Enhanced solubility and dissolution rate of Olmesar tan medoxomil using crystallo-co-agglomeration technique

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ABSTRACT

Olmesartan medoxomil is a novel antihypertensive drug having low aqueous solubility and poor micromeritic properties. Therefore the crystallo-co-agglomeration of olmesartan have been attempted to improve its physicochemical and micromeritic characteristics. The effect of different polymers such as poly-vinyl pyrollidone (PVPK30), and hydroxypropyl-β-cyclodextrin (HPβCD) on solubility, dissolution rate and flowability of olmesartan medoxomil was studied by crystallo-co-agglomeration technique. The agglomerates were characterized by X-ray powder diffractometry (XRPD), Scanning electronic microscopy (SEM) and Fourier transformation-infrared spectroscopy (FTIR). It was found that saturation solubility, micromeritic properties and dissolution characteristics of agglomerates were significantly improved than that of pure olmesartan medoxomil. Hence it could be concluded that crystallo-co-agglomeration could be one of the effective approaches for improved performance of olmesartan medoxomil.

INTRODUCTION

Increasing preference is now being given to the novel crystallo-co-agglomeration technique. It involves modification of pharmaceutical powders so as to improve properties such as flow properties, packability, solubility, dissolution and bioavailability of the product [1]. Generally thermodynamically stable crystalline form of compound is preferred. However inadequate solubility and dissolution rate are the several problems associated with stable crystalline form that results in poor oral absorption and less bioavailability. Now-a-days crystallo-co-agglomeration technique has been attracting attention of researchers for increasing the solubility, dissolution and micromeritic properties of the drug [2, 3]. It is the versatile process to control size and type of crystals and give benefits over granulation technique in which more time, cost and energy is consumed. It can also be a good technique for improvement of dissolution behavior of certain drugs characterized by low solubility and dissolution rate. Crystallo-co-agglomeration is modification of spherical crystallization technique in which drug is crystallized and agglomerated with an excipient or another drug which may or may not be crystallized in system [4, 5, 6, 7].

Olmesartan medoxomil (Figure 1) is chemically 2,3-dihydroxy-2-butenyl 4-[1-hydroxy-1-methylethy]-2-propyl-1-[p(o-1H-tetrazol-5-ylphenyl) benzyl] imida-zole-5-carboxylate, cyclic 2,3-carbonate [8, 9, 10, 11]. Clinical studies
have suggested that olmesartan medoxomil exerts a beneficial effect on the treatment of hypertension. It is an angiotensin antagonist (Angiotensin receptor blocker or ARBs) [8, 9, 10, 11]. It is a white crystalline powder and has limited solubility. Olmesartan medoxomil has poor flow properties and undesirable dissolution properties. In the present study, an attempt was made to improve physicochemical properties by preparing crystallo-co-agglomerates of olmesartan medoxomil in the presence of polymer and/or hydrophilic carrier for the enhancement of overall physicochemical performance. Dichloromethane was used as bringing liquid to prepare agglomerates. Physicochemical properties of raw olmesartan medoxomil and olmesartan medoxomil agglomerates were characterized in the solid state using several techniques such as scanning electronic microscopy (SEM), Fourier transformation-infrared spectroscopy (FTIR), X-ray powder diffraction analysis (XRPD), solubility studies and dissolution test. The improvement in micromeritic properties was determined by calculating angle of repose, Hausner ratio, Carr’s index of olmesartan medoxomil and agglomerates respectively.

**Figure 1 Chemical structure of olmesartan medoxomil**

![Chemical structure of olmesartan medoxomil](image)

**MATERIALS AND METHODS**

**Materials:**
Olmesartan medoxomil, poly-vinyl pyrollidone (PVPK30) and hydroxypropyl β cyclodextrin (HPβCD) were generously supplied by Indoco Remedies, Mumbai, India as gift samples. All the chemicals were of analytical grade purchased from Loba Chemie, Mumbai, India. Distilled water was used throughout the experiment.

**Methods:**
Water soluble carrier PVPK30 and olmesartan medoxomil were weighed in different ratios 1:1 and 1:3. Olmesartan medoxomil was dissolved in 10 and 30 mL of dichloromethane (DCM) as per the ratios 1:1 and 1:3 respectively. Drug agglomerates were formed by adding drug solution to 500 mL of glass vessel containing 100 mL of distilled water (poor solvent) in which a water soluble carrier PVPK30 (1gm) was dissolved with a stirring rate of 1000 ± 50 rpm for 30 min.

