TRANSDERMAL OF ATENOLOL VIA MICROEMULSIONS

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ABSTRACT

Objective: Developing novel non-ionic microemulsions (MEs) for transdermal of atenolol as satisfactory alternative drug delivery systems for the oral route.

Methods: Seven MEs were developed then checked for encapsulation of atenolol using Fourier Transform Infrared Spectroscopy (FTIR-spectroscopy) (1), isotropy, droplet sizes, rheological properties and transdermal flux using Franz diffusion cell. Furthermore, two MEs with best flux values were selected for bioavailability evaluation after transdermal application over rat’s skin.

Results: The results showed that the MEs complies with colloidal systems properties. Also, the developed MEs were stable throughout the study, ideal viscous systems with droplet sizes below 500 nm and isotropic. Besides, FTIR-spectra could reveal the structure of the MEs and encapsulation of atenolol inside the dispersed phase. Moreover, the flux values of atenolol in MEs through rat’s skin varied with different factors such as atenolol concentration, MEs’s composition, and zetapotential. The highest flux value of the developed systems was 243.5±16.3 µg. cm⁻². h⁻¹. Furthermore, the in vitro results showed that using the two tested microemulsions maximum plasma levels of atenolol 5.22±0.43 and 4.06±0.15 mg. ml⁻¹ at 8.18 and 3.64 h respectively could be achieved.

Conclusion: The developed microemulsions can be promise formulations for transdermal administration of atenolol as alternative for oral tablets.

Keywords: Atenolol, Transdermal, Microemulsions

INTRODUCTION

Atenolol is a β1-selective adrenergic blocking agent. It is widely used in the management of hypertension as monotherapy or in combination with other classes of antihypertensive agents [1-4]. Atenolol subjects to extensive first-pass hepatic metabolism and has an absolute oral bioavailability of about 50–60%. Moreover, it was reported that, in the case of oral administration, atenolol can induce side effects such as diarrhea, ischemic colitis and mesenteric arterial thrombosis [5-8]. Transdermal application of a drug such as atenolol can lower the total daily dose and eliminate the gastrointestinal side effects. Also, the ease and self-medication can improve the patient compliance [8, 9]. The short biological half-life (2.8-7.4 h) and lower value of molecular weight (266 g. mole⁻¹) renders atenolol as an ideal candidate for transdermal drug delivery systems [10].

Many studies investigated the transdermal of atenolol using iontophoresis and chemical penetration enhancers [11-15]. Other studies evaluated the transdermal of atenolol such as using gel formulation, ethylene-vinyl acetate matrix or hydroxypropyl methylcellulose and ethyl cellulose matrix [16-18].

Newtonian rheological properties and high penetration enhancing the capacity of microemulsions (MEs) make them ideal carriers for transdermal as well as oral use [19-22]. Only one study was reported about in vitro investigation of the transdermal of atenolol using W/O microemulsion as a carrier. In this study, many lipophilic surfactants such as capmul GMOS05, caprol ET, lauroglycol 90 were screened to evaluate their propensity for emulsification of the aqueous phase to optimize atenolol loading [23]. The present study aimed to develop novel colloidal delivery systems using nonionic surfactants to enable and improve the transdermal application of atenolol and evaluate their bioavailability in vitro and in vivo.

MATERIALS AND METHODS

Materials

Atenolol was offered from a local company (United Pharmaceutical Manufacturing Co.). Ethanol HPLC grade was purchased from scientific and chemicals supplies LTD (Bilston, UK). Methanol HPLC grade was purchased from Fulltime (Anqing, China). Water for HPLC was purchased from LabChem (Zelenopole, USA). Dimethyl sulfoxide (DMSO) was purchased from A2 Chem (Ontario, Canada). Sorbitan monolaurate (Span® 20) and Poloxamers (Brij® and Poloxamer 188) were purchased from Sigma (Lyon, France). Citric acid (CA) and Isopropyl Myristate (IPM) were purchased from Merck (Darmstadt, Germany).

