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# Evaluation of *In-Vitro* Dissolution and *In-Vivo* Absorption for Two Different Film-Coated Pellets of Clarithromycin

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The aim of this study was to compare two formulations of film-coated pellets containing clarithromycin after single oral dose study in healthy male volunteers. Two formulations with different coating polymers were prepared: formulation-1 (F-1) was prepared by incorporating three kinds of pH-dependent gradient-release coated pellets into capsules and formulation-2 (F-2) was prepared by coated with an insoluble semiosmotic film. Release profiles of film-coated pellets were evaluated using paddle method under different conditions. Pharmacokinetic profiles of these formulations were obtained in three healthy male volunteers and compared to commercially available immediate release (IR) tablets. The relative bioavailability based on the $AUC_{0\text{-}24\ h}$ was found to be 96.2% and 58.7% for F-1 and F-2 compared with IR, and the $T_{max}$ was delayed.

**Key words**: Clarithromycin, Film-coated pellets, *In-vitro*, *In-vivo*

## INTRODUCTION

Clarithromycin (CLA) is a macrolide antibiotic with a methoxy group attached to the $C_6$ position of erythromycin which makes it more acid stable than erythromycin (Nakagawa *et al.*, 1992). Clinical efficacy of CLA has been confirmed in the treatment of infections of lower and upper respiratory tracts. It is well absorbed and its systemic bioavailability (about 55%) is reduced because of first-pass metabolism (Chu *et al.*, 1992a, 1993). The primary metabolic pathways for CLA are oxidative *N*-demethylation and 14-hydroxylation, which are saturable resulting in nonlinear kinetics. The elimination half-life for CLA ranged in a dose–dependent manner from 2.3 to 6.0 h in both single and multiple-dose studies (Rodvold, 1999). CLA therapy is often associated with gastrointestinal side effects, such as gastric discomfort, abnormal taste, and diarrhea. Administration of CLA using a modified-release once-a-day dosage form could reduce the dosing frequency and improve patient compliance (Guay *et al.*, 2001).

It is important to evaluate the *in vivo* dissolution of a dosage form containing poorly soluble substances since its *in vitro* dissolution does not necessarily reflect its dissolution *in vivo*. The Biopharmaceutics Classification System (BCS) of the drug substances was compiled (Amidon *et al.*, 1995). According to these criteria, CLA belongs to class II with a low solubility in water, pH-dependent solubility. The solubilities of CLA in phosphate buffer solution of pH 4 and pH 7 are 20.0 and 0.5 mg/mL, respectively (Nakagawa *et al.*, 1992). CLA also exhibits rather high intestinal permeability due to its favorable lipophilicity and close to nearly 90% absorption (Arimori *et al.*, 1998). Drugs in this class often exhibit variable absorption due to various physicochemical, formulation, and gastrointestinal factors that can affect the dissolution performance.

It is generally known that multiple-unit dosage forms such as pellets present some biopharmaceutical advantages, particularly regarding the duration and the individual reproducibility of gastric emptying and intestine transit time, compared with single-unit dosage forms. Moreover, because each dose of multiparticulates consists of many subunits, there is better statistical assurance of drug release, and the risk of dose dumping is therefore minimized (Bodmeier, 1997).

In this investigation two kinds of modified-release CLA formulation coated with different polymers were prepared. *In vitro* dissolution and *in vivo* absorption were evaluated for the two formulations.

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## MATERIALS AND METHODS

### Materials

Methacrylic acid copolymers (Eudragit® L30D-55, Eudragit® L100, Eudragit® S100, Eudragit® RL30D) were supplied by Röhm GmbH, Darmstadt, Germany. Hydroxypropyl methyl cellulose (HPMC, Methocel E5, manufactured by Dow Chemical Co., Michigan, U.S.A.) was supplied by Colorcon (Shanghai, China). Clarithromycin was purchased from Huangyan Biological Product Company (batch 021208, 947 μg/mg, Zhejiang, China). Other excipients used to prepare the pellets were of standard pharmaceutical grade. Methanol was HPLC grade and other reagents were analytical-reagent grade. Water was double-distilled in glass. Commercially available immediately-release clarithromycin tablet (Biaxin, Abbott Laboratories, Italy) was chosen as the reference.

