Preparation, characterization and in vitro intestinal absorption of a dry emulsion formulation containing atorvastatin calcium

Yong-Mei Yin a; Fu-De Cui a; Jung Sun Kim b; Min-Koo Choi a; Byung Chul Choi a; Suk-Jae Chung a; Chang-Koo Shim a; Dae-Duk Kim a

a Shenyang Pharmaceutical University, College of Pharmacy, Shenyang, China
b Seoul National University, College of Pharmacy and Research Institute of Pharmaceutical Science, Seoul, South Korea
c Dongseo University, Division of Health Science, Busan, South Korea
d Chung-Ang University, College of Pharmacy, Seoul, South Korea

Online Publication Date: 01 January 2009

To cite this Article Yin, Yong-Mei, Cui, Fu-De, Kim, Jung Sun, Choi, Min-Koo, Choi, Byung Chul, Chung, Suk-Jae, Shim, Chang-Koo and Kim, Dae-Duk(2009)Preparation, characterization and in vitro intestinal absorption of a dry emulsion formulation containing atorvastatin calcium', Drug Delivery, 16:1, 30 — 36

To link to this Article: DOI: 10.1080/10717540802481380
URL: http://dx.doi.org/10.1080/10717540802481380

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.
Preparation, characterization and in vitro intestinal absorption of a dry emulsion formulation containing atorvastatin calcium

Yong-Mei Yin1,3, Fu-De Cui1, Jung Sun Kim2, Min-Koo Choi3, Byung Chul Choi4, Suk-Jae Chung3, Chang-Koo Shim3, and Dae-Duk Kim3

1 College of Pharmacy, Shenyang Pharmaceutical University, Shenyang, China
2 Division of Health Science, Dongseo University, Busan, South Korea
3 College of Pharmacy and Research Institute of Pharmaceutical Science, Seoul National University, Seoul, South Korea
4 College of Pharmacy, Chung-Ang University, Seoul, South Korea

Abstract
A redispersible dry emulsion (DE) formulation of atorvastatin calcium (AC) was developed to enhance the in vitro dissolution of AC, thereby increasing its gastrointestinal absorption. The spray-drying technology was used where Plurol Oleique CC 497 was chosen as the oil phase. Effects of carriers, surfactants, and homogenizers on the characteristics of DE containing AC were systematically investigated. The final formulation consisted of dextrin and Poloxamer 188 as carrier and surfactant, respectively, and was homogenized by a high pressure homogenizer before spray drying. The in vitro release of AC from the optimized DE was significantly higher than that of pure AC powder (76% vs. 30% at 24 hr). The in vitro intestinal absorption of AC from the DE formulation was 0.77 μg/cm² at 2 hr, which was a 2.33-fold increase compared to the pure unformulated AC powder. These results suggest that the oral dry emulsion formulation could improve the intestinal absorption of AC.

Keywords: Atorvastatin calcium; Dry emulsion; Spray drying; Dissolution; Absorption

Introduction
Statin drugs are effective inhibitors of hydroxy-methylglutaryl-coenzyme A reductase (HMG-CoA), the rate-limiting enzyme associated with the de novo synthesis of cholesterol (Witztum 1996). These agents are known to decrease the low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) levels while increasing that of the high-density lipoprotein cholesterol (HDL-C) in plasma, thereby reducing the risk factor for coronary heart diseases (CHD) (Gordon et al. 1989; Pedersen et al. 1998b; Ballantyne et al. 1999). Atorvastatin calcium (AC), a commonly used form of atorvastatin, is insoluble in aqueous solutions of pH 4 and below, while being very slightly soluble in water and in pH 7.4 phosphate buffer. It is classified by the biopharmaceutical classification system (BCS) as a Class 2 drug (Amidon et al. 1995; Kasim et al. 2004; Wu and Benet 2005) which is often reported to have low bioavailability owing to the insufficient dissolution process in the gastrointestinal tract. In fact, the bioavailability of the commercially available tablet formulation of AC, Lipitor, is about 14% (Kearney et al. 1993).

