PREPARATION AND CHARACTERIZATION OF SPRAY DRIED MICROPARTICLE OF CARBAMAZEPINE

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Article Received on: 02/01/11 Revised on: 05/02/11 Approved for publication: 10/02/11

ABSTRACT
Carbamazepine, an antiepileptic drug, exhibits poor water solubility and flow properties, poor dissolution and poor wetting. Consequently, the aim of this study was to improve the dissolution of Carbamazepine. Microparticle containing Carbamazepine was produced by spray drying using Isopropyl alcohol and water in the ratio of 40:60 (v/v) as solvent system to enhance dissolution rate. The prepared formulations were evaluated for in vitro dissolution and solubility. The prepared drug particles were characterized by scanning electron microscopy (SEM), differential scanning calorimeter (DSC), X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR). Dissolution profile of the spray dried microparticle was compared with pure sample and recrystallized sample. Spray dried microparticle exhibited decreased crystallinity and improved micromeritic properties. The dissolution of the Spray dried microparticle was improved compared with recrystallized and pure sample of Carbamazepine. Consequently, it was believed that spray drying of Carbamazepine is a useful tool to improve dissolution. Hence this spray drying technique can be used for formulation of tablets of Carbamazepine by direct compression with directly compressible tablet excipients.

KEYWORDS: Spray drying, microparticle, Carbamazepine, Solubility dissolution, crystallinity.

INTRODUCTION
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 tabletting method, it is necessary to increase flow-ability and compressibility of the bulk powder in order to retain a steady supply of powder mixture to the tabletting 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 microparticle 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. 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 prepare the microparticle to improve the dissolution rate of poorly water soluble drugs. and amorphous state to improve their dissolution. 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 6-9. 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 wet-ability, and drug precipitation as a meta-stable 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. 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 technique also has the advantages of being free from organic solvents compared to spray drying. The method has also been used by the food industry, for example, to encapsulate vitamins and minerals. Carbamazepine (CBZ), an antiepileptic drug, was chosen as the model drug for this study because its low water solubility (11g/ml) leads to low and variable bioavailability. CBZ consists of an azepine ring with fused benzene rings on either side or an amide group attached to the N of the azepine ring. Given the clinical importance of CBZ, there is a strong interest in improving its dissolution and bioavailability. The present work was conducted to improve the wetability, solubility and hence the dissolution of Carbamazepine using spray drying techniques.

MATERIALS AND METHODS

Materials

Carbamazepine was obtained as a gift sample from IPCA Ltd, Mumbai, India. Isopropyl alcohol was procured from Merck, Mumbai, India. All chemicals and buffers used were of analytical grade.

Preparation of microsphere

Microparticle prepared by spray drying

Spray dried particles consisted of Carbamazepine was prepared by dissolving the 5 gm drug in the mixture of Isopropyl alcohol : water (40:60 (v/v) ratio) solution. The solution was spray dried using Mini Spray Dryer LSD -48; (Jay instrument & systems Pvt. Ltd. Mumbai) at a Feed rate of 12%, an vacuum in the system -65 MM WC, Atomization pressure rate 1 kg/cm², Aspirator level at 35%, inlet temperature at 115 ±2°C and outlet temperature at 45 ±1°C. The formed microparticle were separated using cyclone separator, collected and stored in a desiccators at ambient temperature until ready to be used.

Recrystallization of Carbamazepine

Changes in crystal lattice, being induced by solvents, can influence the physicochemical properties of the substance. Hence the mechanical, micromeritic and dissolution properties of microsphere were compared with commercial sample and recrystallized sample. Recrystallization of Carbamazepine was carried out using same solvent composition as was used for spray drying Carbamazepine was dissolved in 40 ml of Isopropyl alcohol and 60 ml of water with occasional stirring for 30 min. The crystals of Carbamazepine were collected by filtration and were dried at 45°C.

Evaluation of microparticle

Determination of percentage yield and Drug content

The percentage yield of each formulation was determined according to the total recoverable final weight of microparticle and the total original weight of Carbamazepine. Microparticle (50 mg) were triturated with 10 ml of water. Allowed to stand for 10 min with occasional swirling and methanol was added to produce 100 ml. After suitable dilution, samples were measured at 286 nm. Drug content was determined from standard plot.