### Preparation of drug-loaded pellets

Drug-loaded uncoated pellets were prepared in a centrifugal granulator (Model BZJ-360M, Tianmin High Technology Development Co., Beijing, China). The mixed-powder of drug, sucrose, and microcrystalline cellulous (MCC) was layered onto MCC as seeds while continuously spraying the binding agent solution (3% w/w aqueous solution of HPMC) resulting in about 60% w/w drug loading. The process parameters were as follows: rotor speed; 200 rpm, blinder rate; 15 rpm, atomizing air pressure; 0.5 Mpa, power feeding rate; 10 rpm, slit air temperature; 20-55°C, and slit air volume; 10×15 L/min. Finally, drug-loaded pellets were dried in an oven at 40°C for 12 h. The size of the pellet was approximately 18-20 mesh in diameter, which was coated by coating solution.

### Coating of drug-loaded pellets with different coating solution

The HPMC was diluted to 8% (w/w) solution by adding distilled water while stirring. The drug-load pellets were coated equivalent to weight gains of 8% w/w which is calculated from the weight difference between the coated and the uncoated pellets based on the polymer weight gain.

Eudragit® L30D-55 containing 30% of total solids as an aqueous dispersion was diluted to a final solids content of 10% w/w. Triethyl citrate (TEC) as plasticizer was added at a concentration of 8% w/w and 12% w/w micronized talc was also dispersed in water and combined with the polymeric dispersion. The mixture was equilibrated for 30 min prior to coating. The drug-load pellets were coated equivalent to weight gains of 8% w/w.

The formulation of Eudragit® S100 was diluted to 8% w/w by adding 4% w/w TEC, 4% w/w 1 mol/L $NH_3$, 3% w/w micronized talc and 81% w/w distilled water. The formulation of Eudragit® L100 was diluted 8% w/w by adding 4% w/w TEC, 3% w/w 1 mol/L $NH_3$, 5% w/w micronized talc and 80% w/w distilled water. According to the above-mentioned formulations respectively, Eudragit® S100 or Eudragit® L100 was added into water separately while being stirred, making sure that the powder was quickly wetted and no lump formed. After stirring for about 5 min, the ammonia solution was added with stirring by means of a peristaltic pump and stirring continued for another 60 min. The TEC was then added to the dispersion while stirring for a further 60 min. Micronized talc was suspended in surplus water while homogenizing in a high-speed disperse mill. The talc suspension was added to the above aqueous dispersion. After the aqueous dispersions were prepared separately, Eudragit® L100 and Eudragit® S100 were mixed in a ratio of 3:2. The mixing order was that the Eudragit® S100 dispersion was slowly added to the Eudragit® L100 dispersion while stirring carefully. The drug-load pellets were coated equivalent to weight gains of 6% w/w.

Eudragit® RL30D was diluted by water to a final solids content of 15% w/w by adding 8% w/w TEC as plasticizer and 7% w/w talc based on the dry polymer weight. The mixture was equilibrated for 30 min prior to coating. The coating was determined to be complete when a final weight of 8% w/w was gained.

The coating process was carried out in the same equipment as powder layering process at the following conditions: atomizing air pressure; 0.5 Mpa, rotor speed; 150 rpm, coating suspension feed rate; 15 rpm, split air flow volume; 20×15 L/min and slit air temperature; 20-45°C. The coating dispersion was stirred continuously during spraying. After coating, the pellets were cured in the bed for 24 h at 40°C.

F-1 consisted of three kinds of pellets coated with HPMC, Eudragit® L30D-55, and Eudragit® L100-Eudragit® S100 (3:2) at the ratio of 10:60:30 which could sustainedly release the drug following immediate release portion of dosage form. The immediate release portion was included in the final dosage form to prevent any lag time. F-2 was the pellets coated with an aqueous dispersion of Eudragit® RL30D alone. Coated pellets corresponding to 250 mg CLA were filled into size 0 hard gelatin capsules.

