Studies on the Bioavailability Enhancement of Olmesartan Medoxomil: Solid Lipid Nanoparticles as Carrier System

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ABSTRACT

Drugs with low aqueous solubility not only give low oral bioavailability but provide high inter- and intra-subject variability. Olmesartan medoxomil has very poor aqueous solubility and belongs to Class II drugs under Biopharmaceutical Classification Systems. The purpose of the present study was to investigate the bioavailability enhancement of olmesartan medoxomil by solid lipid nanoparticles. Optimized olmesartan medoxomil loaded solid lipid nanoparticles was prepared by hot homogenization and ultra-sonication method. Optimization was by particle size, polydispersity index, shape and surface morphology determination. Physicochemical and other spectroscopic parameters on optimized formulations (F3 and F7 respectively) were determined. In vitro drug release studies were performed using dialysis bag. Bioavailability studies were done using albino rats. The in vitro drug release study demonstrated that drug-loaded formulations gave higher drug release than olmesartan medoxomil. Zero-order kinetic model best described the release kinetics of the drug from the formulations based on the correlation coefficient values. When compared with the oral tablet of olmesartan medoxomil, the pharmacokinetics of olmesartan medoxomil loaded solid lipid nanoparticles formulations exhibited higher plasma drug concentration, larger area under the curve, and more enhanced oral bioavailability.

Keywords: Olmesartan medoxomil; Solid lipid nanoparticles; Entrapment efficiency; In vitro drug release; Bioavailability studies

INTRODUCTION

Active ingredients with poor water solubility are often associated with a number of in vivo effects such as decreased bioavailability, more frequent incomplete release from dosage form and higher inter-subject variability. It also has in vitro formulation development obstacles such as increasing complex dissolution testing and poor correlation to the in vivo absorption. Despite these drawbacks, advances have been made in delivery technologies to improve the bioavailability of poorly water soluble compounds following the realization by synthetic and pharmaceutical scientists that the development of new drugs alone is not sufficient to ensure progress in drug therapy. Such advances in delivery technologies exploited by formulation scientists for bioavailability enhancement include suitable drug carrier systems such as microemulsions [1-3], nanoemulsions [4-6], liposomes [7-9], self-emulsifying drug delivery systems [10-12], solid dispersions [13,14], solid lipid nanoparticles [15-17] etc.

These efforts have allowed promising drug candidates not to be disregarded or have their development disrupted by suboptimal formulations. Olmesartan medoxomil (Figure 1) chemically defined as 2,3-dihydroxy-2-butanyl 4-[1-hydroxy-1-methylethy]-2-propyl-1-[p(o-1H-tetrazol-5-ylphenyl] benzyl] imida-
zole-5-carboxylate, cyclic 2,3-carbonate is a selective AT1 subtype angiotensin-II receptor antagonist. It acts by lowering blood pressure through arterial vasodilatation and reduced sodium retention [18]. Clinically, it used in the treatment of hypertension. Olmesartan medoxomil is available only as tablets in doses of 5 mg, 20 mg and 40 mg respectively [19]. It is practically insoluble in water (<7.75 μg/ml) and rapidly absorbed from the gastrointestinal tract with peak plasma concentration of olmesartan (metabolite) occurring 1–3 h after administration. The absolute bioavailability of olmesartan from olmesartan medoxomil tablets is 28.6% with an elimination half-life of 10-15 hr [20]. Solid lipid nanoparticles (SLN) have been developed for various routes of administration with several objectives including enhancement of bioavailability of poor water soluble drugs. To our knowledge, bioavailability enhancement of olmesartan medoxomil has not been reported using solid lipid nanoparticles. Therefore, the objective of the present study was to evaluate the bioavailability enhancement of olmesartan medoxomil by solid lipid nanoparticles technique.

