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Research Paper

Positively-charged microemulsion for improving the oral bioavailability of alendronate: in-vitro and in-vivo assessment

Jian Meng[a] and Liandong Hu[b]

[a]Shanghai Institute of Materia Medica, Chinese Academy of Science, Shanghai and [b]School of Pharmacy, Hebei University, Baoding, Hebei Province, China

Abstract

Objectives Alendronate is a poorly absorbed bisphosphonate with an oral bioavailability of 0.7%. In this study, a positively-charged microemulsion was prepared with the aim of improving the bioavailability of alendronate.

Methods The positively-charged microemulsion was evaluated for physical stability, cellular uptake and permeability enhancement on Caco-2 monolayers. The bioavailability of alendronate from the microemulsion was compared with the commercially available tablet (Fosmax) for beagle dogs.

Key findings The 2.0, 0.4 and 0.2% positively-charged microemulsion, stable for 4 h after preparation, promoted alendronate transport across the Caco-2 cells by a factor of 194, 146,and 45.1, respectively, compared with the alendronate solution, though no significant cellular uptake enhancement of alendronate was observed. The permeability enhancement was parallel to the reduction in transendothelial electrical resistance, which indicated the microemulsion modulated the tight junctions and widened the paracellular pathway. In-vivo results showed that the microemulsion gave the highest alendronate plasma concentration at 502 ng/ml (C_{max}) after 0.563 h (T_{max}), while tablets gave a C_{max} of 152 ng/ml after 0.750 h (T_{max}). Furthermore, the $AUC_{0-\infty}$ of alendronate from the microemulsion increased by 2.82-fold when compared with the tablets.

Conclusions Based on the results, the oral bioavailability of alendronate could be significantly improved by the positively-charged microemulsion, which opened the tight junctions and thus increased absorption through the paracellular route.

Keywords alendronate; oral bioavailability; paracellular route; positively-charged microemulsion

Introduction

The bisphosphonates are a class of drug considered as stable analogues of pyrophosphate (P-O-P), which are characterized pharmacologically by their ability to inhibit bone resorption.[1] Alendronate (4-amino-1-hydroxybutylidine-1l-bisphosphonate), marketed in 49 countries, is one of the most potent bisphosphonates used for the treatment of osteoporosis and Paget's disease.[2] The drug is clinically administrated orally, but the oral bioavailability of alendronate in the fasted state is approximately 0.7%, with food substantially reducing its bioavailability.[2] The incomplete absorption of alendronate has been attributed to its very high polarity with an octanol/buffer partition coefficient of 0.0017, which prevents transcellular transport across the intestinal membrane.[3] Alendronate is completely ionized and negatively charged at physiological pH (6–8) in the small intestine, which further hampers paracellular transport. Moreover, the unabsorbed alendronate in the intestine causes oesophageal irritation and ulceration.[4]

Many research efforts have been made to overcome the abovementioned difficulties, as well as to increase therapeutic efficacy and to decrease the side effects.[5–8] However, until now no absorption and permeation study proving enhancement of alendronate absorption has been reported.

Lipid microemulsions can solubilize lipophilic drugs and improve their dissolution, and they can also stabilize hydrophilic drugs and protect them from chemical and enzymatic hydrolysis.[9,10] In the last few decades, lipid microemulsions have drawn much attention in

Correspondence: Jian Meng, Shanghai Institute of Materia Medica, Chinese Academy of Science, 646 Songtao Road, Shanghai 201203, China.
E-mail: goodwill_123@163.com

Table 1 Materials and their concentration used for preparing the micelle formulation and microemulsions

Component	Description	Micelle	Negatively-charged microemulsion (%)	Positively-charged microemulsion (%)
Labrasol	Surfactant	9.60	9.60	9.60
Plurol oleique	Cosurfactant	6.40	6.40	6.40
Labrafac CC	Oily phase		4.00	3.70
Oleylamine	Additive		–	0.30
Water	Aqueous phase	84.0	80.0	80.0
Total		100	100	100

terms of their ability to improve the oral bioavailability of drugs.[10,11] Moreover, a study by Sha *et al*.[12] revealed that microemulsions opened tight junctions and enhanced permeability via the paracellular pathway.

Based on the abovementioned considerations, we thought it may be plausible to improve the bioavailability of alendronate by the use of a microemulsion. Thus, in this work, a positively-charged microemulsion was developed in an attempt to increase paracellular transport and bioavailability of alendronate. The physical stability of the microemulsion was investigated, and the cellular uptake and permeability enhancement of alendronate by the microemulsion were evaluated on Caco-2 cells in comparison with a micelle carrier and a negatively-charged microemulsion. The bioavailability and pharmacokinetics of alendronate in the positively-charged microemulsion were assessed in beagle dogs and compared with a commercially available tablet (Fosmax).