### Assay of the drug content

The samples were assayed by a reversed-phase HPLC-UV method according to USP XXIV. Quantities (300 mg) of each batch of coated pellets were accurately weighed, ground to a fine powder then added to a 100 mL volumetric flask containing 70 mL of methanol. After a 30-min shake extraction, the solution was diluted with methanol to 100 mL. The solution was then diluted with mobile phase to a concentration of approximately 400 μg/

mL. The sample solution was filtered and 20 μL was injected for analysis.

### *In-vitro* dissolution

Dissolution tests, according to the USP XXIV paddle method, were carried out on pellets equivalent to 250 mg CLA in 900 mL of dissolution medium maintained at 37 ± 0.5°C with paddle stirred at 50 rpm using an automated sampling procedure. Dissolution tests were carried out under different dissolution media of pH 5.0 sodium acetate buffer, pH 6.0 and 6.8 phosphate buffers in which 3 mL sample was removed at predetermined time intervals, and replaced with an equal volume of fresh medium to maintain the total volume constant. Samples were taken at 1, 2, 3, 4, 6, and 8 h. The collected samples were assayed by a reversed-phase HPLC-UV method according to USP XXIV in which the sample solution was filtered and directly injected. Mean values were calculated based on triplicates. Similarities of the dissolution profiles were compared with the similarity factor $f_2$ (Sathe *et al.*, 1996).

### Bioavailability study

The *in vivo* study was performed on 3 healthy volunteers in good physical health according to findings from physical examinations. The treatment study was performed at People's Hospital of Liaoning Province and was approved by the Local Ethics Committee. Each volunteer was fully informed both in writing and verbally about the aim of the study. Each volunteer was administered the formulation containing 250 mg clarithromycin 30 min after starting a standard breakfast. Study was designed as a single-dose, crossover study in healthy male humans. F-1, F-2 or commercially immediately release tablet was dosed each week and three formulations were dosed sequentially.

### Treatment and sample collection

Blood samples of 4 mL volume were collected at 0, 1, 2, 3, 4, 6, 8, 11, 14, and 24 h after dosing for F-1 and F-2, at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h after dosing for immediately release tablet. An indwelling cannula placed in the forearm was used for drawing the blood during the first 14 h. The last sample was taken by direct venipuncture. The samples were placed in vacutainers (containing sodium heparin as an anticoagulant). Following centrifugation, the plasm was pipetted into polypropylene tubes container. Samples were then immediately frozen and stored (-18 to -20°C) until assayed.

### Sample processing

Each of the test or standard plasma samples was subjected to an extraction procedure as follows. Frozen samples were allowed to thaw at room temperature. To 200 μL plasma in a glass tube were added 200 μL (0.1 mol/L) $Na_2CO_3$, 100 μL mobile phase and 100 μL roxithromycin internal standard solution (4 μg/mL in water). Hexane-dichloromethane-isopropanol (300:150:15, v/v/v) 2 mL were added, the samples vortexed for 60 s, and then centrifuged at 3500 g for 5 min. The organic phase was decanted to a clean 10 mL glass tube and evaporated to dryness under nitrogen stream at 40°C. The extracts were reconstituted in 200 μL mobile phase, by vortexing for 30 s, transferred to autosampler vials, and 20 μL injected onto the LC/MS/MS system.