**MATERIALS AND METHODS**

**Materials**
Olmesartan medoxomil (Sankyo Pharma Inc., USA), glycercyld mono stearate (Sigma-Aldrich, USA), soya lecithin (Himedia Ltd, India), polysorbate 80 (Sigma-Aldrich, USA). All other chemicals were of analytical reagent grade. The HPLC apparatus consists of a Shimadzu model HPLC equipped with quaternary LC-10A VP pumps, variable wavelength programmable UV/VIS detector. Rheodyne injector was fitted with a 20 μl loop. The analytical column was a C18 chromatographic column (Hypersil, 250×4.6 mm, 5 μm; Agilent Technologies, Tokyo, Japan). The mobile phase consisted of acetonitrile:phosphate buffer (60:40). The buffer was adjusted to pH 3.5 with phosphoric acid. The mobile phase was delivered at the flow rate of 1.0 ml/min. Injection volume was 10 μl. Detection was performed at 254 nm.

**Preparation of Olmesartan Medoxomil Loaded Solid Lipid Nanoparticles**
Various solid lipid nanoparticles were prepared by hot homogenization and ultrasonication method. Optimized solid lipid nanoparticles formulation (F3 and F7 respectively) of olmesartan medoxomil was prepared by dissolving olmesartan medoxomil, glycercyl mono stearate and soya lecithin in a beaker containing 10 mL mixture of chloroform and methanol (4:1). Organic solvents were completely evaporated on a water bath. The lipid layer containing the drug was melted at temperature 5°C above melting point of the lipid. An aqueous phase containing polysorbate 80 heated to the same temperature as the oil phase was slowly added to the oil phase while homogenization was carried out at 12,000 rpm using Ultra Turrex T25 homogenizer (IKA labotechnik) for 5 min. The coarse hot oil in water emulsion was ultrasonicated (12T-probe) using a Vibra cell (Sonics, USA) for 20 min. The hot formulation was allowed to cool to room temperature to obtain olmesartan medoxomil loaded solid lipid nanoparticles formulation.

**Characterization of Solid Lipid Nanoparticles Formulations**
**Measurement of particle size and polydispersity index:**
The mean particle size and polydispersity index of the solid lipid nanoparticles preparations were determined using a zetasizer (DTS Version 4.10, Malvern instruments, UK). Samples were appropriately
diluted with deionised water to allow the light scattering intensity to be within the instrument’s sensitivity range. Determinations were done in triplicate.

**Scanning electron microscopy:**
Shape and surface morphology of the solid lipid nanoparticles formulations were analyzed using scanning electron microscopy (SEM). The samples were mounted on alumina stubs using double adhesive tape, coated with gold in HUS-5GB vaccum evaporator. The analysis was done using Hitachi S-3000N SEM at an acceleration voltage of 10KV and a magnification of 5000×. Determinations were done in triplicate.

**Physicochemical parameters:**

- **pH measurement:** The apparent pH of the optimized formulations was determined using a pH meter with combination electrode (Eutech, Japan). The pH test was done in triplicate at 25°C.

- **Conductivity measurement:** The electrical conductivity of the optimized formulations was determined using an S70 Seven Multi™ conductivity meter (Mettler Toledo, Columbus, USA). The conductivity meter was fitted with an Inlab® 730 conductance electrode having a cell constant of 0.58 cm⁻¹. The test was done in triplicate at 25°C.

- **Refractive index measurement:** The refractive index of the optimized formulations was measured at 25°C using a refractometer (Fisher Scientific, USA). The test was done in triplicate

- **Viscosity determination:** The viscosity of the optimized formulations was determined using Brookfield cone and plate viscometer (Brookfield Eng. Lab. Inc, USA). Viscosity was done in triplicate at 25°C.

- **Fourier transform infrared (FTIR) spectroscopy:**
The samples were analyzed by Fourier transform infrared (FT-IR) spectroscopy in the range of 400 to 4,000 cm⁻¹. The infrared spectral analyses of pure olmesartan medoxomil, glyceryl mono stearate, soya lecithin, physical mixture and olmesartan medoxomil loaded solid lipid nanoparticles formulations were carried out. The vibration frequencies of the spectra peaks produced by the pure drug, physical mixture and solid lipid nanoparticles formulations were compared.