Formulation strategies to improve the oral bioavailability of Class 2 drugs include increasing the dissolution rate (Okonogi et al. 1997) and solubilizing the drug in the gastrointestinal tract (Bhargava and Agrawal 2008). Emulsions have been reported to be...
efficient for improving the dissolution rate and increasing bioavailability of poorly water-soluble drugs (Tarr and Yalkowsky 1989). However, creaming, flocculation, coalescence, and phase separation are often observed in emulsions, giving rise to stability problems (Floyd 1999; Welin-Berger and Bergenstahl 2000).

Dry emulsions (DE) could serve as an alternative to overcome the disadvantages of the conventional emulsions (Molina and Cadorniga 1995; Shively and Thompson 1995). DE formulations are typically prepared from O/W emulsions containing a soluble or an insoluble solid carrier in the aqueous phase by spray drying (Takeuchi et al. 1992a, 1992b; Pedersen et al. 1998a), lyophilization (Corveleyn and Remon 1998a, 1998b), or evaporation (Shively and Dec 1994). Solid carriers include gelatin (Nakamoto et al. 1975), lactose (Pedersen et al. 1998a; Heinzelmann and Franke 1999), maltodextrin (Corveleyn and Remon 1999; Heinzelmann and Franke 1999), mannitol (Molina and Cadorniga 1995), povidone (Shively 1993a, 1993b), and sucrose (Shively and Thompson 1995; Porter et al. 1996).

Herein, we report on the development of a new DE type formulation of atorvastatin calcium (AC) which resulted in enhanced solubility and improved stability. The spray drying technology was utilized for preparation followed by a systematic characterization. Moreover, in vitro dissolution and in vitro intestinal permeability studies were performed to optimize the formulation.

Materials and methods

Materials

Atorvastatin calcium (crystalline form) was purchased from Beijing HuaFeng United Technology Co. Ltd (Beijing, China). Labrafil WL 2609 BS, Labrafil M 2125 CS, Lauroglycol FCC, Labrafac Lipophile WL 1349, Capryol 90, Labrafil M 1944 CS, Pecceol, Lauroglycol, Maisine 35-1 were received as gifts from Gattefossé Co. (Saint Priest Cedex, France) while Plurol Oleique CC 497 was purchased from Gattefossé Co. (Saint Priest Cedex, France). Dextrin from corn, soybean oil, mineral oil, castor oil, isopropyl myristate (IPM), and sesame oil were obtained from Sigma-Aldrich Co. (St. Louis, MO), Lactose monohydrate, Tween 80, and Poloxamer 188, Cremophor EL were purchased from Kanto Chemical Co. Inc (Tokyo, Japan), Tokyo Kasel Kogyo Co. Ltd (Tokyo, Japan), and BASF Co. (Ludwigshafen, Germany), respectively. Acetonitrile and methanol were HPLC grade and supplied from Fisher Scientific Korea Ltd. (Seoul, Korea). Sodium dodecylsulfate (SDS) was purchased from Tokyo Kasel Kogyo Co. Ltd (Tokyo, Japan). All other chemicals and solvents were of analytical grade.

Solubility of AC in oils

The solubility of AC was determined in various oils including Labrafil WL 2609 BS, Labrafil M 2125 CS, Lauroglycol FCC, Labrafac Lipophile WL 1349, Capryol 90, Labrafil M 1944 CS, Pecceol, Lauroglycol, Maisine 35-1, Plurol Oleique CC 497, soy bean oil, mineral oil, and castor oil. Excess AC was added into 1 ml of each oil in the centrifugal tube and mixed (100 rpm) in a shaking incubator (Jeio-Tech, Seoul, Korea) at 25°C for 48 hr. The solution was centrifuged at 13,200 rpm for 5 min to remove the excess AC, and then the concentration of AC in the supernatant was measured by HPLC after appropriate dilution with methanol.