Materials and Methods

Materials

Alendronate sodium was obtained from Hanzhong Medicine Chemicals Co. Ltd. (Hanzhong, China). Caprylocaproyl macrogolglycerides (Labrasol), medium-chain triglyceride (Labrafac CC) and polyglyceryl oleate (Plurol Oleique) were kindly provided by Gattefösse (Lyon, France). Oleylamine was purchased from Fluka Production GmbH (Buchs, Switzerland). Caco-2 cells were obtained from the American Type Culture Collection (Manassas, VA, USA). Tablets containing alendronate sodium (Fosmax 70 mg) were purchased from the local market. Other chemicals and solvents were of pure analytical grade or of higher purity.

Preparation of the microemulsions and micelles

The microemulsions and micelles were prepared based on the microemulsion field in the pseudoternary phase diagrams (data not shown). Briefly, the positively-charged microemulsion was prepared by adding a mixture of surfactant (i.e. Labrasol), cosurfactant (i.e. Plurol Oleique) and oleylamine to the oily phase of Labrafac CC in a vial. The vial was capped, placed into a water bath at 50°C and stirred gently until a uniform solution was formed. The aqueous phase was added drop by drop while stirring to form a microemulsion. This was then cooled to room temperature (~25°). The negatively-charged microemulsion was prepared in a similar way to the positively-charged microemulsion, except that oleylamine was not added and the micelles were prepared just by adding aqueous phase to the mixture of the surfactant and cosurfactant. All formulations were stored at room temperature, and the alendronate sodium stock solution was added just before in-vitro and in-vivo assessment. The components of the microemulsions and micelle formulations are listed in Table 1.

Physical stability of microemulsions

Particle size and zeta potential of the microemulsions were measured using a Nicomp 380 specification particle size analyser (Santa Barbara, CA, USA) to assess the effects of dilution and alendronate addition on the physical stability of the microemulsions. The particle size was measured by photon correlation spectroscopy. Zeta potential determinations were based on the electrophoretic mobility of the microemulsions.

Caco-2 cell culture

Caco-2 cells were cultured as described previously.[13] Briefly, cells were cultured at 37°C in a modified Minimum Essential Medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 1% nonessential amino acids, 10 mM HEPES, 100 U/ml penicillin G, and 100 μg/ml streptomycin in an atmosphere of 5% CO_2. Cells were passaged to reach 80 to 90% confluency and plated at a density of 80 000 cells/ml in T flasks. Caco-2 cells (passage numbers: 40–50) were seeded at a density of 80 000 cells/ml on a polycarbonate Transwell membrane (PI1250, Millipore, Billerica, MA, USA). The medium added to the apical and basolateral compartments was changed the day after seeding and every other day thereafter. Cell monolayers with a transendothelial electrical resistance (TEER) exceeding 300 $\Omega \times cm^2$ were used for uptake or transport experiments 21 days after seeding.

Cellular uptake experiments

Uptake experiments were initiated by adding 1 mM alendronate solution, the microemulsions or micelles containing 1 mM alendronate to both the apical and the basolateral sides of Caco-2 cells. After incubation for 2 h at 37°C, the solution, microemulsions or micelles was discarded and the cells were washed with Hank's buffered salt solution three times. The Caco-2 cells were frozen and thawed three times. The cellular uptake of alendronate was then quantified with a high performance liquid chromatography (HPLC) fluorimetric detection (FD) method after precolumn derivatization with *o*-phthalaldehyde.[14]

Transport experiments

Transport studies were performed at 37°C on the filter-grown Caco-2 monolayers. The microemulsions or the micelles con-

taining 1 mM alendronate (400 μl) were added to the apical side of the cells. Blank Hank's buffered salt solution (600 μl) was added to the basolateral side. Samples were removed from the basolateral side at predetermined intervals. The concentration of alendronate was determined using an HPLC-FD method and the resistance across the cell monolayers was monitored during the transport experiments.[13] The apparent permeability coefficients (P_{app}) of alendronate were calculated according to the following equation:

$$p_{app} = \frac{dQ}{dt}\left(\frac{1}{AC_0}\right)$$

where dQ/dt is the permeability rate, C_0 is the initial concentration in the donor compartment, and A is the surface area of the monolayer (i.e. 0.6 cm^2).

Cell recovery

At the end of the experiment, after 180 min, the micelles or microemulsions were replaced by the growth medium. Cells were incubated further for 48 h. TEER values were measured and recorded as the post-experiment TEER values to evaluate the recovery of the cell.