- **Differential scanning calorimetry (DSC):**
The test was done on a calibrated instrument under nitrogen purge (20 mL/min) at a heating rate of 10°C/min and temperature range of 25–2000°C using Netzsch DSC 200PC (Netzsch, Selb, Germany). The sample was weighed into standard aluminum pan while using the empty pan as reference.

**Determination of Entrapment Efficiency (EE)**
The entrapment efficiency of the optimized formulations was done in triplicate by obtaining the concentration of free drug in the aqueous phase of solid lipid nanoparticles formulation following centrifugation of 2 ml of each formulation. Centrifuging of the formulation was done at high speed (15000 rpm) for 30 min at room temperature using Remi cooling centrifuge (Mumbai, India). Absorbance of the aqueous solution was taken at a wavelength of 258 nm. The percent entrapment efficiency was calculated as follows:

\[
\% \text{ EE} = \frac{\text{Total drug content - free drug content}}{\text{Total drug content}} \times 100
\]

**Assay of Drug Content**
A 2 ml of each optimized formulation was diluted to 10 ml using ethanol. The absorbance of the drug in all dilutions, were measured at 258 nm. The drug content in each formulation was obtained from calibration curve. Determinations were done in triplicate.

**Stability Study**
Stability testing was done on olmesartan loaded solid lipid nanoparticles formulations at room and refrigerator temperatures for 0, 30 and 60 days. Particle size, polydispersity index and drug content determinations were parameters used to follow the stability study. Study was done in triplicate. Statistical
analysis of the data was performed using the Student’s t-test and significance of the study was chosen at p<0.05.

**In vitro Drug Release**

Dialysis bag was used for the *in vitro* drug release determination. The bag was soaked in distilled water for 12 h prior to been used. A 5 ml aliquot of solid lipid nanoparticles formulation devoid of free drug or olmesartan medoxomil aqueous suspension was placed into dialysis bag and tied at both ends. The dialysis bag was immersed in a receptor compartment containing 50ml of saline phosphate buffer solution (PBS) pH 7.4. The receptor compartment was placed on a magnetic stirrer and stirred at 37 ± 1°C using a magnetic bar. At various time intervals (5, 10, 20, 30, 40, 50, 60, 90, 120, 180, 240, 300 min up to 12 h) a 5 ml of aliquot was withdrawn, filtered using Whatman filter paper. An equal volume of fresh medium was added to the receptor compartment. The filtered samples were analyzed for drug contents by UV-Visible spectrophotometry at 258 nm. Plot of percent drug released versus time was carried out.

**Pharmacokinetic Studies on Optimized Solid Lipid Nanoparticles Formulations**

The approval to carry out pharmacokinetic studies was received from the Animal Ethics Committee of Faculty of Veterinary Medicine, University of Nigeria, Nsukka. Guidelines of ethics committee were followed for the studies. Pharmacokinetic studies were carried out on optimized solid lipid nanoparticles formulations (F3 and F7 respectively) and marketed olmesartan medoxomil tablet. The male Wistar rats kept in polypropylene cages with free access to standard laboratory diet were kept under standard laboratory conditions (temperature 25 ± 2°C and relative humidity of 55 ± 3%). The rats were divided into 3 groups (n=4). Group I received F3 orally, group II received F7 orally and group III received marketed tablet orally. The dose of olmesartan medoxomil in all groups was 2.0 mg/kg of body weight. The rats were anaesthetized using ether and blood samples (1.0 ml) were withdrawn from the tail vein of rat at 0 (pre-dose), 1, 2, 3, 6, 8, 12 h, into micro-centrifuge tubes in which 10 mg of EDTA was added as an anticoagulant. The blood collected was properly mixed with the EDTA and centrifuged at 5000 rpm for 15 min. The separated plasma was stored at -21°C until use. Prior to drug analysis, the frozen plasma was thawed at room temperature and the plasma protein was precipitated using 4:1 ratio of acetonitrile to plasma [21,22], by mixing and vortex for 5 min. After centrifuging at 5000 rpm for 20 min, the acetonitrile layer was analyzed for drug content using HPLC method. Olmesartan medoxomil in plasma was quantified by the HPLC method that was validated in our laboratory. The concentration of unknown plasma samples was calculated from the calibration curve plotted between peak areas of olmesartan medoxomil versus olmesartan concentrations.