Preparation of dry emulsion (DE)

Based on the result of the solubility study (Table 1, Plurol Oleique CC 497 was selected as the oil phase. The effect of solid carriers (i.e. lactose monohydrate, HPMC, and dextrin) and surfactants (i.e. Tween 80, Cremophor EL, and Poloxamer 188) and homogenizing conditions (i.e. basic homogenizer and high pressure homogenizer) were systematically investigated in mono factorial design (Table 2). An accurately measured amount (430 mg) of AC was dissolved in 25 g Plurol Oleique CC 497 and mixed with 100 ml of water phase containing various surfactants (4%, w/v). The mixture was dispersed by magnetic stirring for 30 min and the resulting coarse emulsion was mixed with 150 ml of solid carrier solution containing 25 g of various solid carrier (Plurol Oleique:carrier = 1:1, w/w) by magnetic stirring for

<table>
<thead>
<tr>
<th>Table 1. Solubility of AC in various oils.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil</td>
</tr>
<tr>
<td>Plurol Oleique CC 497</td>
</tr>
<tr>
<td>Labrafil WL 2609 BS</td>
</tr>
<tr>
<td>Labrafil M 2125 CS</td>
</tr>
<tr>
<td>Labrafil M 1944 CS</td>
</tr>
<tr>
<td>Labrafac Lipophile WL 1349</td>
</tr>
<tr>
<td>Capryol 90</td>
</tr>
<tr>
<td>Lauroglycol FCC</td>
</tr>
<tr>
<td>Pecceol</td>
</tr>
</tbody>
</table>

Each data indicates the mean ± SD of three determinations.
15 min. Further homogenizing either by Ultra-Turrax® T25 Basic Homogenizer or by EmulsiFlex-C5 high pressure homogenizer and spray drying using the Büchi mini spray dryer (Büchi, Switzerland) proceeded under the following conditions: inlet temperature at 120°C, aspiration of 100%, drying air flow at 800 Nl/hr, and feeding rate of the emulsion at 5 ml/min. The resulting dry emulsion powder was stored in well-closed vials at room temperature.

**Characterization of dry emulsion (DE)**

**Droplet size and distribution measurement**

The reconstituted emulsions were obtained from dispersing DE powder into distilled water. The droplet size and distribution of emulsions before spray drying and reconstituted emulsions were determined using a NICOMP 370 Submicron Particle Sizer (Particle Sizing System, Santa Barbara, CA). The SPAN value was employed to express the width of the droplet size distribution which was defined as:

\[
\text{SPAN} = \frac{d(v, 0.9) - d(v, 0.1)}{d(v, 0.5)}
\]

where \(d(v, 0.1)\), \(d(v, 0.5)\), and \(d(v, 0.9)\) were 10%, 50%, and 90% volumetric diameters.

**Scanning electron microscopy (SEM)**

The surface morphology of the DE powder was observed by scanning electron microscopy (JSM-5310LV, JEOL, Tokyo, Japan) at an accelerating voltage of 20 KV. Samples were mounted on a double-faced adhesive tape and sputtered with platinum for 250 sec before scanning electron microscopy.

**Powder X-ray diffraction (pXRD)**

DE powder was observed for X-ray pattern using a D5005 powder X-ray diffractometer (Bruker, Karlsruhe, Germany) with CuK\(\alpha\) radiation (\(\lambda = 1.54,056 \ \text{Å}\)) generated from a copper source operating at a voltage of 40 KV and a current of 40 mA. The test samples were packed into 0.5 mm deep graphite sample holders. The samples were scanned over the range of 3–50° 2\(\theta\) at a scan rate of 5°/min.

**Differential scanning calorimetry**

Differential scanning calorimetry (DSC) measurements were carried out with a DSC-Q1000 modulated differential scanning calorimeter (TA Instruments Inc., UK). About 3–5 mg DE samples were placed in hermetic aluminum pans with lid and clamp sealed. The samples were heated from 30 to 400°C at a rate of 10°C/min. An empty aluminum pan was used as a reference.

**In vitro dissolution test**

In vitro dissolution tests were performed using a dissolution tester (Electrolab, Bombay, India) following the USP paddle method. AC powder or reconstituted DEs equivalent to 10 mg of AC was placed in the dialysis bag (Spectra/Por® membranes, MWCO: 12000, Spectrum Medical Industries Inc. TX) located in dissolution media (900 ml of distilled water) containing 0.2% (w/v) of sodium dodecylsulfate (SDS) at 37 ± 0.5°C and was stirred with a rotating paddle at 50 rpm. Aliquots of dissolution media (5 ml) were withdrawn at predetermined time intervals for 24 hr, and were replaced with equal volumes of the fresh media.