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). Samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-ray analysis
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. The process parameters used were set as scan step size of 0.0170 (2θ).

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 surface topography of the crystals.

Micromeritic properties
Particle size of recrystallized sample, pure samples, spray dried microparticle were determined by microscopic method using calibrated ocular micrometer. Apparent particle densities of microparticle were measured using a Pycnometer. Carr’s index was determined from powder volumes at the initial stage and after 1250 tappings to constant volume (Electrolab, Mumbai). The angle of repose of microparticle and commercial crystals was measured by fixed funnel method.

Mechanical property
Mechanical Properties like tensile strength of microparticle, recrystallized sample and pure sample of Carbamazepine were determined by compressing 500 mg of samples using hydraulic press at different ton/cm² for 1 min. The compacts stored in desiccators 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 (ton/cm²) was calculated using following equation.

\[ \sigma = \frac{2F}{\piDt} \]

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

Solubility studies
The solubility of Carbamazepine microparticle in water was determined by taking excess quantity of microparticle in 50 ml to screw-capped glass vials filled with water. The vials were shaken for 12 hours on mechanical shaker. The solution was filtered through Whatmann filter paper No.1 and drug concentration was determined at 286 nm.

Dissolution studies of microparticle
The dissolution of Carbamazepine pure sample, microparticle (prepared by spray drying) and recrystallized sample was determined by using USP dissolution apparatus XXIV-Type II (Electro Lab, Mumbai). Dissolution medium was 900 ml 7.4 Phosphate buffer. The amount of dissolved drug was determined using UV spectrophotometric method (UV 1601 A Shimadzu, Japan) at 286 nm.

RESULTS
The percentage yield of spray dried microparticle of Carbamazepine was found to be 71%. Drug content for the spray dried formulation was found to be 98.22±0.015.

The DSC thermogram (fig. 1) shows a sharp endothermic peak for all the Carbamazepine. This one step melt might be due to only one crystal form (Triclinic) of the Carbamazepine formed during the crystallization process, thus indicating that Carbamazepine did not undergo any crystal modification.

All the crystals have exhibited general characteristic peaks at 3464 cm⁻¹ (-N-H stretching), 1677 cm⁻¹ (-C=O stretching), 1605 and 1593 cm⁻¹ (range of -C=C- and –C=O vibration and -NH deformation), 1383 cm⁻¹, 1271 cm⁻¹ (-C≡N bond), 1245 cm⁻¹ and 1019 cm⁻¹. (fig. 2).

All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of Carbamazepine was ruled out. However relative intensities of XRD peaks were modified (fig. 3).

The SEM images of all the formulation shown in figs 4. The size of spray dried microparticle was in small in size and has smooth surface.
The Micrometrics properties of Pure Sample, Recrystallized Sample and spray dried microparticle of Carbamazepine shown below: (Table 1).

Spray dried microparticle exhibited superior compressibility characteristics compared to pure sample and recrystallized sample (fig. 5).

The solubility of Carbamazepine spray dried microparticle in water was found to be (0.0526 mg/ml) which was higher greater than recrystallized sample (0.0094 mg/ml) and pure sample (0.0083 mg/ml).

The dissolution profiles of Carbamazepine (fig. 6) exhibited improved dissolution behavior for spray dried microparticle than recrystallized sample and pure sample.

DISCUSSION

The solvents chosen for the spray drying were acetone and water. These both the solvent were miscible in any proportion with each other.

The spray dried microparticle was collected and powders were free-flowing and white in color. The percentage yield of spray dried microparticle of Carbamazepine was found to be 71%. 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 formulation was found to be 98.22±0.015.

The temperature range of the endothermic peak of all the Carbamazepine crystals lies in the range of 186-189°C. Melting points show slight variation as the nature of the crystals might have been affected by the solvent. The Carbamazepine pure sample melted at 189°C with enthalpy of 198.6 J/g. The melting endotherm for spray dried microparticle of Carbamazepine was 186.12°C with decreased enthalpy of (176.17 J/g) indicating decreased crystallinity or presence of amorphous form. The DSC thermograms of recrystallized sample of Carbamazepine showed melting endotherm at the characteristic endothermic peak for the drug at 188.43°C with enthalpy of 194.85 J/g indicating decreased crystallinity but not compare to spray dried microparticle as spray dried microparticle shows more decreased crystallinity then others samples of Carbamazepine.