**Pharmacokinetic and Statistical Analysis**

The pharmacokinetic parameters of olmesartan medoxomil were determined by employing noncompartmental pharmacokinetic analysis. The plasma concentration of olmesartan medoxomil at different time intervals was analyzed to calculate various pharmacokinetic parameters namely maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), and area under the plasma concentration-time curve (AUC_{0→∞} and AUC_{0→t}). The values of C_{max} and T_{max} were read directly from the plot of time and plasma concentration of olmesartan medoxomil. The AUC from time zero to the last measurable concentration time (AUC_{0→t}) was calculated by linear trapezoidal method. The AUC from time zero extrapolated to infinite time (AUC_{0→∞}) was calculated according to the formula:

\[ \text{AUC}_{t_e} = \text{AUC}_t + C_t / k_e, \]

where \( C_t \) is the last quantifiable concentration and \( k_e \) is the terminal elimination rate constant which was determined by least-squares regression analysis during the terminal log-linear phase of the concentration–time curve. The mean residence time (MRT) was calculated based on the trapezoidal rule. Using plasma-concentration data, total clearance (CL_{total}) was estimated as dose (2.0 mg/kg)/AUC_{0→∞}, and the volume of distribution at a steady state (V_{ss}) was calculated as CL_{total} × MRT. The elimination half-life (t\( \frac{1}{2} \)) was estimated by dividing 0.693 by the elimination-rate constant. The relative bioavailability of the olmesartan medoxomil after the oral administration of SLN optimized formulations versus the oral administration of olmesartan medoxomil aqueous suspension was calculated as follows:

\[ \text{Relative bioavailability} = \frac{\text{AUC}_{SLN}}{\text{AUC}_{	ext{ref}}}, \]
AUC_AQ

The pharmacokinetic data between different formulations was compared for statistical significance by one way analysis of variance (ANOVA) and Dunnet’s post hoc test respectively. Probability values were considered significant at \( p < 0.05 \).

RESULTS AND DISCUSSION

The homogenization followed by ultrasonication technique used to prepare the solid lipid nanoparticles formulations have been reported to be simple, reliable and reproducible method for preparation of solid lipid nanoparticles [23].

The solvent mixture of chloroform and methanol (4:1) was found to be very effective in homogenously dispersing olmesartan medoxomil in the lipid phase. The composition of the optimized formulations, are given in Table 1.

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Formulation</th>
<th>F3</th>
<th>F7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmesartan medoxomil (% w/w)</td>
<td></td>
<td>0.038</td>
<td>0.037</td>
</tr>
<tr>
<td>Glyceryl monostearate (% w/w)</td>
<td></td>
<td>1.89</td>
<td>1.82</td>
</tr>
<tr>
<td>Soy lecithin (% w/w)</td>
<td></td>
<td>1.89</td>
<td>3.64</td>
</tr>
<tr>
<td>Polysorbate 80 (% w/w)</td>
<td></td>
<td>1.89</td>
<td>3.64</td>
</tr>
<tr>
<td>Solvent system, ml</td>
<td></td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

(4:1 ratio chloroform and methanol)

The characterization analyses showed that the optimized formulations were spherical in shape with smooth surface. They possess particle size range of 122.8-135.0 nm, and polydispersity index range of 0.205-.206. The particle size results suggest that the formulations have the potential to give high drug release from the nanoparticles matrix and good gastrointestinal uptake of the drug. Previous report has shown that particle sizes less than 300 nm are advisable for the intestinal transport [24]. The polydispersity index results also substantiated the optimum size distribution of the nanoparticles. It has been reported [25] that a polydispersity index value less than 0.3 is often accepted as optimum value. The test on scanning electron microscopy showed that most of the particles were smooth and fairly spherical in shape. It was also noted that the particle sizes of the formulations were in the nanometric range. The results are given in Table 2.