**In vitro intestinal absorption study using the Ussing chamber**

Male Sprague-Dawley rats (250–300 g, Dae-Han Biolink, Daejeon, Korea) were used to perform the in vitro permeation study. All rats were provided with food (SamYang Company, Seoul, Korea) and water ad libitum, and maintained in a light-controlled room (light: 07:00–19:00, dark: 19:00–07:00) kept at a temperature of 22 ± 2°C and a relative humidity of 55 ± 5% (Animal Center for Pharmaceutical Research, College of Pharmacy, Seoul National University, Seoul, Korea). The experimental protocols involving animal study were approved by the Animal Care and Use Committee of the College of Pharmacy, Seoul National University, according to the National Institutes of Health Guidelines (NIH publication #85-23, revised in 1985).

Animals were fasted for 2 days prior to the experiment and the intestinal tissue was excised after

---

**Table 2.** Formulation of dry emulsion of atorvastatin calcium.

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>Carrier</th>
<th>Surfactant</th>
<th>Homogenizing condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx1</td>
<td>Lactose monohydrate</td>
<td>Tween 80</td>
<td>BH*</td>
</tr>
<tr>
<td>Rx2</td>
<td>HPMC</td>
<td>Tween 80</td>
<td>BH</td>
</tr>
<tr>
<td>Rx3</td>
<td>Dextrin</td>
<td>Tween 80</td>
<td>BH</td>
</tr>
<tr>
<td>Rx4</td>
<td>Dextrin</td>
<td>Cremophor EL</td>
<td>BH</td>
</tr>
<tr>
<td>Rx5</td>
<td>Dextrin</td>
<td>Poloxamer 188</td>
<td>BH</td>
</tr>
<tr>
<td>Rx6</td>
<td>Dextrin</td>
<td>Poloxamer 188</td>
<td>HPH*</td>
</tr>
</tbody>
</table>

BH*: Ultra-Turrax® T25 Basic Homogenizer at 24,000 rpm for 5 min.
HPH*: EmulsiFlex-C5 High pressure homogenizer at 10,000 psi for 3 times.
being humanely sacrificed by ketamine. The freshly excised small intestine was immediately rinsed twice with ice-cold phosphate buffered saline (PBS, pH 7.4) and placed in ice-cold PBS under continuous oxygenation with O$_2$/CO$_2$ (95%/5%) bubbling. The specimen was cut open along the mesenteric border with blunt-end scissors and divided into 1 cm segments. The resulting intestinal sheets were mounted as flat sheets between two acrylic half-cells and they were joined to form the complete Ussing chamber. The tissue pieces were bathed on both sides with 1 ml of PBS (pH 7.4) at 37°C controlled by a water-jacketed reservoir. The PBS was also bubbled with an O$_2$/CO$_2$ (95%/5%) mixture gas to circulate fluid in each chamber at 37°C. After 30 min equilibration, 1 ml of the AC suspension or reconstituted dry emulsion containing equal amount of AC (1.72 mg as AC) was infused into the mucosal side of the chamber while 1 ml of fresh PBS (37°C) was added in the serosal side. At predetermined time intervals, 0.5 ml of samples were withdrawn from the serosal side and the same volume of fresh PBS at 37°C was refilled immediately.

### Physical stability of dry emulsion

The physical stability of DE powder in well-sealed containers was tested at 40°C with 75% relative humidity in a climatic chamber (EYELA, Tokyo, Japan) and ambient temperature, respectively. The X-ray diffraction and DSC of DE powder were examined and its morphology observed by SEM for 3 months.

### HPLC analysis of AC

The concentrations of AC were quantified by HPLC with a UV detector, as previously described (Shen and Zhong 2006). HPLC system consisted of a pump (Waters 515), an automatic injector (Waters 717 plus autosampler), and a UV detector set at 248 nm (Waters 2487, Waters Corporation, Milford, MA). An analytical column (LiChrospher® 100 RP-18, 5 µm, Darmstadt, Germany) was eluted with a mobile phase consisting of acetonitrile and 0.05% acetic acid solution (65:35, v/v) at a flow rate of 1.0 ml/min.