In FT-IR studies, 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 a solvent of crystallization.

In XRD analysis, XRD peaks were modified. 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 particle sizes.

Particle of pure sample are of the smallest size (5-9 µm) and they have irregular shapes. Recrystallization produced crystals with intermediate size (3-27 µm). The particle formed by spray microparticle formed by spray drying technique and the resultant Microparticle had a smooth surface. Microparticel obtained were spherical in shape with small size (2-11) µm.

The superior compressibility characteristics of Spray dried microparticle 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 microparticle under plastic deformation compared to that of single crystal.

Tensile strength of the Carbamazepine exhibited compressibility as follow: pure sample > recrystallized sample > spray dried microparticle.

In solubility studied result shown that spray dried particle shows improve solubility then recrystallized sample and pure drug sample. This could be due to the increasing in wettability and reduction in particle size and could be due to the particle has uniform size of microparticle. According to above result spray drying technique has good ability to increasing the solubility of poorly water soluble drug.

The dissolution of spray dried microparticle shows improves dissolution rate compare to other samples. The reason for this faster dissolution could be linked to the better wet-ability of the microparticle. The amount of drug dissolved in 60 min greatly varied for spray dried microparticle.
CONCLUSION
Spray dried microparticle of Carbamazepine were prepared by spray drying technique to improve the dissolution rate. Spray dried microparticle exhibited decreased crystallinity and improved Micromeritic & Mechanical properties. DSC and XRD studies showed that there is no change in the crystal structure of Carbamazepine during the spray drying process i.e., polymorphism has not occurred. The solubility and dissolution of the spray dried microparticle was improved compared with Recrystallized sample and pure sample. Hence this spray drying technique can be used for formulation of tablets of Carbamazepine by direct compression with directly compressible tablet excipients.

ACKNOWLEDGMENTS
The authors are thankful to Micro labs, Bangalore, India for the gift sample of carbamazepine, and Principal, J.S.S.College of Pharmacy, Mysore for providing facilities to carry out this work.

REFERENCES
### Table-1 Micrometrics Property of Carbamazepine of Different Samples

<table>
<thead>
<tr>
<th>Properties</th>
<th>Pure Sample</th>
<th>Recrystallized Sample</th>
<th>Spray Dried Microparticle</th>
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</thead>
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<tr>
<td>Particle size (µm)</td>
<td>5-9</td>
<td>3-27</td>
<td>2-11</td>
</tr>
<tr>
<td>Flow rate (gm/Sec)</td>
<td>No flow</td>
<td>No flow</td>
<td>3.12</td>
</tr>
<tr>
<td>Angle of repose</td>
<td>44.32</td>
<td>34.13</td>
<td>24.93</td>
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<tr>
<td>Tapped density (gm/ml)</td>
<td>0.7638±0.01</td>
<td>0.6836±0.012</td>
<td>0.3973±0.04</td>
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<tr>
<td>Bulk density (gm/ml)</td>
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<td>0.4164±0.01</td>
<td>0.2163±0.02</td>
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<tr>
<td>Carr’s index</td>
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<td>23.18</td>
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<tr>
<td>Porosity (%)</td>
<td>8.72</td>
<td>16.35</td>
<td>27.12</td>
</tr>
</tbody>
</table>

Figure 1 DSC spectra of different samples of Carbamazepine

Figure 2 FT-IR spectra of different samples of Carbamazepine
Figure 3: XRD spectra of different samples of Carbamazepine

Figure 4: SEM graphs of different samples of Carbamazepine

Figure 5: Tensile strength of P.S-pure Sample, R.S-Recrystallized sample, S.M-spray dried microparticle
Figure 6 Shows Dissolution of: P.S-pure drug sample, R.S- recrystallized sample, S.DM-spray dried microparticle

Source of support: Nil, Conflict of interest: None Declared