The physicochemical determination results (Table 2) were considered to be satisfactory and the slight differences between the blank and drug loaded formulations could be due to the intrinsic properties of the drug. The results of the entrapment efficiency of olmesartan medoxomil-loaded solid lipid nanoparticles formulations are listed in Table 3. Entrapment efficiency was found to be 96.0 ± 0.09% and 96.8 ± 0.03% for F3 and F7 respectively. The high entrapment efficiency values obtained for the formulations tend to substantiate the accuracy of the formulation method and suggest the drug to be lipophilic.

The assay of drug content results indicates the sensitivity, specificity, accuracy and reproducibility of the analytical method employed in this study. The results are given in Table 3.

The infrared spectroscopic studies were done to determine possible drug lipid interactions. The IR spectrum of pure olmesartan medoxomil showed sharp characteristic peaks. The drug characteristic peaks also appeared in the physical mixture indicating no modification or interaction between drug and the excipients. However, these characteristic peaks were not found in the solid lipid nanoparticles formulations suggesting that the drug might have been molecularly dispersed within the lipid matrix.
Table 2: Characterization and physicochemical parameters data of solid lipid nanoparticles formulations

<table>
<thead>
<tr>
<th>Characterization data</th>
<th>Formulation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Droplet size (nm)</td>
<td></td>
<td>F3</td>
<td>F7</td>
</tr>
<tr>
<td>135.0 ± 2.23</td>
<td>122.1 ± 2.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polydispersity index</td>
<td>0.206 ± 0.03</td>
<td>0.205 ± 0.18</td>
<td></td>
</tr>
<tr>
<td>Conductivity (µs/cm)</td>
<td>220 ± 0.20</td>
<td>210 ± 0.16</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>5.30 ± 0.15</td>
<td>5.14 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>Refractive index</td>
<td>1.3431 ± 0.01</td>
<td>1.3436 ± 0.02</td>
<td></td>
</tr>
<tr>
<td>Viscosity (mpa.s)</td>
<td>4.3 ± 0.18</td>
<td>3.9 ± 0.14</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Entrapment efficiency, drug content and kinetic model data

<table>
<thead>
<tr>
<th>Analytical data</th>
<th>Formulation</th>
<th>Olmesartan Medoxomil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F3</td>
<td>F7</td>
</tr>
<tr>
<td>Entrapment efficiency</td>
<td>%</td>
<td>96.040.09</td>
</tr>
<tr>
<td>Drug content (assay)</td>
<td>%</td>
<td>98.50.05</td>
</tr>
<tr>
<td>Kinetic model (zero-order)</td>
<td>r²</td>
<td>0.9986</td>
</tr>
<tr>
<td></td>
<td>k_o</td>
<td>0.0699</td>
</tr>
</tbody>
</table>

Figure 2: Sample of Scanning Electron Microscopy image of the optimized formulations (F3 and F7)

The differential scanning calorimetry thermograms of olmesartan medoxomil and drug loaded solid lipid nanoparticles formulation are shown in Figures 2 and 3. The thermogram of olmesartan medoxomil showed endothermic peak at 178.7°C. It was observed (Figure 4) that the melting endotherm of olmesartan medoxomil was shifted to lower temperatures in the formulations. For example, it was shifted to 110.4°C and 124.7°C in the thermograms of drug loaded solid lipid nanoparticles, for F3 and F7 respectively. The observation tends to suggest that olmesartan medoxomil was not in crystalline state but completely solubilized in the formulation.
The stability results suggest the high degree of stability of the formulations. Statistical analysis at p<0.05 showed that there was no significant difference in drug content, particle size and polydispersity index values following storage. The results of the release rate of olmesartan medoxomil loaded solid lipid nanoparticles formulations are shown in Figure 4. The two formulations showed significant release of olmesartan medoxomil. The cumulative percent drug release of olmesartan medoxomil from the formulations after 12 h was found to be 96.5% and 92.7% for F3 and F7 respectively, while that of aqueous drug suspension was 27.8%. The results suggest that solid lipid nanoparticles could be a potential delivery system for olmesartan medoxomil.

