IMPROVED ABSORPTION OF ATORVASTATIN PRODRUG BY TRANSDERMAL ADMINISTRATION

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ABSTRACT
To evaluate the feasibility of sustained controlled delivery of therapeutically effective amount of HMG-CoA reductase inhibitors in matrix type transdermal delivery systems (TDDS). To enhance the transdermal absorption by synthesis of prodrugs with improved lipophilicity and matrix solubility. Atorvastatin (INN) is selected and formulated using drug in adhesive TDDS matrix. The prodrug of atorvastatin (Atorvastatin ethyl ester) was synthesized. In-vitro permeation study was performed using a modified Franz cell and the stratum corneum layer of human cadaver skin. The parent drug of atorvastatin showed low permeation rate due to its poor solubility in the stratum corneum layer of the skin. The TDDS containing atorvastatin prodrug exhibited a significantly higher transdermal penetration rate. Furthermore, the esterase enzyme in the cytosolic fraction of the skin hydrolyses the atorvastatin ester into atorvastatin to a high extent in the permeation processes.

Key words: Atorvastatin (INN), HMG-CoA reductase, and transdermal delivery systems (TDDS).

INTRODUCTION
Coronary artery disease is the largest cause of premature death in industrialised nations and is a growing threat in developing countries as well. The central role of cholesterol in the pathophysiology of coronary artery disease leads to lipid-lowering therapy for the medical management of this condition (Jacobs D et al., 1992). Clinical research with trials using statins have demonstrated the benefits of serum cholesterol lowering in cardiovascular outcome of our population, ranging from healthy subjects to patients with overt cardiovascular risk and patients suffering from acute coronary syndrome (Chen ZM et al., 1991).

The value of lowering low-density lipoprotein (LDL) cholesterol levels in preventing major cardiovascular events and stroke has been well documented. Recent studies have raised the issue of optimal treatment targets for patients with coronary heart disease (CHD).

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a
precursor of sterols, including cholesterol. In addition, atorvastatin reduces VLDL and TG and increases HDL-C (Scirica BM et al., 2006).

Transdermal drug delivery system has gained popularity over the past few decades. Advantages of transdermal delivery include convenience, comfort, by-pass the first phase hepatic metabolism, and control over drug absorption. The delivery system is an effective means for introducing drugs into the blood stream by applying a patch to skin. The major penetration pathway of drug molecules through the stratum corneum of intact human skin is by diffusing through the lipids envelopes of the skin cells.

Atorvastatin undergoes high intestinal clearance and first-pass metabolism, which is the main cause for the low systemic availability (30%). Food has been shown to reduce the rate and extent of atorvastatin absorption. Administration of atorvastatin with food produces a 25% reduction in Cmax (rate of absorption) and a 9% reduction in AUC (extent of absorption). Prodrug of atorvastatin was synthesized by esterifying the carboxylic acid group (LaRosa JC et al., 2005).

**Experimental methods**

1) Atorvastatin ethyl ester was synthesized by reacting atorvastatin calcium with anhydrous ethanol. The reaction was catalyzed with anhydrous HCl gas. The reaction mixture was purified over silica gel column and the compound was eluted with 10% MeOH in CH$_2$Cl$_2$. The purified product was characterized by mass spectrum, $^1$H NMR, and $^{13}$C NMR in CDCl$_3$.

2) Matrix type transdermal delivery system was formulated by mixing 10% atorvastatin ester with ~20% acrylic pressure sensitive adhesive (PSA), ~60% silicone PSA, 5% DPG, and w/o oleyl alcohol as penetration rate enhancer. Enalapril maleate was formulated in similar adhesive matrix for comparison.

3) Stratum corneum layer was obtained by separating human cadaver skin with heat (~55°). Transdermal unit placed on stratum corneum was mounted on modified Franz cell. Standard saline containing 0.01% NaN$_3$ was used as receiving phase. Samples were taken at each specific time point by completely withdrawing the receiving solution. The receiving phase was replenished after each sampling.

4) Samples were analyzed by HPLC using Hypersil C-8 156mm×4.6mm 5µm column (column temperature = 50°C). Mobile phase containing Ammonium acetate buffer pH 5.0: Acetonitrile: Triethylamine (50:50:0.2, v/v). Detector was set at $\lambda$ = 246.0 nm. (Shengjie Bian et al., 2003)

**RESULTS AND DISCUSSION**

1) Atorvastatin ethyl ester, ((3R,5R)-ethyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoate) is oil at ambient temperature with Chemical Formula: C$_{35}$H$_{39}$FN$_2$O$_5$. Molecular weight of MH$^+$ by mass spectrum is 586. $^1$H NMR in CDCl$_3$:

2) The ester group of the side chain is selectively hydrolyzed by the esterase enzyme in the skin. More than 50% of the penetrated atorvastatin ester was hydrolyzed back into atorvastatin after permeation through the skin.

3) The permeation rate was significantly improved with using atorvastatin ethyl ester vs. atorvastatin.

4) This permeation rate corresponds to: 10.0 mg/day; (10000μg = 10 µg/cm$^2$hr × 24 hr × 20 cm$^2$ ×512.75/246.12).This amount is equivalent to 10 mg/day tablet.

512.75: F.W. of Atorvastatin Calcium 246.12: F.W. of Atorvastatin. The calculation is based on 20 cm$^2$ patch size.

![Fig 1. Atorvastatin ethyl ester](image-url)
CONCLUSION
The advantage of inhibitor of HMG-CoA reductase prodrugs is due to “push and pull” mechanism. The increased lipophilicity pushes the prodrug into the skin. The esterase enzyme in the cytosolic fraction of the skin hydrolyses the Atorvastatin ester into Atorvastatin to a high extent in the permeation process, thus the greatly increased hydrophilicity pulls Atorvastatin molecules out of the skin layer into the blood stream. Controlled delivery of Atorvastatin in a therapeutically effective amount for at least 4 days dosing period can be achieved by applying a single 20cm² transdermal patch.

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