized sample and spray dried crystals showed similar characteristic peaks and presented in Fig. 3. Valsartan has two characteristic carbonyl absorption bands at 1730 and 1601 cm\(^{-1}\) that correspond to carbonyl and amide carbonyl stretching, respectively. The peak at 3563 cm\(^{-1}\) indicates the presence of N–H functional group. The band at 2926 cm\(^{-1}\) indicates the presence of C–H group stretching vibration. The spectrum reveals the characteristic peaks in the typical range at 1205–1065 cm\(^{-1}\) confirm the presence of characteristic tetrazole ring in the Valsartan (15). The complex region of 900–600 cm\(^{-1}\) indicates skeletal vibration and an aromatic ring in the drug substance. It was observed that there were no significant changes in the position of characteristic peaks. Spectrum of recrystallized Valsartan was slightly different from pure sample. This suggests that
specific changes in IR spectra are not very clear, could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor distortion of bond angles, or even a result of the presence of solvents of crystallization (15).

Fig 2 Shows FT-IR Spectrum of different samples of Valsartan

X-Ray diffraction was used to analyze potential changes in the inner structure of Valsartan crystal during the formulation of spray dried crystals. The characteristic peak of the Valsartan appeared in the 2θ range of 10–70°, indicating that the unprocessed Valsartan was a crystalline material (14). All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of Valsartan was ruled out. However relative intensities of XRD peaks were modified (Fig. 3). The relative intensities of spray dried crystals reduced much lower than pure Valsartan. This could be attributed to the markedly different crystal habits of the samples. Therefore the relative abundance of the planes exposed to the X-ray source would have been altered, producing the variations in the relative intensities of the peak or may be due to differences in crystal sizes (15). The pure drug exhibits its characteristic diffraction peaks at various diffraction angles indicating the presence of crystallinity. The X-ray diffraction of the RS of drug showed the peak corresponding to the crystalline drug molecules present in the RS, although their intensity was lower than pure drug due to the differences in crystal sizes. The X-ray diffraction pattern of the spray dried crystals showed that Valsartan peak intensity was much lower than the pure drug and RS samples of Valsartan (15). This could be due the
increasing the wettability of Spray dried crystals. These results could explain the observed enhancement of solubility and dissolution of Valsartan in spray dried crystals (16).

![Spray dried crystals Rer crystallized crystals Pure sample](image)

**Fig 3 Shows XRD Spectrums of different samples of Valsartan**

In SEM study showed that crystals of pure sample are of the smallest size (8-16 μm) and they have irregular shapes. Recrystallization crystals with intermediate size (7-27 μm) which had rod like shapes. The resultant spray dried microparticles formed by spray drying technique had a smooth surface and were spherical in shape with small size (6-11) μm (Fig. 4).

![Pure sample Rer crystallized crystals Spray dried crystals](image)

**Fig 4 Shows SEM photographs of different samples of Valsartan**

Spray dried crystals exhibited superior compressibility characteristics compared to conventional drug crystals (Fig. 5). It could be due to the fact that during the process of compression fresh surfaces are formed by fracturing crystals. Surface freshly prepared by fracture enhanced the plastic inter particle bonding, resulting in a lower compression force required for compressing the spray dried crystals under plastic deformation compared to that of single crystal (14, 16).
Spray dried crystals showed increased solubility than the pure sample in water as well in pH 7.2 Phosphate buffer and increased nearly twofold higher (0.563 mg/ml & 0.873 mg/ml) than pure Valsartan (0.286 mg/ml & 0.433 mg/ml) respectively. The higher solubility of Valsartan from spray dried may be due to the reduction in particle size and increased wettability of Valsartan in spray dried crystals (14).

The dissolution profiles of Valsartan (Fig. 6) exhibited improved dissolution behavior for Spray dried crystals (73.42%) than pure sample (31.76%). The reason for this faster dissolution could be linked to the better wettability and reduction in particle size of the spray dried crystals. The amount of drug dissolved in 60 min greatly varied for spray dried crystals.
The best way to guarantee stability is by maintaining their physical state and molecular structure. The results of the stability study of prepared spray dried crystals of Valsartan stored at 40°C and 75% relative humidity for 6 month was found to comparable with initial results. The influence of physical stability on the prepared crystals was investigated. Prepared spray dried crystals of Valsartan were stable and complied with all the properties when compared to initial results of prepared spray dried crystals of Valsartan.

**CONCLUSION**

Spray dried crystals of Valsartan were prepared by spray drying technique. Spray dried crystals exhibited decreased crystallinity and improved mechanical properties. DSC FT-IR and XRD studies showed that there is no change in the crystal structure of Valsartan during the crystallization process i.e., polymorphism has not occurred. The dissolution of the spray dried crystals was improved compared with recrystallized sample and pure Valsartan sample. Stability study showed that prepared spray dried crystals was stable for 6 month. Hence this technique can be used for formulation of tablets of Valsartan by direct compression with directly compressible tablet excipients.

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**REFERENCE**