Bioavailability in beagle dogs

Male beagle dogs (10.0–12.5 kg) were obtained from Shanghai SLRC Laboratory Animal Co. Ltd. (Shanghai, China). The Administrative Committee on Animal Research at the Shanghai Institute of Materia Medica, Chinese Academy of Science approved all the protocols for the animal experiments, which were performed in compliance with the Guiding Principles for the Care and Use of Laboratory Animals, Shanghai Institute of Materia Medica, China.

The bioavailability of the positively-charged microemulsion containing alendronate and the tablet (Fosmax 70 mg) were compared in beagle dogs. Both formulations contained 70 mg alendronate sodium. The composition of the positively-charged microemulsion is given in Table 1 and it was diluted with alendronate sodium stock solution before dosing. The six male beagle dogs were divided into two groups and were orally administrated one of the formulations followed by a 14-day washout period before employing the dose for the other formulation. Before the experiment, the dogs were starved for 12 h, but water was freely available. During the experimental period, each dog was placed in an upright position in a restrainer stand. The legs were shaven and a cephalic vein was cannulated using an 18-gauge cannula. Blood samples (5 ml) were withdrawn into heparinized Vacutainer tubes before and at 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0 and 8.0 h after oral administration of the microemulsion or the tablets. The tubes were centrifuged for 10 min at 2000*g* and plasma was separated and kept frozen at −20°C until analysis.

Alendronate in plasma was analysed using an HPLC fluorimetric detection method after precolumn derivatization with *o*-phthalaldehyde.[14] The concentrations of alendronate were determined from the calibration curve of peak areas, which was obtained by analysis of drug-free plasma samples mixed with different amounts of alendronate ranging from 5.00 to 600 ng/ml. The relevant pharmacokinetic parameters, C_{max}, T_{max}, $AUC_{0\text{-}8}$, $AUC_{0\text{-}\infty}$, and $t^1/_2$, were calculated based on the reported method of Gibaldi and Perrier.[15]

Statistical analysis

All results were presented as mean ± SD Statistical differences were determined using a nonparametric comparison test, Kruskal-Wallis *H*-test.[16] The analyses were conducted by SPSS for windows (Release 12.0, SPSS Inc., USA.). A value of $P < 0.05$ denotes a statistically significant difference for all statistical tests used.

Results

Stability of microemulsions

The particle size and zeta potential of newly prepared negatively-charged or positively-charged microemulsions are listed in Table 2. The results showed that dilution had only a slight effect on the particle size and zeta potential of the microemulsions, indicating that the stability of the microemulsions was not affected by dilution in the range tested. The particle size and zeta potential of the blank positively-charged microemulsion and negatively-charged microemulsion were not changed significantly over 24 h (Figure 1). However, the increase in particle size and decrease in zeta potential were observed after 4 h preparation in the alendronate negatively-charged microemulsion and the alendronate positively-charged microemulsion (Figure 1). These results indicated that the physical stability of the microemulsions could be affected by electrostatic interaction between the ionized amino group and phosphinic groups of alendronate with the negatively-charged microemulsion and the positively-charged microemulsion. Therefore, the alendronate microemulsions used in these studies were newly prepared and used within 4 h of preparation.

Table 2 Particle size and zeta potential of the newly prepared microemulsions diluted

Microemulsion or micelle content (%)	Negatively-charged microemulsion		Positively-charged microemulsion	
	Particle size (nm)	Zeta potential (mv)	Particle size (nm)	Zeta potential (mv)
10	22.1 ± 4.7	−15.6 ± 3.3	30.6 ± 6.1	8.5 ± 1.2
2.0	23.5 ± 3.6	−22.3 ± 4.7	34.1 ± 3.5	12.1 ± 4.5
0.4	24.8 ± 6.4	−23.4 ± 5.2	35.7 ± 6.7	14.4 ± 3.6
0.2	26.5 ± 8.3	−23.3 ± 4.8	34.2 ± 5.1	16.2 ± 5.1

Values are mean ± SD, $n = 3$.