Agglomerates with HPβCD were prepared by another method in which HPβCD and drug were weighed in different ratios 1:1 and 1:3. HPβCD was dissolved along with olmesartan medoxomil in 10 and 30 mL of dichloromethane (DMC) as per the ratios 1:1 and 1:3 and this solution was then added in to 500 mL of glass vessel containing 100 mL of distilled water (poor solvent) with a stirring rate of 1000 ± 50 rpm for 30 min. The prepared co-agglomerates were collected, dried and stored in a desiccator until further analysis.
Saturation Solubility Studies:
Solubility studies were carried out in distilled water according to the method reported by Higuchi and Connors [12]. Excess quantity of olmesartan medoxomil and / or prepared crystallo-co-agglomerates were introduced in 20 mL of distilled water and shaken for 24 hours at room temperature. The content of each flask was then filtered through a Whatmann filter paper. The filtrate was then diluted and assayed spectrophotometrically at 257 nm. Each solubility was determined in triplicate (n=3). The results obtained from saturation solubility studies were statistically analyzed.

Drug Content:
Agglomerates (5mg) were triturated and dissolved in pure methanol and volume was made up to 50 mL and sonicated for 15 minutes. The solution was filtered through Whatmann filter paper. After appropriate dilutions with water it was analysed spectrophotometrically at 257 nm (Shimadzu 1800, Japan).

Dissolution Studies:
The dissolution rate studies of olmesartan medoxomil alone and crystallo-co-agglomeration were performed in triplicate in a dissolution apparatus (Lab India, Model Disso 2000 Tablet dissolution test apparatus, Mumbai, India) using the paddle method (USP Type II). Dissolution studies were carried out using 900 mL of phosphate buffer (pH 6.8) at 37 ± 0.5 °C at 50 rpm. The volume of dissolution medium was adjusted to 900 mL by replacing each 5 mL aliquot withdrawn with 5 mL of fresh phosphate buffer (pH6.8). The solutions were immediately filtered through a 0.45 μm membrane filter, suitably diluted and the concentrations of olmesartan medoxomil in samples were determined spectrophotometrically at 253.5 nm. The results of dissolution studies were statistically analyzed.

X-Ray Powder Diffractometry (XRPD):
The XRPD data of pure olmesartan medoxomil and crystallo-co-agglomerates were recorded on a Philips Analytical X-ray-PW 3710 ( Phillips, Almedo, The Netherlands) diffractometer with tube anode Cr over the interval 10-70°/2θ under following set of conditions: The generator tension (voltage): 40 kV and generator current: 25 mA.

Fourier Transformation Infrared Spectroscopy (FTIR):
FTIR spectra were obtained using a Shimadzu FTIR spectrometer (IR Affinity 1 Model, Japan) spectrometer. The samples were prepared into KBr disks. The scanning range was kept from 4000 to 500 cm-1.

Scanning Electron Microscopy (SEM):
The surface morphological properties of pure drug and crystallo-co-agglomerates were investigated by scanning electron microscopy (SEM-Jeol Instruments, JSM-6360, Japan). Samples were mounted on a double-faced adhesive tape, sputtered with gold. Scanning electron photographs were taken at an accelerating voltage of 15 kV and obtained micrographs were examined at X2000, X5000, X10000 and X15000 magnifications.

Measurement of Flowability:
Flowability of olmesartan medoxomil and their agglomerated crystals were determined in terms of Angle of repose, Carr’s Compressibility Index and Hausner ratio. The angle of repose of drug powder and the agglomerates were assessed by fixed funnel method. The Carr’s index reflects the compressibility of the agglomerates and there is a correlation between the compressibility index and the flowability of the crystallo-co-agglomerates. The results presented are mean ± S.D. (n = 3).

RESULTS AND DISCUSSION

Determination of Drug Content:
Percentage drug contents of prepared crystallo-co-agglomerates were found to be in the range of 99.15 ± 1.20 w/w to 100.00 ± 1.18w/w.

