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Research Article

# PREPARATION AND EVALUATION OF OLMESARTAN MEDOXOMIL PELLETS BY LIQUID LAYERING TECHNIQUE

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## ABSTRACT
Olmesartan medoxomil is poorly soluble in water and the rate of dissolution as well as bioavailability is less. In the present study, an attempt has been made to improve the dissolution of drug by coating the drug and carrier over sugar spheres. The prepared pellets were evaluated for their physicochemical properties and *in-vitro* dissolution. The optimized pellet formulation was selected for stability study and the *in-vitro* dissolution study showed that was no difference in percent of drug released between initial and sixth month sample.

## KEY WORDS
Olmesartan medoxomil, solubility, carrier, pellets, dissolution, stability

## INTRODUCTION

Olmesartan medoxomil is an angiotensin II receptor antagonist used in the treatment of hypertension. It is poorly soluble in water. Olmesartan medoxomil is a prodrug which is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is selective $AT_1$ subtype angiotensin II receptor antagonist. It is difficult to formulate olmesartan medoxomil as oral solid dosage formulations because of its physicochemical properties. In tablet formulations of olmesartan, a compressing force or compactor is used to have a compact powder mixture to obtain tablet formulations. But this may cause capping in finished dosage tablet forms or a decrease can be observed in dissolution rate especially during the shelf life. Another important problem is its degradation, because under high pressure and heat it can easily convert to its degradation products. Literature survey revealed various techniques for the improvement of solubility of Olmesartan medoxomil.[1-7] The aim of work was to develop stable olmesartan pellets having high dissolution rate throughout the shelf-life.

## MATERIAL AND METHODS

### Materials:

Olmesartan medoxomil was generous gift sample from Aescul Pharma, Ongole, India. Polyvinyl pyrrolidone (PVP K 30), mannitol and starch were purchased from Sigma-

Aldrich (Hyderabad, India). Solvents and other chemicals were of analytical grade.

**Preformulation Studies**

**Compatibility:**

*Accelerated Storage Test (40±2 ℃/75±5% RH and 60±2 ℃/80±5% RH)*

Duplicates of drug and excipients mixture were taken in the amber colored bottle; these mixtures were kept in the accelerated storage condition in which one bottle is closed with aluminium foil and other one in an open condition. After two to four weeks, the mixtures were observed for any physical change.

*Infrared Red Spectrum:*

The physicochemical compatibility between olmesartan and the excipients used in research was tested by IR spectroscopy using Bruker Fourier transform Infrared spectrophotometer. The samples were scanned under diffuse reflectance mold directly. The spectra were recorded in the wave number region between 4400$cm^{-1}$ to 400$cm^{-1}$. The individual spectra obtained for olmesartan pure drug and excipients were compared with the spectra of the prepared olmesartan pellets.

**Preparation of olmesartan medoxomil loaded pellets**

50g of carrier pellets were charged into the coating pan (United technologies, Mumbai). Temperature was set to 60°C and the pan was allowed to rotate at a speed of 40 rpm. Drug and binder (PVP K-30) were dissolved in acetone: isopropyl alcohol (50:50 v/v). The solution was sprayed onto the pellets which are maintained at 60°C. Pressure was adjusted to 0.1MPa and spray rate was maintained at 3ml/min using peristaltic pump. The coating process was continued till all the solution was deposited on the sugar spheres. They were dried in hot air oven 60°C for about 2h.

**Optimization of Formulation Variables**

*Influence of Nature of Carrier*

The three carriers employed were mannitol, starch and microcrystalline cellulose. The carriers were coated with drug solution containing olmesartan medoxomil and PVP K-30 dissolved in acetone: isopropyl alcohol (50:50 v/v) and the process conditions were set to 30rpm, 60º C, 0.1 M Pa maintaining flow rate at 3ml/min. The composition of the pellets prepared with different carriers is given in **Table 1**.

**Table 1: Composition of Olmesartan medoxomil pellets formulated using different carriers**

| Ingredient | F01 | F02 | F03 |
|---|---|---|---|
| Carrier in pellets | Mannitol pellets 50 g | Starch pellets 50g | MCC pellets 50g |
| Olmesartan medoxomil | 3.9 g | 3.9g | 3.9g |
| PVP K-30 | 3.7 g | 3.7g | 3.7g |
| Acetone | 50 ml | 50 ml | 50 ml |
| Isopropyl alcohol | 50 ml | 50 ml | 50 ml |

*Influence of Size of carrier pellets*

Different sizes of the selected carriers like #30/44, #24/30, #16/24 and #10/16 were taken and coated with drug solution containing olmesartan medoxomil and PVP K-30 dissolved in acetone: isopropyl alcohol (50:50 v/v) and the process conditions were set to 30rpm, 60ºC, 0.1 M Pa maintaining flow rate at 3ml/min. The composition of the pellets formulated with different sizes of core pellets is given in **Table 2**.