### Bioanalytical method

CLA concentration in plasma was determined by means of liquid chromatography-tandem mass spectrometry method. A Thermo Hypersil-Keystone-$C_{18}$, 5 μm, 150×3.0 mm column (San Jose, CA, U.S.A.) was used for separation at a flow-rate of 0.5 mL/min. The mobile phase consisted of methanol-water-formic acid (80:20:1, v/v/v). HPLC system was equipped with Shimadzu LC-10AD pump (Kyoto, Japan), attached to an autosampler injection valve (Agilent, Wilminton, DE, U.S.A.). Mass spectrometric detection was performed by a TSQ API II triple-quadrupole mass spectrometer in the selected reaction monitoring mode using electrospary ionization source (Thermo Finnigan, San Jose, CA, U.S.A.). The spray voltage was set at 4.5 kV performed in the positive mode. The sheath and auxiliary gas (nitrogen) was set at 80 p.s.i and 3 L/min, respectively. The capillary temperature was set at 280°C. The transitions of protonated molecules for CLA at *m/z* 748.2 to the predominant product ion *m/z* 158.0, and for roxithromycin (internal standard) *m/z* 837.4 to *m/z* 158.0 were monitored. The relative collision energy was set at 35 eV. Argon was used as the collision gas at a pressure of approximately 1.4 mTorr. The mass spectrometer was interfaced to a computer workstation running Xcalibur 1.1 software. The standard curve was found to be linear (r = 0.9976) over the concentration range of 10-5000 ng/mL. The analytical method was validated in terms of accuracy, precision, limit of quantification, selectivity, and reproducibility.

### Pharmacokinetics

The pharmacokinetic parameters were calculated based on non-compartmental model. The area under the plasma concentration-time curve from time zero to time t ($AUC_{0-t}$) was calculated using the trapezoidal method. Peak concentration ($C_{max}$) and time to peak concentration ($T_{max}$) were obtained directly from the individual plasma concentration-time profiles. The area from time t to infinity was calculated by:

$AUC_{0-\infty} = AUC_{0-t} + C_t / k_e$, where $C_t$ is the plasma CLA

concentration observed at time t, and $k_e$ is the apparent elimination rate constant of CLA obtained by least square fit of the slope of log-transformed terminal plasma concentrations.

Analysis of differences for AUC, $C_{max}$, and $T_{max}$ between the formulations (F-1 and IR, F-2 and IR) was performed with the paired t-test and a 95% confidence interval was used to measure the statistical differences, and $P < 0.05$ was considered significant.

## RESULTS AND DISCUSSION

### *In-vitro* dissolution

During the development of a dosage form, the physico-chemical property of the drug has to be taken into account. Clarithromycin is a weak base, only slightly water soluble and pH-dependent solubility. In order to control the amount of drug release in a defined period of time in gastrointestinal tract, one of the methods is to mix pellets coated with different pH-sensitive coating materials. In this paper, F-1 was the pH-dependent system that was prepared by coating pellets with HPMC, Eudragit® L30D-55, and Eudragit® L100-Eudragit® S100 (3:2). The reason for the most ratio of pellets coated by Eudragit® L30D-55 is the solubility obtained at a neutral pH represents better physicochemical and biopharmaceutical properties for the molecule of CLA. As soon as the dosage form arrives in the intestine, the film solubility must increase with increasing pH values in order to offset the important decrease of drug solubility at pH higher than 5.0. The process for producing F-1 was complex, so F-2 was designed and the coating component was determined by factorial design. *In vitro* dissolution and *in vivo* absorption were evaluated for the two formulations.

Release of CLA from F-1 is controlled by film soluble at different pHs and surface erosion mechanisms. The release of CLA from F-2 depends on diffusion mechanism. Basically, three different processes contribute to the drug release from such a system, i.e. inflow of liquid through the coating, dissolution of the drug in the pellet core and efflux of the dissolved drug. The dissolution curves obtained are shown in Fig. 1. Each data point presents the mean of triplicate measurements. The effect of the different film coated pellets on drug release was evaluated at pH levels 5.0, 6.0, and 6.8 with a rotation speed of 50 rpm. An almost 100% dose release profiles was achieved at the three conditions for F-1 and F-2. The release profiles of F-1 were increased with increasing pH values. The F-2, on the other hand, showed pH-independent drug release. At pH 6.8 and 6.0, the differences of release profiles between F-1 and F-2 were noted. At pH 5.0, the dissolution profiles of F-1 and F-2 were almost identical and initial release rate were low under this condition. The