Saturation Solubility Studies:
Table 1 shows results of saturation solubility studies. The solubility of crystallo-co-agglomerates was found to be increased than pure olmesartan medoxomil. There was 4.6 and 6.6 fold increase in solubility of agglomerates with HPβCD of 1:1 and 1:3 ratios respectively. In case of PVPK30 (1:1), there was 4.8 fold while in PVPK30 (1:3) ratio it was found to be 4.6 fold. The improvement in solubility by crystallo-co-agglomeration was found to be extremely significant. This might be due to changes in crystal habit, structure and surface morphology [3]. In addition to that, solvent included in crystal form solvates that might have changed the reactivity of drug particles, surface
morphology and internal energy of the molecules which would be responsible for increasing solubility of agglomerates [3]. The solubility of HPβCD (1:3) and PVPK30 (1:1) was found to be greater than raw olmesartan and other ratios demonstrating that the incorporation of PVPK30 and HPβCD enhanced the drug solubility by improving wettability [14].

Table 1. Saturation solubility of pure olmesartan medoxomil and crystallo-co-agglomerates

<table>
<thead>
<tr>
<th>System</th>
<th>Saturation solubility (mg/mL)*</th>
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</thead>
<tbody>
<tr>
<td>O</td>
<td>0.1961 ± 0.009</td>
</tr>
<tr>
<td>OP1</td>
<td>0.898 ± 0.25</td>
</tr>
<tr>
<td>OP3</td>
<td>1.301 ± 0.12</td>
</tr>
<tr>
<td>OH1</td>
<td>0.944 ± 0.15</td>
</tr>
<tr>
<td>OH3</td>
<td>0.8432 ± 0.16</td>
</tr>
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</table>

*significant difference compared to pure drug and crystallo-co-agglomerates

O: Olmesartan medoxomil, OP1: Olmesartan medoxomil + PVPK30 (1:1), OP3: Olmesartan medoxomil + PVP K30 (1:3), OH1: Olmesartan medoxomil + HPβCD (1:1), OH3: Olmesartan medoxomil + HPβCD (1:3)

Dissolution Studies:
The results of dissolution studies are shown in Table 2 and dissolution patterns are depicted in Figure 2A and 2B. The results reflected high improvement in dissolution of agglomerates as compared to pure olmesartan medoxomil. It was observed that dissolution rate of agglomerates were increased significantly compared to original drug (p < 0.001). The increase in dissolution rate was found to be 4.4 fold greater in PVPK30 (1:1) ratio, 1.96 fold in PVPK30 (1:3) ratio, 2.5 fold greater in HPβCD (1:1) ratio and 6.13 fold greater in HPβCD (1:3).

The drug release in drug: PVPK30 (1:1) ratio was found to be 100% in 45 min and in (1:3) ratio it was 43% after 2 hours. Moreover in drug: HPβCD (1:1) ratio, drug release after 120 min was observed to be 71% and in (1:3) ratio complete drug release was obtained in only 30 min. The stastical analysis revealed significant improvement in dissolution at (DE30) (p < 0.001). Faster dissolution from crystallo-co-agglomerates was attributed to changed crystalline shape, size and habit which might be responsible for increase in dissolution of agglomerates as compared to pure drugs in dissolution medium.

The mechanism for the enhanced dissolution rate in crystallo-co-agglomerates might be similar to the mechanism in solid dispersion though particle size of the agglomerates was larger [14-17]. The adsorbed PVPK30 on the surface of crystals might have improved wettability and would lead to enhanced dissolution [14-17]. These results clearly revealed that the dissolution rate of olmesartan was increased in the form of agglomerates when compared to its pure form. The results also demonstrated that PVP is a suitable polymer and HPβCD is suitable stabilizer for the preparation of crystallo-co agglomerates of olmesartan [14-18].