**Table 2: Composition of Olmesartan medoxomil pellets formulated with different sizes of core pellets**

| Ingredient | F04 | F05 | F06 | F07 |
|---|---|---|---|---|
| Mannitol pellets | 50 g (#30/44) | 50 g (#24/30) | 50 g (#16/24) | 50 g (#10/16) |
| Olmesartan medoxomil | 3.9 g | 3.9 g | 3.9 g | 3.9 g |
| PVP K-30 | 3.7 g | 3.7g | 3.7g | 3.7 g |
| Acetone | 50 ml | 50 ml | 50 ml | 50 ml |
| Isopropyl alcohol | 50 ml | 50 ml | 50 ml | 50 ml |

**Optimization of Process Variable**

*Influence of pan speed*

Pan was loaded with selected starter seeds and the drug was coated onto them using alcohol at different pan speeds such as 20,30,40,50 and 60rpm. The composition of pellets formulated is given in **Table 3**.

**Table 3: Composition of olmesartan medoxomil pellets formulated at different pan speeds**

| Ingredient | F08 | F09 | F10 | F11 | F12 |
|---|---|---|---|---|---|
| Mannitol pellets | 50 g | 50 g | 50 g | 50 g | 50 g |
| Olmesartan medoxomil | 3.9 g | 3.9 g | 3.9 g | 3.9 g | 3.9 g |
| PVP K-30 | 3.7 g | 3.7 g | 3.7 g | 3.7 g | 3.7 g |
| Acetone | 50 ml | 50 ml | 50 ml | 50 ml | 50 ml |
| Isopropyl alcohol | 50 ml | 50 ml | 50 ml | 50 ml | 50 ml |
| Pan Speed (RPM) | 20 | 30 | 40 | 50 | 60 |

**Evaluation of Olmesartan medoxomil loaded pellets:**

*Yield of pellets*

The yield of the spheroids was determined as a percentage of the ratio of the final weight obtained after the production processes and the initial weight of the powder blend.

*Moisture content*

1 gm of pellets were weighed and kept in an oven at 70º. Its weight was noted as initial weight ($W_1$). They were removed from the oven after regular tine intervals of 15 min and weighed. Loss in weight of pellets was noted. After attaining constant weight, it was noted as final weight ($W_2$) and percent moisture content was calculated.

*Friability*

Roche friabilator was used to determine the friability. Pre weighed pellets were placed in friabilator and rotated at a speed of 25 rpm for 4 min or upto 100 revolutions. The pellets were then reweighed after removal of fines and the percentage of weight loss was calculated.

*Angle of repose, Bulk and Tapped density*

Angle of repose was determined by two sided open end cylinder method; bulk density and tapped density were determined by tapping methods.

*Estimation of Drug loading efficiency*

100 mg of pellets were taken in a mortar, crushed and mixed thoroughly with 10 mL of methanol, the solution was filtered and filtrate was collected. It was suitably diluted with pH 6.8 phosphate buffer and absorbance was noted at 258 nm using UV-Visible spectrophotometer. Amount of the drug present in pellets was calculated from the calibration curve.

*In-vitro Dissolution studies*

*In-vitro* dissolution studies for various formulations were performed in triplicate in dissolution rate testing apparatus (Electrolab) at 37 ± 0.5º employing USP apparatus type II at 50 rpm. Pellets equivalent to 20 mg of drug were weighed and kept in the dissolution bowel containing 900 ml of dissolution media (pH 6.8 phosphate buffer). Percent drug released was determined by taking an aliquot of 5 ml at different time intervals (5, 10 and 15 min). An equal volume of fresh dissolution medium was replaced to maintain the original volume. The samples were suitably diluted for estimating percent released and analyzed at 258 nm using UV visible spectrophotometer.

*Stability Study*

Stability study was conducted as per ICH (International Conference on Harmonization) guidelines. The selected formulation was subjected to real time (25±2 °C/60±5% RH) and accelerated stability (40±2 °C/75±5% RH) test. After specified period of time (1, 2, 3, 4, 5, 6 month) samples were withdrawn and *in-vitro* dissolution study was conducted.

## RESULTS AND DISCUSSION

The accelerated storage test showed that there were no physical changes (colour and appearance) in the mixture after two and four weeks.