Instruments and methods

Microemulsions (MEs) preparation

MEs were prepared by the titration method [24]. Atenolol was dissolved in the hydrophilic phase composed of a mixture of water and ethanol or water, ethanol and DMSO. Two ml of IPM was added to atenolol solution. Either span 20 or mixture of span 20, tween 80 (3:2) were added dropwise with constant stirring over magnetic stirrer to the lipophilic and hydrophilic phase mixture until a clear microemulsion was formed. The added amounts of surfactants were recorded. Compositions of the developed microemulsions are listed in table 1.

Pseudo-ternary phase diagrams of microemulsion systems

A pseudo-ternary phase diagram was plotted to find the existence area of MEs. Another three-phase diagram for MEs with 100 mg atenolol was accomplished for testing the influence of atenolol on this area. Formulations were made using three components which are the hydrophilic phase, lipophilic phase, and surfactants. Each phase forms one face of the triangle. The formulations were made with fractions of the three components according to crossing points which formed by plotting three parallel lines to the three faces of the triangle. More formulations were made between the cross points on the border of MEs area. After mixing, clear and stable formulations were identified to be MEs [24].

Viscosity measurement

An electric Rheometer made by Anton Paar, universal tool, model MCR 301 (Ostfildern, Germany) was used to determine the viscosity and rheological properties of MEs. Rheograms were established for the MEs with increasing and decreasing shear force at 25°C on the bob and cup viscometers.
was filled with 5 ml of 75% methanol in water. Only 0.2 ml of each
stored in a deep freeze at a temperature below than-70 °C.
executing. The adipose tissues were removed from the peeled skin and
were carried out in harmony with the NIH guidelines for the care and use
In vitro
using HPLC. Each time withdrawn samples were replaced by 0.5 ml
3, 5, 7 and 24 h for analyzing the penetrated drug through the skin
microemulsion was allocated over the skin using an insulin syringe.

Preparing rat’s skin
shaved area of 4 cm² on the back of each of 4 rats weighing 270-300g for

Droplet size measurement (Zeta-potential measurement)
A laser doppler electrophoresis was carried out on the
microemulsions with a Zeta-sizer made by Microtrac (Pennsylvania, USA)
equipment which is capable of measuring particle size ranging
between 0.8 nm to 6.54 µm, Zeta potential range-125 to+125 mV.
The sample was introduced into the apparatus cell without dilution
as the formation of microemulsions depends on the concentration.
Samples were measured at a temperature of 32 °C without filtration.

Polarized microscope
A polarized microscope model ML9030 made by MEI Techno (Saitama,
Japan) was used for testing the isotropy of the microemulsions.

Fourier transform infrared spectroscopy (FTIR) measurements
The encapsulation of atenolol, as well as the structure of the MEs, was
assessed by recording spectra by FTIR-spectrometer UATR Two,
Pharmacokinetic and statistical analysis
Tests were triplicated then the mean and standard deviation values
calculated. Origen program was used for statistical evaluation with a
confidence interval of 95%. A linear regression with its standard
Trend graphs are plotted by using excel® program (Microsoft® Excel
Version 8.0, Certara, L. P.) by applying one compartment open model.

RESULTS
HPLC method and the calibration curve

Pharmacokinetic and statistical analysis
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Fig. 1: Chromatograms of atenolol using HPLC A: in standard solutions for concentration between 0.05-2 mg/ml; B: in samples taken from Franz diffusion cell after 1-24 h; C: in blood samples after transdermal application between 1-24 h

Fig. 2: Three phase diagrams of microemulsions (MEs) composed of IPM, water and a mixture of span 20: tween 80 (2:3) A: without atenolol; B: with atenolol

Fig. 3: Rheograms of developed MEs containing atenolol
The area of clear MEs free of atenolol was estimated at fractions more than 0.6 of IPM and less than 0.6 of hydrophilic phase. After addition of 100 mg of atenolol this area of ME was shifted to fractions less than 0.6 of IPM, more than 0.4 of hydrophilic phase and less than 0.6 of the surfactants. Consequently, the MEs containing atenolol consumed less surfactants amounts and solubilized higher hydrophilic phase fractions.