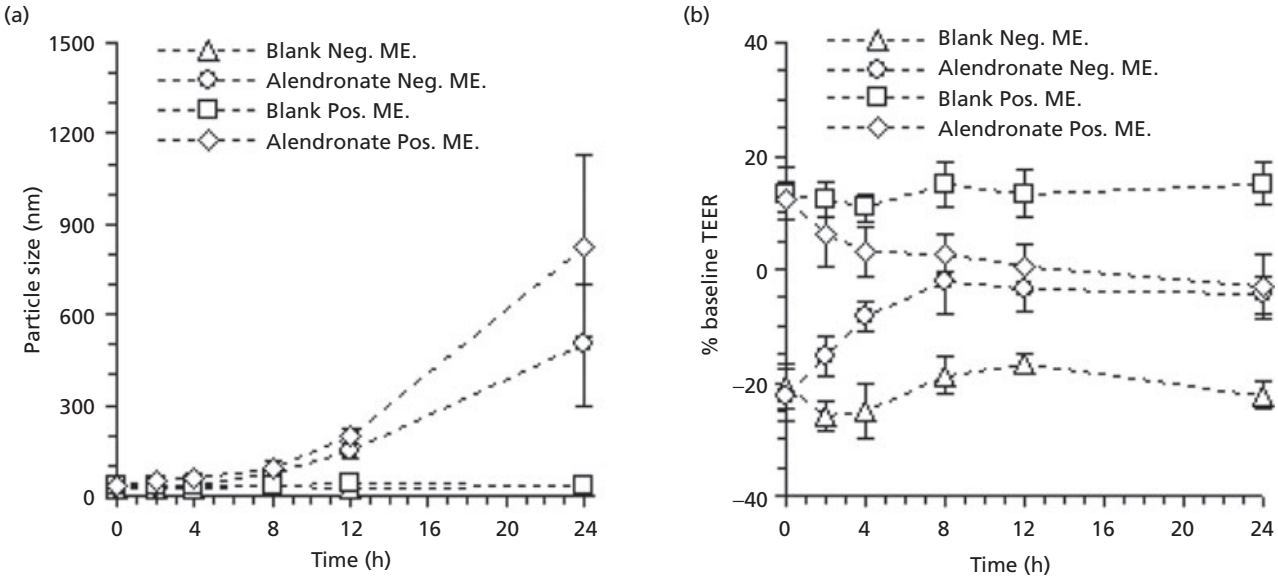

Figure 1 Particle size (a) and zeta potential (b) of the 2% microemulsions over 24 h. Values are mean ± SD, $n = 3$. Neg. ME, negatively-charged microemulsion; Pos. ME, positively-charged microemulsion.

Table 3 Effects of the micelles, negatively-charged microemulsions and positively-charged microemulsion on the Caco-2 cellular uptake and transport of 1 mM alendronate

Formulation		Cellular uptake (μmol/cm^2)	Transport ($P_{app} \times 10^7$ cm/s)
Solution		0.249 ± 0.036	0.112 ± 0.021
Micelles	0.2%	0.246 ± 0.031	0.235 ± 0.011 (2.10)*
	0.4%	0.248 ± 0.046	0.134 ± 0.011 (1.20)
	2.0%	0.272 ± 0.047	0.125 ± 0.003 (1.12)
Negatively-charged microemulsion	0.2%	0.241 ± 0.025	1.36 ± 0.091 (12.1)*
	0.4%	0.255 ± 0.036	0.224 ± 0.011 (2.00)*
	2.0%	0.242 ± 0.042	0.162 ± 0.006 (1.45)*
Positively-charged microemulsion	0.2%	0.298 ± 0.028	21.7 ± 3.22 (194)*,[a]
	0.4%	0.262 ± 0.028	16.3 ± 2.92 (146)*,[a]
	2.0%	0.298 ± 0.015	5.04 ± 0.525 (45.1)*,[a]

The number in the bracket indicates the enhancement ratios versus solution (1 mM alendronate). $n = 3$. *$P < 0.05$: significantly different from the solution. [a]$P < 0.05$: the positively-charged microemulsion significantly different from the negatively charged.

Effect of microemulsions and micelles on alendronate uptake by Caco-2 cells

The amount of alendronate taken up by the Caco-2 cells was 0.249 μmol/cm^2 when the cells were treated with 1 mM alendronate for 2 h (Table 3). The uptake corresponded to only 0.015% of total alendronate. Such a low cellular uptake could be attributed to the very low octanol/buffer partition coefficient of alendronate, which makes alendronate transport in the Caco-2 monolayer via the paracellular way.[3] Ion-pairing complex between alendronate and the ionized lipophilic constituents might have formed through electrostatic interaction, which might have promoted transport of alendronate. However, the microemulsions and micelles failed to increase the cellular uptake of alendronate. These results indicated that microemulsions and micelles could not promote alendronate transport by the transcellular pathway. This might be attributed to the fact that micelles and microemulsions could not be absorbed by the intestinal epithelial cells.[17]

Effect of microemulsions and micelles on alendronate transport and transendothelial electrical resistance across Caco-2 cell monolayers