### Statistical analysis

A value of $p$ less than 0.05 was considered to be statistically significant when $t$-test was performed between the two means for the unpaired data. All data are expressed as the mean ± standard deviation.

### Results and discussions

#### Formulation of dry emulsion (DE)

To select a suitable oil phase for the DE formulation, the solubility of AC in various oils was determined, as shown in Table 1. AC has a solubility ranging from 0.022 mg/ml in mineral oil, 3.21 mg/ml in Labrafil WL 2609 BS, to 16.24 mg/ml in Plurol Oleique CC497. Based on the solubility study, Plurol Oleique CC497 was chosen as the oil phase and the formulation was designed as shown in Table 2.

All freeze-dried DE formulations containing AC could be reconstituted by dispersing them in distilled water. Droplet size of each formulation both in liquid emulsion before spray drying and in reconstituted emulsion after spray drying showed a mono-modal distribution (data not shown). The mean droplet size and SPAN values of each formulation listed in Table 3 shows that the droplet size and distribution were affected by carriers, surfactants, and homogenizing conditions. The mean droplet size of Rx3, where dextrin was used as the carrier, was relatively smaller than that of Rx1 and Rx2. This may be due to lactose monohydrate's sensitivity to moisture causing coalescence after spray drying.

HPMC seemed to increase the viscosity of the emulsion before spray drying, thereby increasing the droplet size during the spray drying process. Compared to Tween 80 (Rx3) and Cremophore EL (Rx4), Poloxamer 188 (Rx5) resulted in the increase of the mean droplet size of DE, although the reason is not clear from this study. However, homogenizing conditions seemed to exert the most significant effect on the mean droplet size, as shown in Rx5 and Rx6 (Table 3). The use of a high pressure homogenizer as in the case for Rx6 resulted in the smallest droplet size. Rx6 could therefore show better gastrointestinal absorption of the drug compared

| Table 3. Droplet size and distribution of the dry emulsions. |
|-------------|------------|-------------|------------|----------|
|              | Liquid emulsion before spray drying | Reconstituted emulsion after spray drying |
|              | $d(v, 0.5)$ (µm) | SPAN        | $d(v, 0.5)$ (µm) | SPAN     |
| Rx1          | 0.69 ± 0.04 | 0.86 ± 0.02 | 1.30 ± 0.05 | 0.74 ± 0.03 |
| Rx2          | 0.65 ± 0.01 | 0.59 ± 0.01 | 1.21 ± 0.03 | 0.78 ± 0.04 |
| Rx3          | 0.50 ± 0.01 | 0.64 ± 0.02 | 0.94 ± 0.03 | 0.75 ± 0.03 |
| Rx4          | 0.55 ± 0.02 | 0.68 ± 0.01 | 1.17 ± 0.04 | 0.59 ± 0.01 |
| Rx5          | 0.69 ± 0.03 | 0.81 ± 0.03 | 1.21 ± 0.05 | 0.75 ± 0.02 |
| Rx6          | 0.45 ± 0.01 | 0.59 ± 0.01 | 0.72 ± 0.02 | 0.68 ± 0.01 |

The values are average values of three determinations (mean ± SD).
to others since reports have shown that the reduction of droplet size of emulsions enhances the gastrointestinal absorption of poorly water-soluble drugs (Tarr and Yalkowsky 1989).

Scanning electron micrographs of the AC powder and freshly prepared DE formulations containing AC are shown in Figure 1. As expected from the results of the droplet size study, the morphology of Rx1 and Rx2 powder showed agglomeration during the preparation of the SEM samples due to lactose monohydrate and HPMC, respectively. On the other hand, Rx3 and Rx4 powder showed well separated particles, although with wrinkles and deep dents on the surface, which are probably due to the liquid surfactants Tween 80 and Cremophor EL that can induce the shrinkage of particles during the spray drying process. Rx5 and Rx6 powder were well separated spherical particles with smooth surfaces, which was consistent with the report by Elversson and Millqvist-Fureby (2006). Thus, Rx6 formulation where dextrin and Poloxamer 188 were used as carrier and surfactant, respectively, was chosen for further evaluation studies, and compared with the Rx2 and Rx5 formulations.

