Preparation and evaluation of amorphous olmesartan medoxomil with porous silica microparticles using spray-drying technique

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ABSTRACT

Olmesartan medoxomil (OLM) is an orally active nonpeptide angiotensin II receptor antagonist. It is approved by the US FDA in 2002 for the treatment of hypertension, either alone or in combination with other anti-hypertensive. OLM is a poor water soluble drug BCS-class II drug. The current work explores utility of porous silica Neusilin US2 (N-US2) for preparation of amorphous solid dispersion of OLM by spray-drying technique. This solid dispersion is expected to increase pharmaceutical properties of OLM. The obtained product was analyzed by yield, drug content, differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), fourier transform infrared (FT-IR), scanning electron microscopy (SEM), in-vitro drug release study. Moreover, the solid dispersion was examined for vitrification if any during its storage.

Keywords: Olmesartan medoxomil, Neusilin US2, Spray-drying and Solid dispersion

INTRODUCTION

Olmesartan medoxomil (OLM) (Figure no. 1) is an orally active nonpeptide angiotensin II receptor antagonist. It is approved by the US FDA in 2002 for the treatment of hypertension, either alone or in combination with other anti-hypertensive. It is a prodrug that is rapidly converted in vivo to the pharmacologically active metabolite, olmesartan due to an endogenous esterase. It simply act by inhibiting the vasoconstrictor effects of angiotensin II by selectively blocking angiotensin II type 1 receptor sites in vascular smooth muscle.[1-3]

OLM is weakly basic (pKₐ 4.3) in nature, has an experimental log P value of 5.55. It comes under BCS class II drugs. Due to its low aqueous solubility and high lipophilicity, it shows low bioavailability (29%) after oral administration, leading to poor therapeutic application.[4, 5] Various methods have been reported to improve the solubility and dissolution rate of poorly water soluble drugs such as grinding, inclusion complex with cyclodextrin and solid dispersion with water soluble polymers such as PEG (polyethylene glycol) and PVP (polyvinyl pyrolidine).[6]

According to the Noyes-Whitney equation the dissolution rate of a drug depends on its surface area and solubility. Surface area and solubility increased by above mentioned techniques which have some limitation such as grinding generates smaller crystals with high energy surface which eventually agglomerate reducing the effective surface area for dissolution, slow process of complexation, high molecular weight of cyclodextrin and specific pH requirement limit their practical utility and solid dispersion using water-soluble carriers were stick or tacky in nature leads to difficultly in handling and processing.[7] Milling or mixing with other excipients required for solid dispersion to prepare final dosage forms which facilitate crystallization of the drug and
subsequently affects its oral bioavailability. Granulation and drying process have been achieved in one step for direct compressible carrier using spray-drying technique which produces smaller spherical shape particles with narrow size distribution. In pharmaceutical field, various porous microparticles such as calcium silicate [8], controlled pore glass [9,10], porous cellulose [11] and porous cavilink beads [6] were used to improve the pharmaceutical properties of bioactive as well as to formulate various solid dosage forms. Silica, a novel porous microparticle which has been used to improve the solubility of poor-water soluble molecules. They were two types of silica such as porous (Neusilin US2) and nonporous (Aerosil 200) which are varying in particle size, degree of hydrophilicity and pore structure. The silanol groups of silica have ability to form hydrogen bonds with drug molecules.[12] Solid dispersion of tolbutamide were prepared with nonporous silica using spray-drying method, resulted products showed good flow properties with remarkable improvement in the dissolution profiles.[13] Solid dispersion of water-insoluble drugs using porous silica carriers enhances drug dissolution and bioavailability by the reduction of particle size to the microcrystalline or molecular level. Silica has been demonstrated to retard and inhibit the crystallization of drugs, decreasing melting point, producing amorphous solid dispersions with increased drug dissolution rates, solubility, stability and minimal enthalpy relaxation, thus offering stabilization of the higher-energy amorphous systems. [9, 10, 13, 14] Thus, it was hypothesized that porous silica microparticles by way of decreasing crystallinity and shall increase OLM solubility and bioavailability.