The effect of micelles and microemulsions on the alendronate transport across Caco-2 cell monolayers was evaluated relative to the 1 mM alendronate solution (Table 3). The transport of 1 mM alendronate through the Caco-2 cells was very low: the P_{app} obtained for 1 mM alendronate from the apical to the basolateral direction was $(0.112 \pm 0.021) \times 10^{-7}$ cm/s ($n = 9$). Such a low permeability coefficient indicated alendronate transport via the paracellular pathway, as for other bisphosphonates.[18,19] All the micelles and microemulsions promoted the transport of alendronate with a dilution-dependence. The 2.0, 0.4 and 0.2% micelle solutions increased the transport of 1 mM alendronate by factors of 2.10, 1.20, and 1.12, respectively. When Caco-2 cells were treated with 2.0, 0.4 and 0.2 negatively-charged microemulsion, the transport speed of

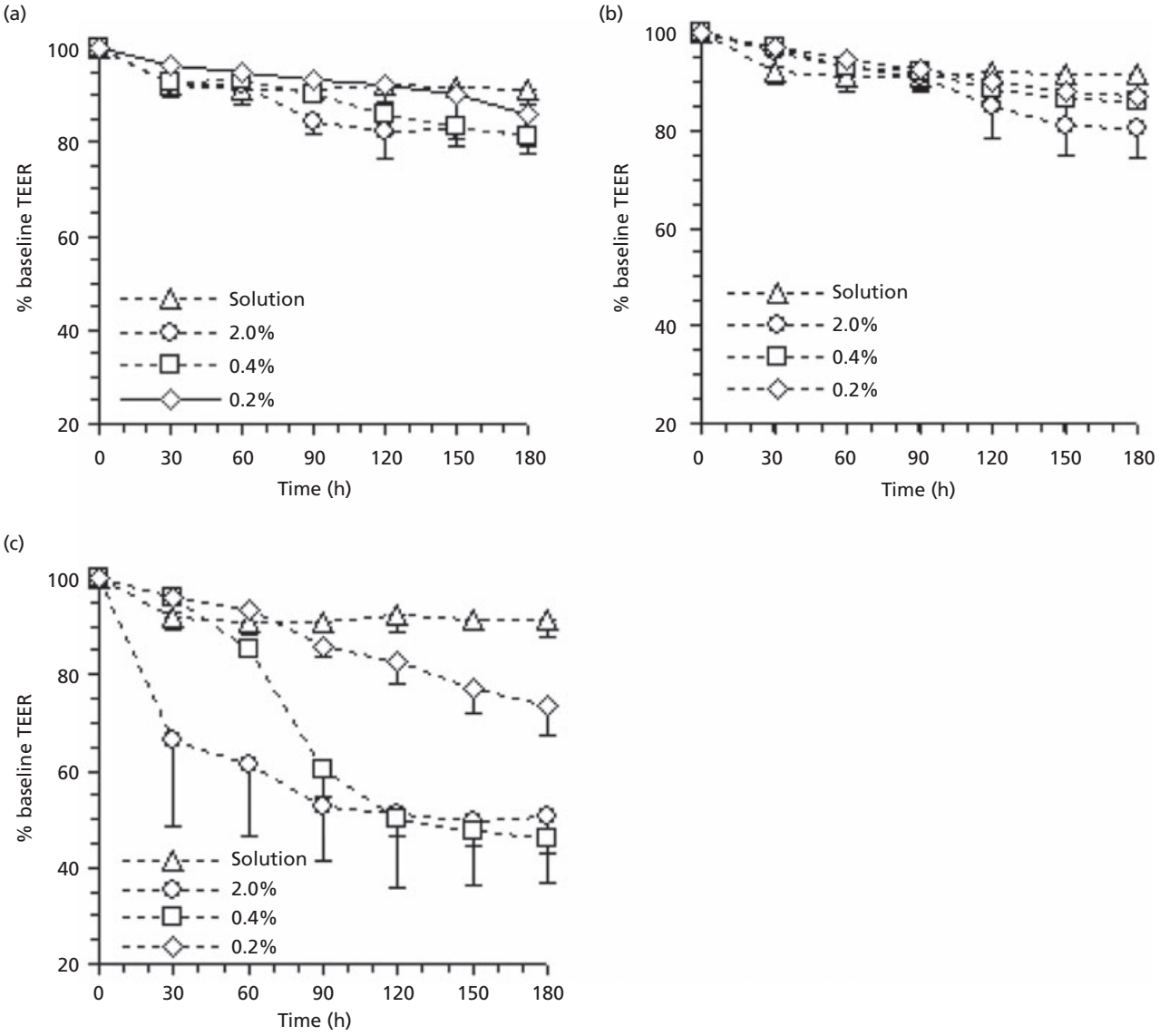

Figure 2 Effect of various concentrations of micelles (a), negatively-charged (b) or positively-charged (c) microemulsions on the Caco-2 monolayer transepithelial resistance. $n = 3$. TEER, transepithelial resistance.

alendronate was increased by 12.1-, 2.00-, and 1.45-times, respectively. The transport of alendronate by the positively-charged microemulsions was increased even more, by 194-, 146-, and 45.1-times when it was incubated with the 2.0, 0.4 and 0.2% microemulsions ($n = 3$).