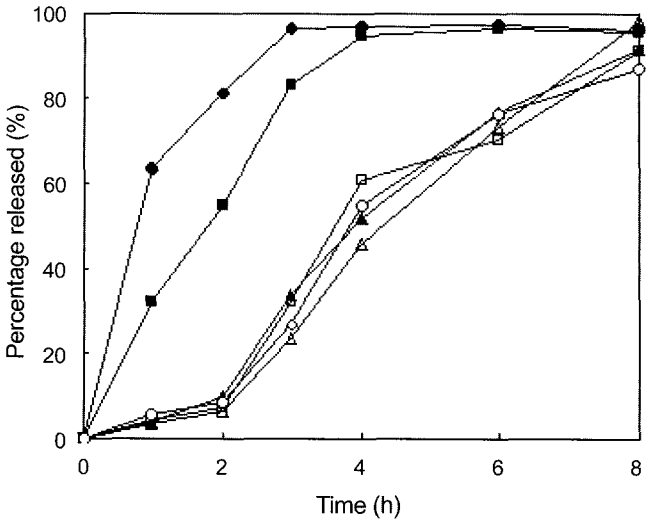


**Fig. 1.** *In vitro* release versus time from F-1 (filled symbols) and F-2 (open symbols) as a function of pH Symbols: (-▲-) pH 5.0; (-■-) pH 6.0; (-●-) pH 6.8

calculated similarity factors ($f_2$) confirmed the conclusion (Table I). This discrepancy may be ascribed to the different drug release principles. The coated-films for F-1 were soluble and pellets eroded with time, the pellet diameter is reduced during the dissolution *in vitro*. The film of F-2 coated by Eudragit® RL30D was insoluble during dissolution, just hydrate and permeable to drug, the films maintained intact during all the dissolution process. In view of these results, F-1 and F-2 showing distinct release characteristics were selected in order to evaluate their adequacy of use and possible difference during the *in vivo* study.

### Pharmacokinetics

Though some macrolide antibiotics can be inactivated by gastric acid, CLA is relatively stable above pH 3 (Erah *et al.*, 1996). Because food intake just before dosing increased the extent of absorption lightly, the volunteers administered the dosage form in a nonfasting state (Chu *et al.*, 1992b). The dissolution medium of pH 5.0 was used, since the pH in the stomach may be elevated to values above pH 5 after a standard breakfast (Dressman *et al.*, 1990).

Fig. 2 shows mean plasma concentration-time curves after administration of three formulations of CLA. The pharmacokinetic parameters determined by non-compart-

**Table I.** Similarity factor $f_2$ for clarithromycin pellets at different dissolution conditions F-1 vs. F-2[a]

| pH | 5.0 | 6.0 | 6.8 |
|---|---|---|---|
| $f_2$ | 54.9 | 12.3 | 2.2 |

[a] $f_2 > 50$ indicates similarity and $f_2 < 50$ indicates dissimilarity

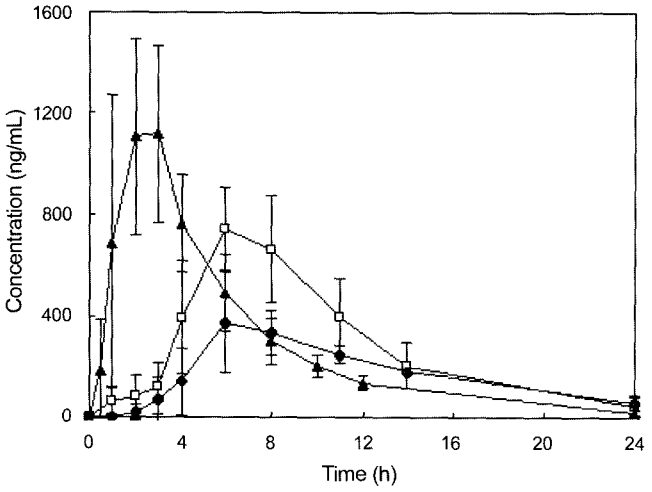


**Fig. 2.** Mean plasma concentration after administration of 250 mg CLA different forms. Each value represents mean (n=3), and error bars indicate S.D. Symbols: (-▲-) IR; (-□-) F-1; (-●-) F-2.