Table 2: The dissolution data of olmesartan medoxomil and its crystallo-co-agglomerates phosphate buffer (pH 6.8) at 37 ± 0.5°C

<table>
<thead>
<tr>
<th>System</th>
<th>DP5 ± S.D.</th>
<th>DP30 ± S.D.</th>
<th>DE5 ± S.D.</th>
<th>DE30 ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>6.25 ± 1.6</td>
<td>15.97 ± 2.8</td>
<td>5.21 ± 1.4</td>
<td>10.74 ± 1.25</td>
</tr>
<tr>
<td>OP1</td>
<td>13.95 ± 1.4</td>
<td>97.82 ± 1.6</td>
<td>14.43 ± 1.47</td>
<td>47.25 ± 1.92</td>
</tr>
<tr>
<td>OP3</td>
<td>8.56 ± 2.7</td>
<td>30.34 ± 2.5</td>
<td>8.26 ± 1.46</td>
<td>65.86 ± 2.26</td>
</tr>
<tr>
<td>OH1</td>
<td>15.19 ± 2.3</td>
<td>38.79 ± 2.4</td>
<td>12.37 ± 1.275</td>
<td>37.69 ± 2.19</td>
</tr>
<tr>
<td>OH3</td>
<td>23.19 ± 1.7</td>
<td>100 ± 2.2</td>
<td>23.10 ± 1.81</td>
<td>65.86 ± 1.97</td>
</tr>
</tbody>
</table>

S.D.: Standard deviation; DP: % drug dissolved; DE: dissolution efficiency; *significant difference compared to pure olmesartan medoxomil i.e. significant (p <0.001)

O: Olmesartan medoxomil, OP1: Olmesartan medoxomil + PVPK30 (1:1), OP3: Olmesartan medoxomil + PVP K30 (1:3), OH1: Olmesartan medoxomil + HPβCD (1:1), OH3: Olmesartan medoxomil + HPβCD (1:3)
Flowability:
The micromeritic properties have shown in Table 3. Good flowability was reflected by values of angle of repose, Carr’s index and Hausner ratio as shown in Table 3. Statistical analysis indicated significant reduction in values of angle of repose and Carr’s index of agglomerates as compared to original drug ($p < 0.001$) [19]. However no significant differences among the formulations were observed ($p > 0.05$) in the above parameters. Olmesartan medoxomil had significantly higher angle of repose in comparison to agglomerates which might be due to the irregular shape of pure drug and put barrier in uniform flow crystals from funnel. The perfect shape and larger size of crystals decreased interparticle friction and it could be suggested as one of the reason for easy and uniform flow of agglomerates leading to excellent flowability [13]. Further the agglomerates had lower Carr’s index than pure drug which revealed that the flowability of olmesartan was significantly poor than that of agglomerated crystals ($p < 0.01$). The value of Hausner ratio in agglomerated crystals was found to be less than 1.25 which also indicated improvement in flowability [20].
Figure 3 FTIR spectra of pure olmesartan medoxomil, polymer and crystallo-co-agglomerates

A: Olmesartan medoxomil, B: PVPK30, C: HPβCD, D: Olmesartan medoxomil + PVPK30 (1:1), E: Olmesartan medoxomil + PVP K30 (1:3), F: Olmesartan medoxomil + HPβCD (1:1), G: Olmesartan medoxomil + HPβCD (1:3)
Figure 4 XRPD patterns of pure olmesartan medoxomil, polymer and crystallo-co-agglomerates
A: Olmesartan medoxomil, B: PVPK30, C: HPβCD, D: Olmesartan medoxomil + PVPK30 (1:1), E: Olmesartan medoxomil + PVP K30 (1:3), F: Olmesartan medoxomil + HPβCD (1:1), G: Olmesartan medoxomil + HPβCD (1:3)
Table 3: Flowability parameters of olmesartan medoxomil and their agglomerated crystals.

<table>
<thead>
<tr>
<th>Agglomerates code</th>
<th>O</th>
<th>OP1</th>
<th>OP3</th>
<th>OH1</th>
<th>OH3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose</td>
<td>38.65 ± 1.5</td>
<td>31.88 ± 1.2</td>
<td>32.46 ± 0.9</td>
<td>32.11 ± 0.8</td>
<td>30.96 ± 1.3</td>
</tr>
<tr>
<td>Carr’s index (%)</td>
<td>22.00 ± 0.45</td>
<td>11.00 ± 0.31</td>
<td>9 ± 0.23</td>
<td>12.2 ± 0.21</td>
<td>7 ± 0.33</td>
</tr>
<tr>
<td>Hausner’s ratio</td>
<td>1.29 ± 0.006</td>
<td>1.12 ± 0.003</td>
<td>1.09 ± 0.008</td>
<td>1.13 ± 0.004</td>
<td>1.08 ± 0.005</td>
</tr>
</tbody>
</table>