Rheological properties

The rheological properties were determined using the bob and cup instrument with increased shear rate for different systems and the results are represented in fig. 3. The rheograms of different formulations show that the shear rate against the viscosity was constant. Accordingly, all the systems exhibited Newtonian characteristics.

Table 2: The measured mean droplets sizes, zeta potential and polydispersity index (PDI) of different formulated microemulsions using Zeta-sizer

<table>
<thead>
<tr>
<th>ME</th>
<th>Mean droplet size (nm)</th>
<th>PDI</th>
<th>Zeta potential [mv]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME600ts</td>
<td>270.1±27.5</td>
<td>10.88</td>
<td>10.72</td>
</tr>
<tr>
<td>ME800ts</td>
<td>163.6±60.4</td>
<td>6.20</td>
<td>12.29</td>
</tr>
<tr>
<td>MEfree atenolol</td>
<td>52.2±19.4</td>
<td>2.14</td>
<td>-0.55</td>
</tr>
<tr>
<td>ME1000-0.1CA</td>
<td>107.4±28</td>
<td>8.53</td>
<td>0.54</td>
</tr>
<tr>
<td>ME900-1CA0.7</td>
<td>557±112</td>
<td>0.16</td>
<td>0.57</td>
</tr>
<tr>
<td>ME900-1CA0.3</td>
<td>530±145</td>
<td>0.30</td>
<td>3.02</td>
</tr>
<tr>
<td>MEG free Atenolol</td>
<td>162.9±56.1</td>
<td>0.27</td>
<td>1.83</td>
</tr>
<tr>
<td>ME1000dmso-s</td>
<td>378±138</td>
<td>0.51</td>
<td>0.55</td>
</tr>
<tr>
<td>ME1000dmso-ts</td>
<td>320±321</td>
<td>1.74</td>
<td>4.29</td>
</tr>
<tr>
<td>MEdmso free Atenolol</td>
<td>139.2±41.8</td>
<td>0.56</td>
<td>16.8</td>
</tr>
</tbody>
</table>

Data given in this table is presented as mean±SD, n=3, SD: Standard deviation, PDI: Polydispersity index

Fig. 4: Droplet size distribution curve of the ME1000 0.1CA using Zeta sizer

Fig. 5: FTIR-spectra (Fourier transform infrared) of A: pure components which used in formulation the microemulsions atenolol; B: microemulsion with atenolol and microemulsion without atenolol
Droplet size measurement

The results of zeta sizer (fig. 4) including the mean zeta, zeta potential droplets size and poly disparity index of the MEs with atenolol are summarized in table 2.

Loaded systems with atenolol containing only water and ethanol showed 270, 163 and high polydispersity index. Using 0.1 M citric acid solution reduced the droplet size to 107 nm in ME1000-0.1CA. However, droplets sizes were around 500 nm when 1 M citric acid solution was used in ME1000-1CA0.7 and ME1000-1CA0.3 with relatively low polydispersity index and zeta potential. Also, by means of DMSO as penetration enhancer increased the concentration of atenolol in MEs as well as the droplets sizes to exceed 300 nm. Measurements of the same three systems free of atenolol showed smaller droplet size in comparison to loaded systems with atenolol.

Incorporation of atenolol in the ME600st and ME800st increased the zeta potential with increasing atenolol concentration from negative to positive values. In loaded systems with atenolol containing only water and ethanol showed a smaller droplet size in comparison to loaded systems with atenolol.

ME-spectrum was similar to IPM-spectrum which represents the outer phase of the ME except for the band between 2700-3000 which is possibly related to carbon chains of span 20 and tween 80. The declining of C-O stretching and appearing C-H stretching indicates that sorbitol ring and an ester bond in tween 80 and span 20 oriented to inside the hydrophilic phase where carbon chains of the side groups oriented to the outer surface of the droplets in the outer phase. Moreover, FTIR-spectra of MEs with and without atenolol were similar and the bands of atenolol disappeared from ME-spectrum with AT. However, C-O stretching at wavelength 1045 cm⁻¹ of ethanol appeared in ME-FTIR-spectrum near of C-O stretching of IPM.