The positively-charged microemulsions also had the strongest effect on the TEER across the Caco-2 cells (Figure 2). When treated with the 2.0, 0.4 or 0.2 microemulsion for 180 min, the TEER across the Caco-2 cells was reduced to 50.4, 46.2, and 73.3% from the initial value, respectively. However, the negatively-charged microemulsion and micelles showed a slight change in TEER. Treatment with the negatively-charged microemulsion or micelle solution diluted 50-times, caused only a 9.5 and 10.8% drop in TEER at 180 min, respectively, compared with the control (1 mM alendronate).

Recovery of Caco-2 monolayers exposed to microemulsions

To determine whether the effect of the formulations on the TEER of Caco-2 cell monolayers was reversible, apical-contained formulations were replaced with fresh cell culture medium after 3-h treatment, and the TEER was monitored for an additional 48 h. Results are presented as a percentage of the initial value (Figure 3). After an additional 48 h incubation, the TEER of the monolayers treated with the micelle solution or the negatively-charged microemulsion was consistent with those before the transport experiment, indicating that

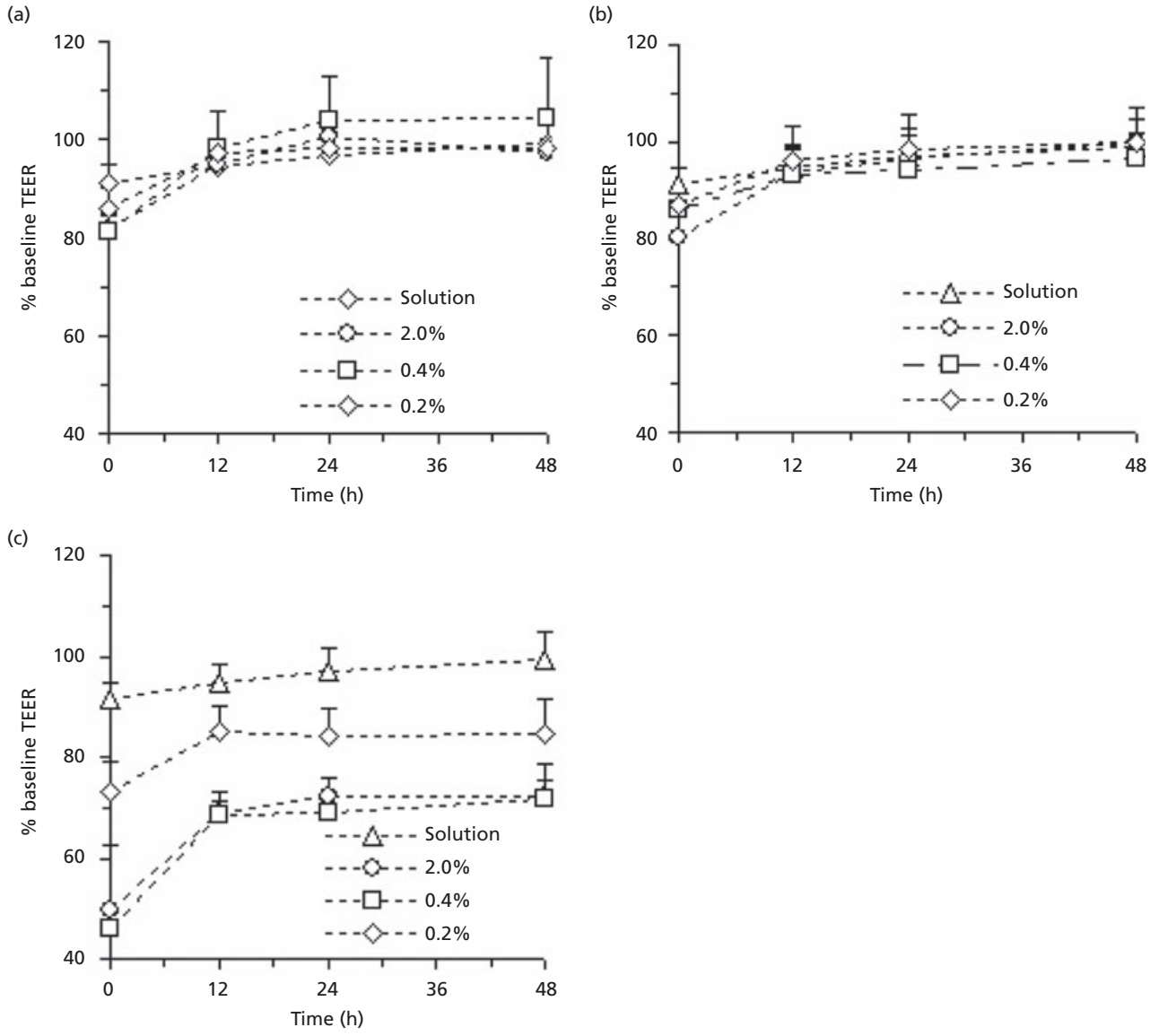

Figure 3 Recovery of Caco-2 monolayer barrier properties after removal of various concentration micelles (a), negatively-charged (b) or positively-charged (c) microemulsions. After 3 h treatment with the micelles or microemulsions in different dilutions, the medium was changed. $n = 3$. TEER, transepithelial resistance.