*significant difference compared to pure olmesartan i.e. significant (p < 0.001); O: Olmesartan medoxomil, OP1: Olmesartan medoxomil + PVPK30 (1:1), OP3: Olmesartan medoxomil + PVP K30 (1:3), OH1: Olmesartan medoxomil + HPβCD (1:1), OH3: Olmesartan medoxomil + HPβCD (1:3)

Fourier Transformation-Infrared Spectroscopy (FTIR):

The possible interaction between the drug and the carrier was studied by FTIR spectroscopy (Figure 3). IR spectra of olmesartan showed characteristic peaks at 2974 cm⁻¹ (Aliphatic C–H stretch), 3039 cm⁻¹ (Aromatic C–H stretch), 3271 cm⁻¹ (Broad, intermolecular hydrogen bonded, O–H stretch), 1720 cm⁻¹ (C=O of carboxylic group), 1504 cm⁻¹ (ring C=C stretch), 1483 cm⁻¹ (C–N stretch), 1371 cm⁻¹ (in plane O–H bend), 1053 cm⁻¹ (ring C–O–C stretch).

The FTIR spectra of HPβCD displayed prominent peaks at 3,395 cm⁻¹ (O–H), 2,930 cm⁻¹ (C–H), 1,647 cm⁻¹ (H–O–H bending) and 1,035 cm⁻¹ (C–O–C). PVPK30 showed characteristic broad band at 3454 cm⁻¹(O–H, stretch, broad), 1666 cm⁻¹ (C=O) owing to its oxygen functionalities.

It was found that there were no considerable changes in the IR peaks of the agglomerates when compared to pure olmesartan. In the FTIR study, the breakdown of the intermolecular hydrogen bond between the crystalline drug molecule and formation of hydrogen bond between the drug and the polymers might be related to the slight shift of the absorption band. However FTIR spectra of agglomerates showed that no changes have occurred in chemical structure. The strong interaction between drug and carrier, often leads to identifiable changes in the IR profile of the drug but the results of IR spectra indicated an absence of any well-defined interaction between olmesartan and PVPK30 and/or HPβCD [21, 22].

X-Ray Powder Diffractometry (XRPD):

The presence of polymorphs, crystal habit modifications in drug crystals and/or generation of new crystal form during crystallo-co-agglomerates process can be elegantly examined using XRPD technique [23, 24] (Figure 4). Examination of XRPD patterns of pure drug and crystallo-co-agglomerates confirmed formation of agglomerates. While studying the X-ray diffractograms of agglomerates it was observed that some of the peaks were appeared while some of them were disappeared when compared to diffractogram of pure olmesartan. The formation of different polymorphic form was stated on the basis of changes in intensity of peaks in diffractograms of polymer indicating different rearrangement of molecules [13]. Thus the agglomerates exhibited spectra with different peak positions (patterns) from their respective host and guest crystals which depicted that different internal structure might have formed with significant modification in crystals habit.

Scanning Electron Microscopy (SEM):

The results of surface morphology studies are shown in Figure 5. The pure olmesartan powder was appeared in the form of irregular shaped crystals. This form of olmesartan leads to very poor flow and compressional difficulties. These photo-micrographs showed that the prepared agglomerates were regular in shape with a smooth and regular surface, which enabled them to flow very easily. On the basis of these findings, it was considered that good flowability and packability for agglomerates were attributed to the regular shape and smooth surface, [25] since the area of contacts in the powder bed for agglomerates was smaller than that for conventional irregular crystals [26].
Figure 5 Scanning electron microphotographs pure olmesartan medoxomil and crystallo-co agglomerates
A: Olmesartan medoxomil, B: Olmesartan medoxomil + PVPK30 (1:1), C: Olmesartan medoxomil + HPβCD (1:3)

CONCLUSION

The present study revealed that crystallo-co-agglomerates of olmesartan prepared with PVPK30 and HPβCD exhibited improved solubility and dissolution rate in addition to improving the micromeritic properties. This technique might be applicable for producing oral solid dosage forms of olmesartan medoxomil with improved dissolution rate and oral bioavailability. Thus instead of preparation of granules, formation of agglomerates of olmesartan medoxomil would be expected to enhance physicochemical, biopharmaceutical and tabletting properties.

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