Transdermal studying using Franz diffusion cell

Seven MEs containing atenolol were developed to study the transdermal of atenolol using MEs as carriers. Ethanol was used as a cosolvent in the formulation. Also, 0.1 and 1 M citric acid solutions were added to the hydrophilic phase as a buffering agent to improve the solubility of atenolol in the hydrophilic phase in three of the developed MEs. Besides, the effect of DMSO as penetration enhancer atenolol was studied in two other MEs; one of them was stabilized with DMSO, and the second with mixture of tween 80 and span 20.

The in vitro transdermal testing for atenolol was performed using Franz diffusion cell through shaved rat's skin over 24 h. The penetrated atenolol was quantified by removing 0.5 ml samples from the acceptor and analyzing the using HPLC (fig. 1B). Penetrated atenolol amounts per cm² were assessed over 24 h and the cumulative measured amounts per cm² plotted against the time. Transdermal profiles for different formulations are represented in fig. 6.

The Flux (Jss) and lag time (tlag) were calculated from the slope and from intersect with time axis respectively of the line at steady state (eq.1). The results are tabulated in table 4.

![Cumulative transdermal Atenolol through rat's skin](image)

**Fig. 6.** Cumulative transdermal of atenolol from different formulated MEs over 24 h using Franz diffusion cell. Data given in this fig. is presented as mean±SD, n=3, SD: Standard deviation

Table 3: The most important detected bands of the different components of MEs and their chemical bonds assignment

<table>
<thead>
<tr>
<th>Bands (cm⁻¹)</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>450-850</td>
<td>C-H stretching and bending</td>
</tr>
<tr>
<td>1045</td>
<td>C-O stretching of Ethanol</td>
</tr>
<tr>
<td>1104</td>
<td>C-O stretching of IPM</td>
</tr>
<tr>
<td>1092</td>
<td>(disappeared to be weaker bands in IPM at 1118 and 1189 cm⁻¹ in ME spectra)</td>
</tr>
<tr>
<td>1720-1740</td>
<td>C-O ester group stretching of IPM</td>
</tr>
<tr>
<td>2700 to 3000</td>
<td>OH, C-H stretching and bending</td>
</tr>
<tr>
<td>3100-3671</td>
<td></td>
</tr>
</tbody>
</table>

**Assignment**

- C-H and C-O stretching
- C-O stretching of Ethanol
- C-O stretching of IPM
- OH, C-H stretching and bending

**ME1000-0.1CA**

The Flux (Jss) and lag time (tlag) were calculated from the slope and from intersect with time axis respectively of the line at steady state (eq.1). The results are tabulated in table 4.

**ME1000-0.1CA**

The Flux (Jss) and lag time (tlag) were calculated from the slope and from intersect with time axis respectively of the line at steady state (eq.1). The results are tabulated in table 4.
The plasma level of atenolol increased rapidly and the two MEs were similar. The maximum concentration of ME1000-0.1CA more than 7 folds in comparison to ME1000dmso-s. Furthermore, the calculated AUC showed higher bioavailability of ME1000-0.1CA and system ME1000dmso-s which showed the best in vitro flux on 4 shaved rat’s skin. The penetrated amount of atenolol through the skin in plasma was quantified in 0.5 ml collected blood samples over 24 h using HPLC-method (fig. 1C). The two plasma level time curves over 24 h are represented in fig. 7. Furthermore, elimination rate constant half-life (K10_HL), the area under the curve (AUC), the absorption rate constant half-life (K01_HL), time of maximum absorption (tmax) and maximum concentration (Cmax) were calculated using phoenix program. Results are summarized in table 5.

**In vivo transdermal of atenolol loaded microemulsion penetration study**

The transdermal bioavailability of atenolol loaded microemulsion was studied by applying each of ME1000-0.1CA and system ME1000dmso-s which showed the best in vitro flux on 4 shaved rat’s skin. The penetrated amount of atenolol through the skin in plasma was quantified in 0.5 ml collected blood samples over 24 h using HPLC-method (fig. 1C). The two plasma level time curves over 24 h are represented in fig. 7. Furthermore, elimination rate constant half-life (K10_HL), the area under the curve (AUC), the absorption rate constant half-life (K01_HL), time of maximum absorption (tmax) and maximum concentration (Cmax) were calculated using phoenix program. Results are summarized in table 5.