In vitro drug release data were fitted into various kinetic models such as zero order (cumulative amount of drug released versus time), first order (log cumulative percentage of drug remaining versus time), Higuchi model (cumulative percentage of drug released versus square root of time) Hixson Crowell model (cubic root of initial drug concentration minus cubic root of drug concentration at a given time versus time, $Q_0^{1/3} - qt^{1/3}$ vs $t$) and Korsmeyer-peppas model (logarithm of fraction of drug released versus logarithm of time, log ($Q_t/Q_\infty$) vs log $t$). The results revealed that zero-order model best-fitted the kinetics models based on the highest correlation coefficient obtained from the regression analysis. Diffusion of the drug from the lipid matrix was suggested to be the probable mechanism of action.
A noncompartmental pharmacokinetic analysis was conducted to estimate the rate and extent of olmesartan medoxomil absorption into the systemic circulation. The graph between plasma concentration and time was plotted for the SLN formulations and the oral tablet formulation (Figure 5). It was seen from the figure that the plasma concentration profile of olmesartan medoxomil for the SLN formulations showed greater improvement of drug absorption than the oral tablet formulation. The maximum plasma concentration ($C_{\text{max}}$) of olmesartan medoxomil was 62, 161 and 168 ng/ml for oral tablet formulation, F3 and F7 respectively. The time ($T_{\text{max}}$) to reach maximum plasma concentration was 3 h for olmesartan medoxomil in all formulations. The formulations F3 and F7 were found to enhance the bioavailability of olmesartan medoxomil by 2.2 and 2.5 folds respectively, with reference to the oral tablet (Table 4). The observed increase in bioavailability of solid lipid formulations might be due to enhanced solubilization of the drug, stimulating the intestinal lymphatic transport pathway or altering its intestinal permeability.

![Figure 5: Plasma concentration of F7, F3 and olmesartan medoxomil versus time](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formulation</th>
<th>Olmesartan Medoxomil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>F3</td>
<td>F7</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>0.161 ± 0.002</td>
<td>0.168 ± 0.005</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>3 ± 0.001</td>
<td>3 ± 0.002</td>
</tr>
<tr>
<td>AUC$_{0}$ (µgh/ml)</td>
<td>0.594</td>
<td>0.6725</td>
</tr>
<tr>
<td>AUC$_{\infty}$ (µgh/ml)</td>
<td>2.4216</td>
<td>3.0788</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>4.1528</td>
<td>4.5046</td>
</tr>
<tr>
<td>CL$_{\text{total}}$</td>
<td>0.413</td>
<td>0.3248</td>
</tr>
<tr>
<td>V$_{ss}$ (L/kg)</td>
<td>1.7151</td>
<td>1.4631</td>
</tr>
<tr>
<td>$K_e$ (h$^{-1}$)</td>
<td>0.2408</td>
<td>0.222</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>2.8779</td>
<td>3.1216</td>
</tr>
</tbody>
</table>

Abbreviations: $C_{\text{max}}$; maximum concentration; $T_{\text{max}}$; time to reach $C_{\text{max}}$, AUC; area under the plasma concentration–time curve from 0 to measurable time, AUC$_{\infty}$; area under the plasma concentration–time curve from 0 to infinity, MRT; mean residence time; CL$_{\text{total}}$; total clearance, $K_e$; elimination-rate constant, V$_{ss}$; steady-state volume distribution, $t_{1/2}$; elimination half-life.
CONCLUSION

Olmesartan medoxomil was successfully incorporated into solid lipid nanoparticles by hot homogenization and ultrasonication method. The formulations were found to be in nanometric range with smooth spherical structure. The drug was found to be efficiently entrapped in the lipid matrix. FT-IR study revealed no interaction between drug and excipients. The release of drug from the formulations best-fitted zero-order kinetics model. The pharmacokinetic studies in vivo showed the solid lipid nanoparticles formulations improved the bioavailability of olmesartan medoxomil. Thus, the developed solid lipid nanoparticles may be an effective vehicle for oral administration of olmesartan medoxomil.

REFERENCES