The current work explores utility of porous silica Neusilin US2 (N-US2) for preparation of amorphous solid dispersion of OLM by spray-drying technique. This solid dispersion is expected to increase pharmaceutical properties of OLM. The obtained product was analyzed by yield, drug content, differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), fourier transform infrared (FT-IR), scanning electron microscopy (SEM), in-vitro drug release study. Moreover, the solid dispersion was examined for vitrification if any during its storage.

2. MATERIALS AND METHODS

2.1. Materials:

NeusilinUS2 (Fuji Chemical Industry, Toyama, Japan) was obtained as a gift sample from Gangwal Chemicals, Mumbai. OLM was obtained as a gift sample from Glen mark, Navi Mumbai. All other chemicals and solvents were of analytical grade.

2.2. Preparation of OLM solid dispersion microparticles:

The solid dispersion microparticles of OLM were prepared with fine silica particles using spray-drying technique. Briefly, as shown in Table 1, different amount of porous silica (NeusilinUS2) was suspended in 40 ml of methanolic OLM (1 g) solution. After ultrasonication for 5 min, the resultant suspension was spray dried using scale spray dryer (Labultima LU – 222, India) under the following set of condition: inlet temperature, 65°C; outlet temperature, 45°C; feed rate, 8 ml/min; atomization air pressure, 0.12-0.15MPa and aspiration, 280 mm WC. The spray dried OLM microparticles without carrier were prepared from the methanolic solution OLM under the same conditions. The obtained microparticles were dried under the desiccator for 1 day before analyzing their pharmaceutical properties. The spray dried OLM microparticles without carrier were prepared from the methanolic solution OLM under the same conditions. The obtained microparticles were dried under the desiccator for 1 day before analyzing their pharmaceutical properties. Physical mixtures of OLM and NeusilinUS2 were prepared by dry blending and passing through a fine mesh (150 μm).

2.3. Evaluation of pharmaceutics properties:

2.3.1. Yield and drug content:

The dried weight of spray-dried product was recorded as practical yield and percentage yield was calculated (Table no. 1). The solid dispersions were dissolved in a suitable quantity of methanol by use of a cyclomixer and ultrasonicator. The drug content was determined at 257 nm using a spectrophotometer (V-530; JASCO, Japan) after suitable dilutions. The results of triplicate measurements and their means were reported.
Table 1: Percentage yield and drug content of different batches of OLM and Neusilin US2 solid dispersion

<table>
<thead>
<tr>
<th>Batch code</th>
<th>OLM: N-US2</th>
<th>Yield (% w/w)</th>
<th>Drug Content (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-0</td>
<td>N-OLM</td>
<td>35.6 ± 2.3</td>
<td>-</td>
</tr>
<tr>
<td>S-1</td>
<td>1:1</td>
<td>50.6 ± 1.1</td>
<td>79.05 ± 1.7</td>
</tr>
<tr>
<td>S-2</td>
<td>1:2</td>
<td>55.7 ± 1.3</td>
<td>85.59 ± 2.3</td>
</tr>
<tr>
<td>S-3</td>
<td>1:3</td>
<td>56.1 ± 1.2</td>
<td>91.88 ± 1.9</td>
</tr>
<tr>
<td>S-4</td>
<td>1:4</td>
<td>58.2 ± 1.6</td>
<td>98.14 ± 1.4</td>
</tr>
<tr>
<td>S-5</td>
<td>1:5</td>
<td>58.7 ± 1.2</td>
<td>99.83 ± 0.1</td>
</tr>
</tbody>
</table>

S-OML: Spray-dried OLM (Data are means ± SD, n = 3.)

2.3.2. Residual solvent content determination:
The amount of total residual solvent in solid dispersions was determined by using a thermal gravimetric analyzer (TGA-60WS0; Shimadzu Corporation, Japan). Thermal gravimetric analysis was performed by heating a weighed amount of sample in nitrogen atmosphere from 25°C to 80°C at the rate of 2°C/min and the loss of weight as a function of temperature was recorded.

2.3.3. Scanning electron microscopy:
The external morphology of the OLM and spray-dried products were determined by scanning electron microscope (SEM) (Stereoscan S120; Cambridge, UK) operated with an acceleration voltage of 10 kV. Samples were mounted on double-faced adhesive tape and coated with a thin gold-palladium layer (20 nm) by a sputtercoated unit (VG-Microtech, Uckfield, UK) and surface topography was analyzed at various magnifications.