**DISCUSSION**

Using FTIR-spectroscopy, incorporation of atenolol inside the MEs and distribution of ethanol in the external phase with IPM could be proved. Construction of three-phase diagram helps to prepare a stable homogeneous system of water and oil with as little surfactant as possible that can be diluted with water in all proportions without phase separation [30]. However, the observed shifting in required

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**Table 4: The flux of different formulated microemulsions (MEs) through rat’s skin using Franz diffusion cell**

<table>
<thead>
<tr>
<th>MEs</th>
<th>Flux (Jss) µg. cm⁻². h⁻¹</th>
<th>Tlag (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ME600ts</td>
<td>81.9±2.28</td>
<td>0.8</td>
</tr>
<tr>
<td>ME800ts</td>
<td>111.8±5.7</td>
<td>0</td>
</tr>
<tr>
<td>ME1000-0.1CA</td>
<td>243.5±16.3</td>
<td>3.5</td>
</tr>
<tr>
<td>ME900-1CA0.7</td>
<td>123.3±19.2</td>
<td>0</td>
</tr>
<tr>
<td>ME900-1CA0.3</td>
<td>111.7±42.1</td>
<td>2.4</td>
</tr>
<tr>
<td>ME1000dmso-s</td>
<td>190.3±21.3</td>
<td>2.4</td>
</tr>
<tr>
<td>ME1000dmso-ts</td>
<td>67.9±14.8</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Data given in this table is presented as mean±SD, n=3, SD: Standard deviation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>ME1000-0.1CA</th>
<th>CV%</th>
<th>ME1000dmso-s</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>mg. h. ml⁻¹</td>
<td>285.5±61.11</td>
<td>21.40</td>
<td>39.9±8.37</td>
<td>20.93</td>
</tr>
<tr>
<td>K01_HL</td>
<td>H</td>
<td>0.91±0.13</td>
<td>14.33</td>
<td>0.99±0.25</td>
<td>24.86</td>
</tr>
<tr>
<td>K10_HL</td>
<td>H</td>
<td>45±1.86</td>
<td>26.36</td>
<td>26.17±7.59</td>
<td>29.04</td>
</tr>
<tr>
<td>Cl_F</td>
<td>ml. h⁻¹</td>
<td>1.84±0.39</td>
<td>21.42</td>
<td>11.69±2.45</td>
<td>20.95</td>
</tr>
<tr>
<td>Tmax</td>
<td>H</td>
<td>5.22±0.43</td>
<td>8.18</td>
<td>4.85±0.69</td>
<td>14.184</td>
</tr>
<tr>
<td>Cmax</td>
<td>mg. ml⁻¹</td>
<td>4.06±0.15</td>
<td>3.64</td>
<td>0.93±0.05</td>
<td>5.63</td>
</tr>
</tbody>
</table>

Data given in this table is presented as mean±SD, n=3, SD: Standard deviation

**Fig. 7: Plasma level time curve of atenolol in rats from ME1000 0.1CA; and ME1000dmso-s. Data given in this fig. is presented as mean±SD, n=3, SD: Standard deviation.**

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**Table 5: The different transdermal bioavailability parameters of atenolol using phoenix program including elimination rate constant half-life (K10_HL), the area under the curve (AUC), the absorption rate constant half-life (K01_HL), time of maximum absorption (tmax) and maximum concentration (Cmax) of ME1000m0.1CA and ME1000dmso-s**

The maximum times of absorption and the absorption half-lives of the two MEs were similar. The maximum concentration of ME1000-0.1CA was 4.06 mg ml⁻¹ and in the case of ME1000dmso-s was 0.93 mg. ml⁻¹. Also, no lag time was observed for two formulated system. Furthermore, the calculated AUC showed higher bioavailability of ME1000-0.1CA more than 7 folds in comparison to ME1000dmso-s. However, the plasma level of atenolol increased rapidly and decreased very slowly to remain relatively high at over 24 h.
fractions for forming clear MEs in the three-phase diagram towards more fractions of hydrophilic phase can be explained by the change in the polarity of the hydrophilic phase because of the presence of atenolol which led in its turn to change in the interfacial tension. As a result, the solubility of the hydrophilic phase was increased after the addition of atenolol.