The IR spectrums of Olmesartan medoxomil pure drug and Olmesartan medoxomil loaded pellets revealed that there was no appearance or disappearance of peaks in the spectrum of Olmesartan medoxomil pellets when compared to pure Olmesartan medoxomil drug spectrum in the IR study. These show that there was no interaction between drug and excipients used in the formulation.

Three variables of potential importance with respect to the pharmaceutical quality of the initial beads were evaluated. The parameters studied were the nature of the carrier, size of starter seeds, and pan rotation speed. Also, it is important to determine the flow properties, yield of pellets, drug loading efficiency, friability and moisture content as these parameters determine the quality of pellets produced.

From the physical properties and flow properties of the Olmesartan medoxomil loaded pellets presented in **Table 4**, it was revealed that all the pellets exhibited good flow properties and the drug loading efficiency was also good.

The results obtained in the *in-vitro* drug release studies for the formulations F01 to F03 were tabulated in **Table 5**. The graphs are depicted in **Figure 1.** Pellets containing mannitol as carrier exhibited 99.77% cumulative drug release within 15 min when compared to pellets containing MCC and starch as carriers.

This result clearly indicates that lower drug was released for the systems containing MCC and starch as carrier. Because mannitol particles are highly water swellable, they enhances the penetration of dissolution media into pellets leading to higher solubility and thus improving rapid dissolution and drug release from pellets. The rate of drug release followed first order kinetics. Mannitol is a water-soluble nonionic carrier. Mannitol pellets exhibit most outstanding characteristics like non-hygroscopicity, high sphericity, dense and hence can be used as a core for pellet formulations. These mannitol pellets were selected to study the influence of other variables.

The inert starting seed must be of sufficient density and strength to enable it to undergo coating process. Particle size analysis by far the simplest and most widely used method is a simple sieve analysis. The results obtained in the *in-vitro* drug release studies for the formulations F04 to F07 were tabulated in **Table 6.** The graphs are depicted in **Figure 2**. The mannitol pellets with a mesh size of 30/44 are preferred as they showed 99.038% cumulative drug release within 10 minutes.

Drug-layered pellets with a spherical shape, higher density and flowability were obtained by increasing the relative pan rotation speed. The results obtained in the *in-vitro* drug release studies for the formulations F08 to F12 were tabulated in **Table 7**. The graphs are depicted in **Figure 3.** The in vitro studies of layered pellets prepared at pan speed of 40

rpm showed 99.88% cumulative drug release. Hence these optimized drug layered pellets (F10 batch) are selected for further studies.

Formulation F10 was selected for stability study. *In-vitro* dissolution results of 6th month stability sample showed that there was no significant change in drug release between initial sample (99.85% drug release), real time sample (96.64% drug release) and accelerated study sample (95.37% drug release). The results indicated that the formulation was stable under the tested conditions of storage.

**Table 4: Physical properties and flow properties of Olmesartan medoxomil loaded pellets**

| S. No | Formulation | Yield of pellets (%) | Drug loading efficiency (%) | Friability (%) | Moisture content (%) | Bulk density ($gm/cm^3$) | Tapped density ($gm/cm^3$) | Angle of repose (θ) |
|---|---|---|---|---|---|---|---|---|
| 1 | F01 | 93.11 | 89.02 | 0.47 | 1.1 | 0.515 | 0.608 | 26.4 |
| 2 | F02 | 87.03 | 98.04 | 0.36 | 1.7 | 0.520 | 0.606 | 26.9 |
| 3 | F03 | 94.26 | 88.01 | 0.51 | 1.5 | 0.526 | 0.617 | 26.7 |
| 4 | F04 | 96.00 | 89.14 | 0.40 | 1.4 | 0.526 | 0.624 | 25.8 |
| 5 | F05 | 88.43 | 93.27 | 0.71 | 1.4 | 0.532 | 0.633 | 27.5 |
| 6 | F06 | 98.07 | 98.01 | 0.12 | 1.7 | 0.537 | 0.613 | 25.1 |
| 7 | F07 | 95.51 | 80.72 | 0.36 | 1.6 | 0.543 | 0.611 | 25.5 |
| 8 | F08 | 87.03 | 95.16 | 0.33 | 1.7 | 0.510 | 0.599 | 25.7 |
| 9 | F09 | 85.23 | 89.05 | 0.82 | 0.9 | 0.515 | 0.610 | 25.1 |
| 10 | F10 | 96.11 | 97.04 | 0.29 | 1.9 | 0.510 | 0.623 | 20.7 |
| 11 | F11 | 92.15 | 87.36 | 0.21 | 1.2 | 0.512 | 0.607 | 23.7 |
| 12 | F12 | 94.23 | 89.75 | 0.34 | 0.8 | 0.542 | 0.610 | 24.3 |