2.3.4. Powder X-ray diffraction:
The crystalline properties of OLM, Neusilin US2, physical mixtures and spray-dried product of batch 1:5 were studied by powder X-ray diffraction (PXRD) using an X-ray diffractometer (PW 1729; Philips, Almelo, Netherlands). The samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed at 2θ between 5 and 50°. The voltage and current used were 30 kV and 30 mA, respectively. The range and the chart speed were 2× 10³ CPS and 10 mm/degree 2θ, respectively.

2.3.5. Differential scanning calorimetry:
Thermal properties OLM, Neusilin US2, physical mixtures and spray-dried product of batch 1:5 were studied using differential scanning calorimetry (DSC) in a calorimeter equipped with an intracooler (DSC 821e; Mettler-Toledo, Greifensee, Switzerland). Indium standards were used to calibrate the temperature and enthalpy scale. Approximately 5 mg of sample was hermetically sealed in an aluminum pan with a hole and heated at a constant rate of 10°C/min over a temperature range of 10-250°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

2.3.6. Fourier transform infrared spectroscopy:
Fourier transform infrared spectroscopy (FT-IR) spectra OLM, Neusilin US2, physical mixtures and spray-dried product of batch 1:5 were recorded after appropriate background subtraction using an FTIR spectrometer (FTIR-8400; Shimadzu Corporation, Kyoto, Japan) equipped with a diffuse reflectance accessory (DRS-8000; Shimadzu Corporation, Japan) and a data station. About 2-3 mg of the sample was mixed with dry potassium bromide and the samples were scanned from 4000 to 400 cm⁻¹ wave numbers at a resolution of 2 cm⁻¹.

2.3.7. In-vitro dissolution study:
Dissolution studies were performed using the USP 24 type II dissolution test apparatus (Electrolab TDT-08L, Mumbai, India). Pure OLM, spray-dried products (100 mg) were placed in the dissolution vessels containing 900 ml of phosphate buffer pH 6.8, maintained at 37 ± 0.2°C and stirred at 50 rpm. Periodically, samples were collected and replaced with fresh dissolution medium. After filtration through 0.45 μm filter paper, concentration of OLM was determined UV-spectrophotometrically at 257 nm after suitable dilution. The results of triplicate measurements and
their means were reported. Data were analyzed by PCP-Disso software (V3; Poona College of Pharmacy, Pune, India).

2.3.8. Stability study:
The spray-dried products were stored at 40 ± 2°C/75 ± 5% RH for 4 weeks and the effect of temperature and humidity on the products was studied by measuring in-vitro drug release and the presence of crystallinity was assessed using PZRD and DSC studies.

3. RESULTS AND DISCUSSION
Olmesartan medoxomil (OLM), a potent selective angiotensin II receptor blocker, used for the treatment of hypertension. However, because poor aqueous solubility limits its bioavailability, solid dispersion using a spray-drying technique in the presence of NeusilinUS2 was attempted to overcome this problem. The batches containing OLM-NeusilinUS2 in a ratio of 1:1, 1:2, 1:3, 1:4 and 1:5 parts by weight were prepared and denoted as S-1, S-2, S-3, S-4 and S-5 respectively. Pure OLM was spray-dried without NeusilinUS2 denoted as S-0 and the physical mixture containing OLM-NeusilinUS2 in a ratio of 1:5 was also prepared denoted as PM S-5.

3.1. Yield and drug content:
The yield and drug content of the product obtained by spray drying were 35.6 ± 2.3 to 58.7 ± 1.2% (w/w) and 79 ± 1.7 to 99.8 ± 0.1% (w/w), respectively. The total residual solvent in all the solid dispersion batches was below 0.24% (w/w). The higher yield and low residual solvent content justifies use of the spray-drying technique to obtain solid dispersion.