the monolayers had fully recovered. However, cells treated with the positively-charged microemulsion were only partly recovered. The TEER values of the monolayers after 48 h were 72.0, 71.5 and 84.7% relative to the values before the transport experiment.

Oral bioavailability

The plasma profiles of alendronate in beagle dogs following the oral administration of the positively-charged microemulsion containing alendronate or alendronate tablets (Fosmax) were compared. The plasma alendronate concentration versus time profiles are shown in Figure 4, and the pharmacokinetic parameters are given in Table 4. The results obtained revealed that the absorption of alendronate from the microemulsion resulted in a 2.82-fold increase in bioavailability (as indicated by AUC) compared with the tablets. No significant difference was observed between the two preparations for the T_{max} values and $t^{1}/_{2}$.

Discussion

As with other bisphosphonates, alendronate is poorly absorbed and the paracellular pathway is its main permeation route across the intestinal lumen into the bloodstream.[3] The low permeability of paracellularly transported drugs are a consequence of the small surface area of intercellular spaces and tight junctions between the epithelial cells.[20] Therefore, our strategy for improving alendronate oral bioavailability was to modulate the tight junctions and promote absorption via the paracellular pathway. A number of absorption enhanc-

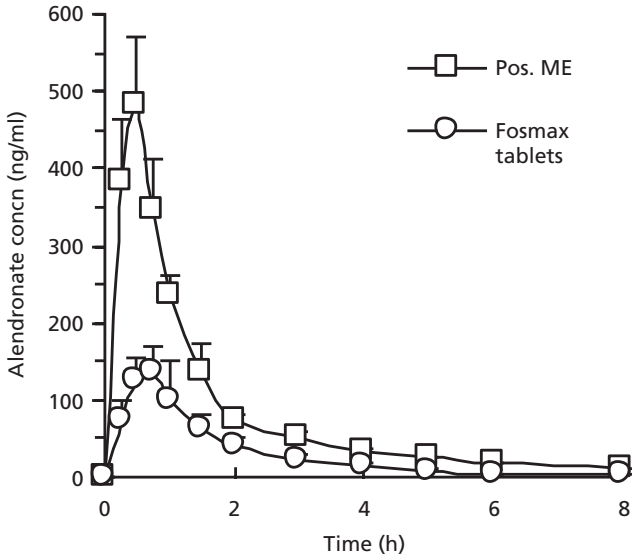

Figure 4 Plasma concentration of alendronate after oral administration of the conventional tablets or the positively-charged microemulsion to beagle dogs. Values are mean (± SD). $n = 6$. Tablets were Fosmax 70 mg and the positively-charged microemulsion (Pos. ME) contained 70 mg alendronate sodium.

Table 4 Pharmacokinetic parameters after oral administration of the conventional tablets and the positively-charged microemulsion to beagle dogs

Parameter	Tablets (Fosmax 70 mg)	Positively-charged microemulsion (70 mg alendronate sodium)
$AUC_{0\text{-}8\ h}$ (ng/ml · h)	303 ± 45.1	676 ± 112*
$AUC_{0\text{-}\infty}$ (ng/ml · h)	319 ± 46.7	682 ± 18.7*
C_{max} (ng/ml)	152 ± 27.3	502 ± 53.2*
T_{max} (h)	0.750 ± 0.204	0.563 ± 0.125
$t^{l}/_{2}$ (h)	1.75 ± 0.267	1.86 ± 0.327
Relative bioavailability (%)		2.82

Relative bioavailability = $AUC_{0\text{-}\infty}$(Test)/($AUC_{0\text{-}\infty}$(Fosmax) × 100%.
*$P < 0.05$: significantly different from the tablets. $n = 6$.

ers are available that can open tight junctions to allow water-soluble drugs to pass. These include substances such as bile salts, surfactants, medium chain glycerides, fatty acid, and chelating agents, like EDTA.[21] The intestinal absorption of hydrophilic drugs is known to be enhanced by medium-chain glycerides and fatty acids. Six poorly absorbed drug tablets prepared using Gastrointestinal Permeation Enhancement Technology with medium-chain glycerides and fatty acid have been approved for phase I studies.[22] Labrasol contains saturated polyglycolysed C_6-C_{14} glycerides, where C_8 is 58.1% and C_{10} is 39.8%. The surfactant is a representative surfactant having a strong absorption-enhancing effect on poorly absorbed drugs, such as gentamicin, vancomycin and insulin.[23–25] Therefore, Labrafac CC and Labrasol were selected and used as oil and surfactant in the microemulsion.