**Table 5: *In-vitro* dissolution data of Olmesartan medoxomil pellets formulated using different carriers**

| Time (min) | Cumulative % drug released | | |
|---|---|---|---|
| | F01 | F02 | F03 |
| 0 | 0 | 0 | 0 |
| 5 | 93.999 | 81.976 | 89.689 |
| 10 | 98.829 | 94.593 | 97.101 |
| 15 | 99.779 | 96.717 | 98.949 |
| R | 0.9858 | 0.9637 | 0.9738 |
| K($min^{-1}$) | 0.4293 | 0.2543 | 0.3289 |
| $T_{50}$(min) | 1.6 | 2.7 | 2.1 |
| $T_{90}$(min) | 5.4 | 9.1 | 7 |

**Table 6: *In-vitro* dissolution data of Olmesartan medoxomil pellets formulated using different sized starter seeds:**

| Time (min) | Cumulative % drug released | | | |
|---|---|---|---|---|
| | F04 | F05 | F06 | F07 |
| 0 | 0 | 0 | 0 | 0 |
| 5 | 95.02 | 89.982 | 86.543 | 71.248 |
| 10 | 99.038 | 98.209 | 95.868 | 93.007 |
| 15 | 99.038 | 99.685 | 95.868 | 94.368 |
| R | 0.9833 | 0.9962 | 0.9868 | 0.9614 |
| K($min^{-1}$) | 0.4916 | 0.3947 | 0.3352 | 0.2171 |
| $T_{50}$(min) | 1.4 | 1.8 | 2.1 | 3.2 |
| $T_{90}$(min) | 4.7 | 5.8 | 6.9 | 10.6 |

**Table 7: *In-vitro* dissolution data of Olmesartan medoxomil pellets formulated at different pan speeds**

| Time (min) | Cumulative % drug released | | | | |
|---|---|---|---|---|---|
| | F08 | F09 | F10 | F11 | F12 |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 92.263 | 95.02 | 97.203 | 98.316 | 90.211 |
| 10 | 95.106 | 98.165 | 99.858 | 99.506 | 97.073 |
| 15 | 95.106 | 99.455 | 99.858 | 99.506 | 97.073 |
| R | 0.9127 | 0.9488 | 0.9984 | 0.9457 | 0.9805 |
| K($min^{-1}$) | 0.3438 | 0.3806 | 0.6679 | 0.5883 | 0.3755 |
| $T_{50}$(min) | 2 | 1.8 | 1 | 1.2 | 1.8 |
| $T_{90}$(min) | 6.7 | 6.1 | 3.4 | 3.9 | 6.1 |

**Figure 1: *In-vitro* dissolution profiles of Olmesartan medoxomil pellets formulated using different carriers**

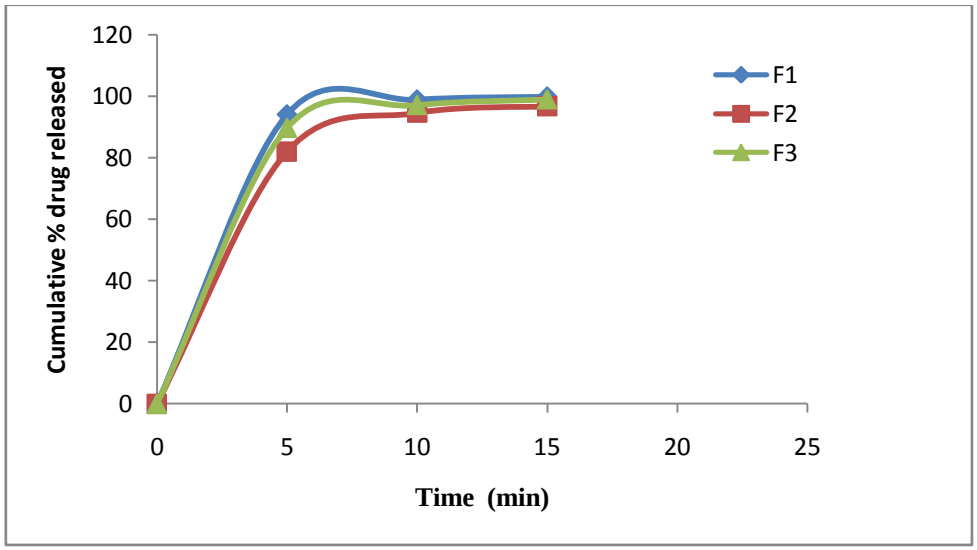


**Figure 2: *In-vitro* dissolution profiles of Olmesartan medoxomil pellets formulated using different sized starter seeds**