3.2. Scanning electron microscope:
Particle surface morphology influences various pharmaceutical engineering and biopharmaceutical properties like flowability, packability, compatibility, compressibility, solubility and dissolution characteristic of drug powder. SEM photograph of pure OLM, NeusilinUS2, spray dried sample are shown in Figure no. 2. The surface topography of the solid dispersions can be explained on the basis of formation of microparticles by solidification of droplets with preferential loss of solvent from the surface simultaneously with hardening. Pure OLM consisted irregular crystals and NeusilinUS2 consisted agglomerated spherical shaped particles with rough surface whereas spray dried sample (S-5) consisted the clusters of aggregated smaller particles than the agglomerated carrier. No OLM crystals were found on the surface of spray-dried product suggesting OLM was dispersed into NeusilinUS2 particles.

3.3 X-ray diffraction study:
The XRD patterns of pure OLM, NeusilinUS2, spray dried product (S-5) and physical mixture (PM S-5) were shown in Figure no. 3. The X-ray diffractogram of pure OLM from 5 to 50° 2θ showed numerous distinctive peaks at 7.2°, 12.7°, 16.6°, 19.7°, 21.9° and 24.8° that indicated a highly crystalline nature. Due to its amorphous nature NeusilinUS2 did not display diffraction peaks. The XRD peaks of crystalline OLM in physical mixtures were similar, having low intensity compared with those in pure OLM, indicating that the
crystallinity of OLM did not change in the physical mixtures. The solid dispersions showed no detectable OLM diffraction peaks, which indicated the existence of the amorphous form. Effect of spray drying on the drug particle properties, pure OLM was spray-dried without carrier; resulted particles showed that no significant differences between pure OLM and spray dried OLM without carrier in XRD patterns indicated that only spray drying does not produce amorphous from (data not shown). Thus, NeusilinUS2 was playing important role in the conversion of drug crystals to amorphous from which may be due to formation of hydrogen bonding between the carboxylate group of OLM with silanol group of NeusilinUS2 which reduced the crystallinity of the OLM.

**Figure 3:** XRD patterns of (a) spray dried s-5, (b) physical mixture, (c) OLM and (d) Neusilin US2.

### 3.4. Differential scanning calorimetry:
Thermal properties of pure OLM, NeusilinUS2, solid dispersion S-5 and physical mixture S-5 were studied using DSC and their thermograms are shown in **Figure no. 4.** Thermogram of pure OLM showed a sharp endotherm at 180.02°C. In physical mixture, the drug endoderm was boarded with decrease in enthalpy. No peaks were observed in the thermogram of NeusilinUS2 and solid dispersion S-5 indicating amorphous natures. The crystallization inhibition of NeusilinUS2 may also be attributed to the amorphous state was confirmed by XRD and DSC patterns. In general, the process of crystallization of drug from supersaturated solution consists of two processes creation of crystal nucleus and growth of the crystal. NeusilinUS2 might inhibit the association of the drug molecule to form the crystal nucleus and inhibit the crystal growth, thus the OLM–NeusilinUS2 interaction is an inhibitory factor in the crystallization. In addition, the strong electrostatic interaction between the OLM and NeusilinUS2 and the entrapment of drug molecule in the carrier matrix during spray drying may inhibited drug recrystallization.

**Figure 4: DSC patterns of**
- a- Pure Olmesartan medoxomil, b-physical mixture, c- Spray dried sample, d- NeusilinUS2.

### 3.5. Fourier transform infrared spectroscopy:
FT-IR spectroscopy was carried out to study the possibility of chemical interaction between OLM and NeusilinUS2 at a structural level during spray drying. **Figure no. 5.** show FT-IR spectra of Pure OLM, NeusilinUS2, physical mixture of S-5 and spray-dried product S-5. The FT-IR spectrum of OLM showed a characteristic peaks at 952.66 cm⁻¹ (O–H bending out of plane), 3289 cm⁻¹ (secondary amine N–H stretching or O–H stretching), 1707.66 cm⁻¹, 1740.44 cm⁻¹ (–C=O stretching) 1553.38 cm⁻¹, 1503.24 cm⁻¹ (C=C stretching of aromatic) and some prominent bands such as 1301.72 cm⁻¹, 225.54 cm⁻¹ (–C–O stretching). The FT-IR spectra of physical mixtures showed all the characteristic peaks of drug and NeusilinUS2, suggesting no chemical interaction, whereas, solid dispersion of S-5 showed peak near at 3,469.63 cm⁻¹ indicating formation of formation Si–O–C bridging between OH of isopropyl alcohol group which is further attached to the imidazole ring and Si of NeusilinUS2. Although, there was shifting of peak from 1707.66 cm⁻¹ to 1833.01 cm⁻¹ was observed may be due to interaction between carboxylate group and imidazole ring of OLM. This might be a consequence...
of intermolecular interaction, such as hydrogen bonding, which demonstrates the transformation of drug crystals into amorphous form.