In the transport studies, all the micelles and microemulsions enhanced the transport of alendronate. However, the enhancement produced by the positively-charged microemulsion was stronger compared with the negatively-charged microemulsion, while the enhancement of the negatively-charged microemulsion was stronger than the micelle solution. The reduction in TEER across the Caco-2 monolayers was parallel to the transport enhancement of the micelles and microemulsions. Since the reduction in TEER is an indicator for the opening of tight junctions, the results suggested that the micelles and the microemulsions could open the tight junctions and promote alendronate transport.[26]

Different formulations for the negatively-charged microemulsion and the micelles showed that Labrafac CC improved alendronate transport. The much more prominent effect of the positively-charged microemulsion on the permeability of alendronate and TEER across Caco-2 cells could most likely be explained by the nature of the droplet charge that caused the electrostatic attraction of the droplets to the negatively-charged cell surface. The interaction of the droplets with the mucosal surface resulted in an increasing adhesion of the positively-charged droplets to the cell surface. Therefore, the concentration of the surfactants and the medium-chain glycerides partitions directly between the microemulsion and the cell membrane was higher than that of the negatively-charged microemulsion. Schipper *et al*. [27] suggested that the mucosal charge density could be important in enhancing mucosal absorption via the paracellular pathway. Furthermore, Gershanik *et al*. [28] found that the interaction of the positively-charged emulsion could improve the permeability of the hydrophilic marker, fluorescein. Our results were consistent with those reports. Since the microemulsions changed the TEER and altered the epithelial barrier properties, the recovery of the cells after the experiment was evaluated by measuring the TEER. The TEER of cells treated with the negatively-charged microemulsion or micelles was not significantly different from their values before the transport experiments, which indicated that the loss of cell viability was not responsible for the decrease of tight junction integrity (Figure 3). However, the reduction in TEER by the positively-charged microemulsion was only partly recovered. The lack of recovery of the barrier properties in an epithelium may contribute to the cytotoxicity caused by the positively-charged microemulsion. These are often associated with some problems such as increased risk of infection of the area. However, taking into account the presence of the protecting mucus layer normally bound to the apical cell surface and the peristaltic movements causing the quick spread of droplets along the gastrointestinal tract, the positively-charged microemulsion does not appear to pose any danger to the cells under real physiological conditions.[28]

The in-vivo performance of the positively-charged microemulsion containing alendronate was evaluated by oral administration to beagle dogs. The dogs remained in good health throughout the entire study. Compared with alendronate tablets, the microemulsion improved the bioavailability by 2.82-fold, but the bioavailability enhancement *in vivo* by the positively-charged microemulsion was not as significant as the permeability enhancement on Caco-2 cells *in vitro*.

There could be several explanations for this observation. First, the protecting mucus layer normally bound to the apical cell surface restricted the absorption enhancement of the microemulsion. Second, the peristaltic movements of the gastrointestinal tract could have spread the microemulsions, as well as decreasing the droplet concentration and exposure time, to the epithelium. Third, for poorly permeable drugs, the determined paracellular permeability on Caco-2 monolayers is usually lower than that in intestinal tissues *in situ* due to their differences in the regulation of tight junction permeability and paracellular water fluxes in the cell monolayers.[20] This also might make the absorption enhancement *in vitro* greater compared with that *in vivo*.

Conclusions

The positively-charged microemulsions containing Labrasol and Labrafac CC significantly promoted the paracellular transport of alendronate across Caco-2 cell monolayers. The promotion was parallel with the reduction in TEER, which indicated that the microemulsion could open tight junctions. Moreover, the promotion was enhanced by the electrostatic attraction of the droplets to the negatively-charged cell surface. The influence of the positively-charged microemulsion on the oral bioavailability of alendronate was investigated *in-vivo* in beagle dogs. A relative bioavailability of 282% for alendronate was obtained compared with the commercially available tablets (Fosmax). According to the results, the oral bioavailability of alendronate could be significantly promoted by the positively-charged microemulsions, which caused the widening of the tight junctions and thus increased the absorption through the paracellular route. This work established a new method for developing and generating formulations for extremely hydrophilic drugs, like the bisphosphonates, which exhibit very low bioavailability.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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