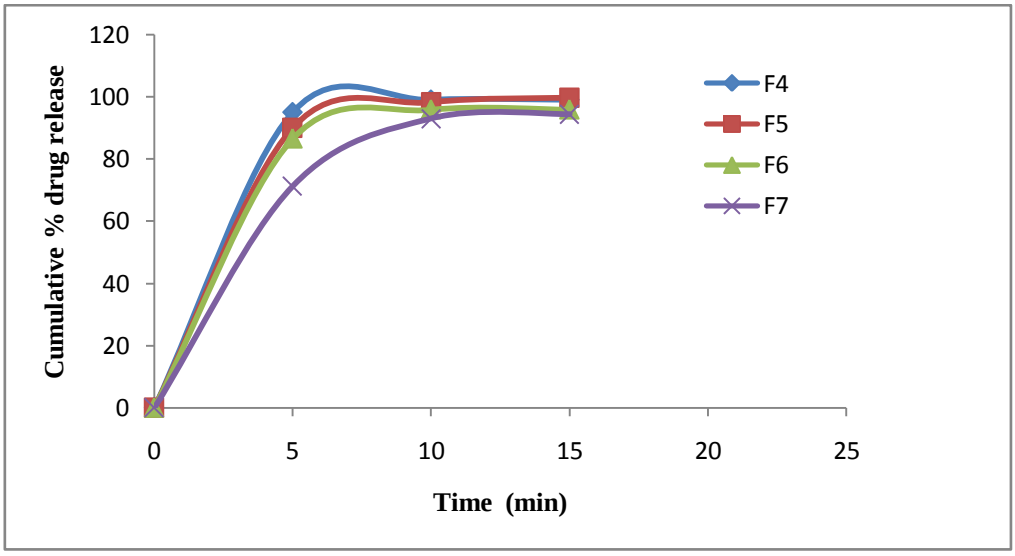
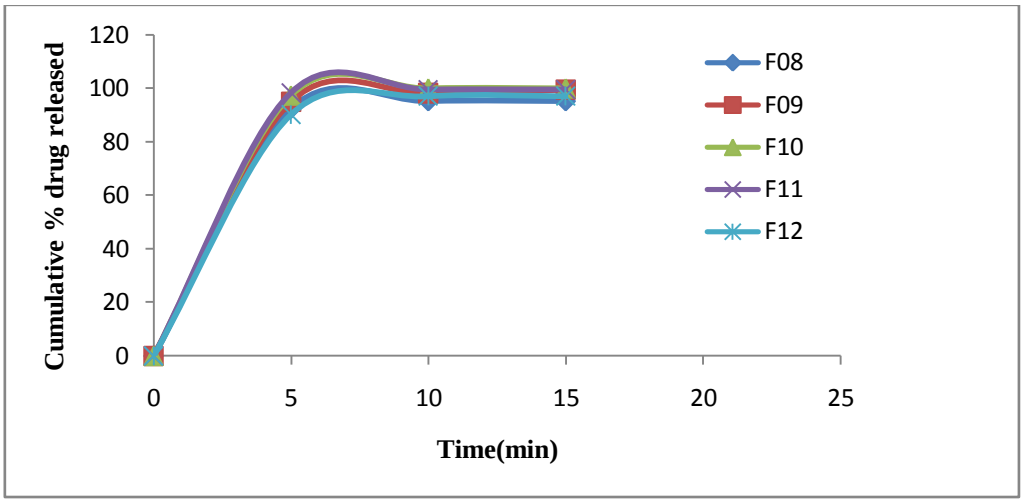



**Figure 3: *In-vitro* dissolution profiles of Olmesartan medoxomil pellets formulated at different pan speeds**




## CONCLUSION

Olmesartan medoxomil pellets were formulated by coating the olmesartan medoxomil on different carrier pellets using a conventional coating pan. Various evaluation tests like yield, drug loading efficiency, moisture content and flow properties were performed on the Olmesartan medoxomil loaded pellets. All the pellets exhibited good flow properties and the drug loading efficiency was also good.

IR study revealed the compatibility of the drug with excipients. Stability studies reveal that the product does not undergo degradation on storage and hence expected to maintain the integrity during storage with reasonable shelf life.

Based on the results, Olmesartan medoxomil coated on mannitol pellets with a mesh size of 30/44 at 40 rpm showed high drug dissolution rate and hence leads to improved bioavailability of Olmesartan medoxomil.

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