**Table II.** Pharmacokinetic parameters of clarithromycin F-1, F-2, and reference formulation[a]

| Parameter | F-1 | F-2 | Reference |
|---|---|---|---|
| $AUC_{0\text{-}24\,h}$ (μg h/mL) | 6.78 ± 1.95 | 4.13 ± 0.64[b] | 7.0 5 ± 1.43 |
| $AUC_{0\text{-}\infty}$ (μg h/mL) | 7.07 ± 2.23 | 4.57 ± 0.60[b] | 7.16 ± 1.50 |
| $C_{max}$ (ig/mL) | 0.744 ± 0.160 | 0.375 ± 0.198[b] | 1.118 ± 0.349 |
| $T_{max}$ (h) | 6.70 ± 1.20[b] | 7.70 ± 2.90[b] | 2.30 ± 0.60 |
| $K_e$ ($h^{-1}$) | 0.181 ± 0.033 | 0.137 ± 0.019 | 0.155 ± 0.049 |

[a] Mean ± SD, n = 3

[b] Significantly different ($P < 0.05$) versus reference

mental model are listed in Table II. There was significant difference in time to maximum concentration, $T_{max}$, compared F-1 and F-2 with IR ($P < 0.05$). The relative bioavailability judged from the $AUC_{0\text{-}24\,h}$ was found to be 96.2% and 58.7% for F-1 and F-2 compared with IR, respectively. There was significant difference of F-2 values for $C_{max}$ and $AUC_{0\text{-}24\,h}$ to those observed for IR. The plasma level of IR clarithromycin rose quickly and maximum concentration was reached at 2 h after administration. There was a major fall in plasma concentration between 4 and 12 h. The plasma level of F-1, on the other hand, increased slowly and maximum concentration was reached at 6 h after administration. F-1 showed a sustained manner in plasma level profiles. Lag time for 2 h was observed in the plasma profiles of F-2. The erratic bioavailability from F-2 can be attributed to their poor dissolution exacerbated in the gastro-intestinal pH values due to an extremely low solubility of CLA at high pH values.

Therefore, the pH variation resulted in substantial differences in the dissolution profiles of the F-1, the drug release rate increased as the pH value increased. This means that conditions of absorption will be much dependent on such physiological parameters as stomach-emptying time, rate of intestinal transit, and variations in pH at the gastrointestinal tract. It is flexible to change the release character by adjusting the ratio of the three pellets. F-2 did not improve its dissolution rate when pH was changed from pH 5.0 to pH 6.8 because Eudragit® RL30D is a pH-independent film by which the drug is released by diffusion in the range of pH 2-7. Lag time for 2 h was observed in the plasma profiles of F-2 after administration to volunteers. It is apparent that the drug release *in vivo* takes place at a much slower rate than *in vitro* dissolution, indicating a possible difference in the hydrodynamic condition between *in vitro* and *in vivo* conditions. CLA may have remained entrapped in the pellet cores under *in vivo* condition resulting an incomplete drug release *in vivo*, therefore, the relative bioavailability for F-2 was found to be lower than that of F-1.

The current study investigated the impact of sustained release formulation coated with different polymers on the pharmacokinetics of CLA. The pellets coated with Eudragit® RL30D alone are not suitable as sustained-release systems because the drug is weakly basic with $pK_a$ of 8.76 and with pH-dependent solubility. The formulation problems encountered are in agreement with those in previous reports (Grubel *et al.*, 1998). A further optimization of F-2 could improve CLA dissolution by adding hydrophilic pore-form ingredients such as HPMC or lactose to enhance the film permeability, or by adding water-soluble excipients, surfactants or disintegrants inside the cores to improve the *in vivo* absorption of CLA (Amighi *et al.*, 1998; Sousa *et al.*, 2002).

## CONCLUSION

In this study two different modified release formulation containing pellets of CLA were prepared and the pharmacokinetic was evaluated *in vivo*. F-1 coated by three different pH-sensitive coating film was observed to be effective in preparing weakly basic drug substance of CLA exhibiting pH-dependent solubility. However, F-2 was shown incomplete absorption in the gastrointestinal tract after a prolonged passage time *in vivo*. Our current work is directed toward further determining the *in vitro-in vivo* correlation for the product.

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