**Figure 5:** FT-IR spectra of (a) spray dried s-5, (b) physical mixture (c) pure Olmesartan medoxomil, (d) NeusilinUS2.

3.6. **In vitro dissolution:**

In-vitro drug release of OLM, S-0, S-1, S-2, S-3, S-4 and S-5 were carried out in phosphate buffer pH 6.8. The pure OLM and S-0 were characterized by only 50.74% and 59.11% drug release within 60 min indicating poor dissolution profiles of OLM, whereas all the solid dispersion showed significantly higher dissolution rate in between 87.69% and 99.61% indicating remarkable improvement in the solubility (Figure no. 6, Table no. 2). \( Q_{30\text{ min}} \) (cumulative percentage release in 30 min) and \( t_{80\%} \) (time required for 80% w/w drug release) were calculated using the Korsmeyer-Peppas equation: \( Q = k t^n \) (where \( Q \) is the cumulative percentage release, \( t \) is the time required for \( Q \) release and \( k \) and \( n \) are constants). As shown in Figure no. 6 and Table no. 2, all solid dispersion showed higher values of \( Q_{30\text{ min}} \) and lower values of \( t_{80\%} \) which were greater than those for pure OLM and S-0.

<table>
<thead>
<tr>
<th>Batch code</th>
<th>( Q_{30\text{ min}} ) (%)</th>
<th>( t_{80%} ) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLM</td>
<td>42.92 ± 1.63</td>
<td>&gt;60</td>
</tr>
<tr>
<td>S-0</td>
<td>45.62 ± 1.81</td>
<td>&gt;60</td>
</tr>
<tr>
<td>S-1</td>
<td>86.94 ± 2.16</td>
<td>25.46 ± 0.43</td>
</tr>
<tr>
<td>S-2</td>
<td>93.60 ± 1.71</td>
<td>25.52 ± 0.32</td>
</tr>
<tr>
<td>S-3</td>
<td>93.94 ± 1.83</td>
<td>25.54 ± 0.36</td>
</tr>
<tr>
<td>S-4</td>
<td>94.04 ± 1.63</td>
<td>25.64 ± 0.71</td>
</tr>
</tbody>
</table>

OLM, olmesartan medoxomil; Data are means ± SD, n = 3.

The improvement in the drug release from the solid dispersions might be due to the significant reduction in particle size during spray drying which improved the surface area, wettability and dispersibility for the drug to dissolve in dissolution media and the conversion of crystalline to amorphous form of OLM via formation of hydrogen bonding.

3.7. **Stability study:**

Many researchers have reported the re-conversion of drugs from the amorphous form into the crystalline form on storage. \[13\] Hence, solid dispersions were subjected for stability testing at 40 ± 2°C/75 ± 5% RH for 4 weeks. During the stability study, almost no significant difference in the XRD, DSC, FTIR and dissolution profiles was observed over a period of 4 weeks as compared with freshly prepared solid dispersions. The improved stability of solid dispersions could be due to hydrogen bonding between the drug and the carrier.

4. **CONCLUSION**

The present study demonstrates the utility a novel porous carrier NeusilinUS2 to improve the pharmaceutical properties of Olmesartan medoxomil, a BCS Class II drug. Solid dispersion was adopted to convert crystalline form to amorphous form using spray drying technique. The improved primary and secondary properties were shown by solid dispersion due to porous NeusilinUS2 which enhance the dissolution, stability of OLM. Amorphous formulations...
of PLM could be used in the design of various dosage forms. This approach can be further extended for dissolution enhancement of other BCS class II drugs.

REFERENCES


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