**Powder X-ray diffraction (pXRD)**

Powder X-ray diffraction diffractograms of pure AC powder, Rx2, Rx5, and Rx6 formulations are shown in Figure 2. Distinct peaks found in the diffractogram indicate that the AC powder is present in crystalline form. The spectrum of Poloxamer 188 also showed a distinct peak pattern. In the Rx5 and Rx6 formulations, Poloxamer 188 still seemed to remain, while the diffraction peaks corresponding to AC crystalline disappeared, indicating that AC was in the amorphous state.

**Differential scanning calorimetry (DSC)**

DSC thermograms obtained from AC powder, Rx2, Rx5, and Rx6 formulations are shown in Figure 3. An endothermic peak near 171°C, which indicates the melting point of the AC powder, disappeared in the thermograms of the formulations. Thus, no crystalline form of AC seems to be present in those formulations, which is consistent with the data from the X-ray diffraction studies.

**In vitro dissolution test**

The dissolution profiles of the Rx6 formulation and pure AC powder into 0.2% SDS solution are shown in Figure 4. Release of AC from the Rx6 formulation was significantly faster than that from the pure AC powder. Also, the amount of AC released for 24 hr was higher from Rx6 than that of the AC powder (i.e. 76% vs. 30%, respectively). Initial burst release was not observed for DE, indicating that AC was dispersed in the oil phase and was not crystallized on the surface even after spray-drying, as confirmed from the results of the X-ray diffraction and DSC study.

**In vitro intestinal absorption study by Ussing chamber**

The intestinal absorption of class 2 drugs could be increased by enhancing the dissolution rate, thereby increasing the bioavailability (Grove et al. 2006; Ahmed and Aboul-Einien 2007). Based on previous reports, the feasibility of the DE formulation as a drug delivery system which can enhance the intestinal absorption...
of AC was investigated in vitro by using the Ussing chamber. As shown in Figure 5, the amount of AC permeated through the rat intestine from the Rx6 formulation was significantly higher than that from pure AC powder at 2 h (i.e. 0.77 mg/cm² vs. 0.33 mg/cm², p < 0.05). As mentioned above, the Rx6 formulation consisted of dextrin and Poloxamer 188 as carrier and surfactant, respectively, and was homogenized by high pressure homogenizer before spray drying. Well homogenized emulsion with smaller droplet size and narrow distribution was obtained through the high pressure homogenizer, which may be the reason for improved permeation of AC in the Rx6 formulation (Itoh and Matsui 2002).

**Physical stability of dry emulsion**

Rx5' and Rx6' in Figure 1 are SEM images for Rx5 and Rx6 formulations after being stored at 40°C with 75% relative humidity for 3 months, respectively. The results showed that the outer structures of Rx5 and Rx6 formulations remained unchanged after storage. That is, well-separated spherical particles with smooth surface were observed in the formulations. The X-ray diffraction and DSC results also support that the inner properties of the dry emulsion of the Rx5 and Rx6 formulations did not significantly change at the above-mentioned storage conditions. However, when Tween 80 was used as surfactant and dextrin as carrier (Rx3), the dry emulsion powder melted into a sticky liquid under the same storage conditions (data not shown). Even though the dry emulsion consisting of Tween 80 and HPMC (Rx2) kept the solid form after storage in the above condition for 3 months, the SEM results showed that the particles were sticky together and there was no clear boundary between the particles (data not shown).

**Conclusion**

In the present study, DE containing AC was successfully prepared by the spray-drying method. Carriers and surfactants affected the outer morphology and stability of the DE formulations when Plurol Oleique CC 497 was used as an oil phase. At the same time, the homogenizing method influenced the droplet size and distribution of the emulsion, which seemed to be the most critical factor affecting the in vitro dissolution and intestinal absorption of AC from the DE. In conclusion, dry
emulsion formulation of AC could be a feasible approach for enhancing the dissolution rate, thereby increasing the bioavailability of AC after oral administration.

Acknowledgment

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References


Tarr BD, Yalkowsky SH (1989). Enhancement intestinal absorption of cyclosporine in rats through the reduction of emulsion droplet size. Pharm. Res. 6, 40–43.