Furthermore, all systems had Newtonian properties with relatively low viscosity which impart them good favorable properties for penetration through the skin [31]. The viscosities of different formulations were similar and less than 0.1 Pa. s. However, ME900-1CA0.1 showed the highest viscosity compared to other MEs which may be attributed to the small amount of used surfactants (0.1 ml) and hydrophilic phase volume (1.4 ml). The ME900-1CA0.3 had the lowest viscosity which may be related to the hydrophilic phase composition.

The droplet size is an important factor in controlling the rate and extent of drug release as well as permeation of drugs through the skin. ME1000-0.1CA which had the smallest droplet size showed a good penetration through rat's skin and a higher flux than other formulated systems

The droplet size of the MEs varied between 100–500 nm which complied with the colloidal system's characteristics [32]. Furthermore, low droplet size of free atenolol in comparison to the same composition loaded atenolol systems gave another proof of encapsulation of atenolol inside the inner phase.

Hence, a sufficient volume of hydrophilic phase had to be used to solubilize atenolol before addition to 2 ml of lipophilic phase, the consumed surfactant amount varied with the varying volume of encapsulated hydrophilic phase and its composition.

The in vitro transdermal using Franz diffusion cell didn’t show a consistent correlation between the flux and atenolol concentration in MEs according to fick’s law but was more related to MEs compositions of hydrophilic phase, surfactants type and droplet size [33].

Using 0.1M citric acid as buffering agent led to an increase in the solubilized atenolol in ME, decrease the droplet size, decrease the zeta potential and increase in the flux. However, further increasing in citric acid concentration to 1M increases the incorporated atenolol and the droplet size. Hence, the flux of atenolol decreased.

DMSO as penetration enhancer didn’t enhance the penetration in case of ME1000dmso-st. Conversely, DMSO enhanced the penetration of atenolol in system ME1000dmso-s which was stabilized using span 20 which only may be attributed to the small structure of span 20 in comparison to tween 80 and hydrophilic property of tween 80. Moreover, a greater volume of span 20 was consumed for stabilizing ME1000dmso-st which also may be related to a small structure of span 20. However, the developed microemulsion ME1000-0.1CA and ME1000dmso-s showed higher flux (24.35±1.63 and 190.3±2.15 mg cm⁻² h⁻¹ respectively) in comparison to the reported best-developed microemulsions by Dhingani et al. (14.069 μg cm⁻² h⁻¹) [23]. Furthermore, the evaluated AUC (12.4±3.06*10⁻³ mg. h. ml⁻¹) of atenolol in ethylene-vinyl acetate (EVA) matrix system containing polyoxyethylene-2-oleyl ether was much lower than estimated in our study [17].

ME1000-0.1CA showed higher flux and bioavailability in comparison to ME1000dmso-s which may be associated to the lower droplet size and the higher concentration of atenolol in ME1000-0.1CA compared to ME1000dmso-s. Furthermore, the transdermal application of both two systems maintained a high plasma level over 24 h during the investigation.

CONCLUSION
The flux of atenolol didn’t correlate always with the concentration of atenolol. Contrariwise, it related with surfactant nature, the composition of the inner phase or even with zeta potential. However, the composition of MEs, their influence on zeta potential and the impact of their zeta potential on the transdermal (that non-ionized form is preferable for penetration through cell membranes) need more investigation.

In the present study, atenolol could be incorporated successfully in novel microemulsions which showed rapid and high transdermal flux with a relatively constant and high plasma level of atenolol during 24 h.

AUTHORS CONTRIBUTIONS
All the author have contributed equally

CONFLICT OF INTERESTS
Declared none

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