Stability of Ester Prodrugs with Magnesium Oxide Using the Simple Suspension Method

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The simple suspension method is a method of administering drugs via a feeding or gastrostomy tube, and it involves allowing tablets or capsules to be disintegrated and suspended in warm water at 55°C without crushing. The present study evaluated the stability of two prodrugs suspended alone or in combination with an alkaline agent according to the simple suspension method. The study used two ester-prodrugs, acemetacin (AMT) and cefpodoxime proxetil (CPP), which are hydrolyzed at higher pH. Drug concentrations in the suspension were measured by high-performance liquid chromatography. AMT and CPP were not hydrolyzed when suspended alone, but decomposed under alkaline conditions with the addition of magnesium oxide (MgO). The AMT concentration decreased to 55.5% and 38.9% at 30 min and 60 min, respectively, whereas its active metabolite, indomethacin (IMT), increased from 0 to 90.7 µg/mL and 122.7 µg/mL at 30 and 60 min, respectively. The CPP concentrations with MgO were decreased to 47.9, 28.5, 20.8 and 12.7% at 30, 60, 90, and 120 min, respectively. Therefore, AMT and CPP should not be administered in the simple suspension method in combination with an alkaline drug that increases the suspension pH.

Key words — acemetacin, cefpodoxime proxetil, simple suspension method, hydrolysis, magnesium oxide

Introduction

Many medicines are administered to older patients as suspensions in clinical practice, because it is sometimes difficult for patients to take medicines orally in the form of tablets and capsules. A common method to prepare such suspensions is to crush tablets and/or capsules and suspend them in water. Another method is to administer drugs in suspension in warm water (55°C), which is called the “simple suspension method”. The simple suspension method is an easy and rapid method for making suspensions of tablets and capsules to be administered via a feeding tube or gastrostomy tube. This new method does not require crushing, and thus can avoid drug exposure to pharmacists and the loss of drug due to adhesion to instruments.

Some previous studies have been reported on the stability of drugs when applied alone to the simple suspension method. In these studies, all medicines tested were shown to be stable in each suspension when applied alone to the simple suspension method. With regard to concomitant suspensions with other medicine, chemical decomposition was observed for L-dopa, aspirin and capecitabine when suspended with an alkaline drug or under pH-altered conditions. The use of this method has been increasing in Japan, but its application to drugs that are susceptible to chemical hydrolysis, such as prodrugs, remains controversial.

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A prodrug is defined as a pharmacologically inert chemical derivative that can be enzymatically or non-enzymatically converted in vivo to an active drug to exert its therapeutic effect. Prodrugs are developed to accomplish a variety of purposes such as improving drug absorption, avoiding gastrointestinal side effects, or accumulating drug in target sites. For example, some prodrugs of non-steroidal anti-inflammatory drugs (NSAIDs) can avoid damage to the gastric mucosa through the inhibition of cyclooxygenase-1 (COX-1).

Acemetacin (AMT) is a glycolic acid ester of indomethacin (IMT), a NSAID, and is subjected to a hepatic first-pass effect after oral administration to generate IMT. The indole moiety is a fundamental constituent for a number of both natural and synthetic compounds with biological activity. AMT may represent a useful alternative to conventional NSAIDs for the treatment of inflammation and pain.

Cefpodoxime proxetil (CPP) is an orally administered prodrug that is de-esterified by the intestinal mucosa to release cefpodoxime (CP). CPP is stable to most common plasmid-mediated beta-lactamases. This antibiotic has a broad antibacterial spectrum with a potent activity against both Gram-positive and Gram-negative bacteria. CPP is therefore a good candidate for the treatment of a wide range of community acquired infections. CPP is stable in intestinal juice and phosphate buffer under neutral pH conditions, but unstable under high pH conditions.

The aim of this study was to investigate whether AMT and CPP suspended using the simple suspension method remain intact or is decomposed to their active drugs when suspended with an alkaline agent, magnesium oxide (MgO).

**Materials and Methods**

1. **Materials**

Acemetacin tablets (30 mg, RANTUDIL®), were purchased from Kowa Company, Ltd. (Aichi, Japan), cefpodoxime proxetil tablets (100 mg of CP, equivalent to 130.4 mg of CPP, BANAN®) from Daiichi Sankyo Co., Ltd. (Tokyo, Japan), and magnesium oxide tablets (500 mg, Magmitt®) from Nihon Shinyaku Co., Ltd. (Kyoto, Japan). Acemetacin powder, indomethacin powder, and cefpodoxime proxetil powder were purchased from Sigma Chemical Company (Tokyo, Japan). Acetonitrile and methanol were obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All the chemicals were of reagent grade and were used without any further purification.

2. **Methods**

1) Preparation of standard solutions of AMT and IMT

AMT and IMT were prepared in methanol at 1 mg/mL, as stock solutions. Consequently, the stock solution was diluted and used for constructing calibration curves in the range of 25 - 200 µg/mL.

2) Preparation of standard solutions of CPP

CPP was prepared in a mixture of water and acetonitrile in a ratio of 1:1 v/v to obtain concentrations of 1 mg/mL, the primary stock solution was diluted and used for constructing calibration curves in the range of 25 - 300 µg/mL.

3) Stability of the prodrugs in the simple suspension method

A prodrug (AMT tablet or CPP tablet) and an MgO tablet were placed in the tube and 20 mL of warm water (55°C) was added to make a suspen-
The suspension pH was measured with a pH meter (Seven Easy pH, Mettler-Toledo AG, Schwerzenbach, Switzerland). A portion of the suspension (100 µL for AMT and 50 µL for CPP) was sampled at designated times, i.e., at 5, 10, 15, 30, and 60 min for AMT and at 10, 15, 30, 60, 90 and 120 min for CPP. Methanol (1 mL) and phosphate buffer (150 µL) were added to the samples, vortexed for 2 min (AMT) or 5 min (CPP), and centrifuged at 3000 g for 2 min. The supernatant was filtered through a 0.45 µm filter. Finally, the concentrations of each compound were measured with a high-performance liquid chromatography (HPLC). The stabilities of AMT and CPP were expressed as percentage [%] of the theoretical initial concentrations, i.e., 1500 µg/mL (30 mg / 20 mL) and 6520 µg/mL (130.4 mg / 20 mL) for AMT and CPP, respectively.

4) Analysis of chemicals

The HPLC system (Shimadzu Corporation, Kyoto, Japan) contained a solvent pump (LC-20AT), a line-degasser (DGU-20A3), a manual injector, a spectrophotometric detector (SPD-20A), and an ODS column, TSKgel ODS-80Ts (4.6 mm I.D. × 15 cm, Tosoh co., Tokyo, Japan). Two mobile phases, A and B, were used for ATM and CPP, by using the gradient method. Mobile phase A was 80% acetonitrile -5 mM heptanesulfonic acid Na containing 20 mM phosphate buffer (pH 2.3), and mobile phase B was 10% acetonitrile -5 mM heptanesulfonic acid Na containing 20 mM phosphate buffer (pH 2.3). The analytical wavelength for detection was 254 and 235 nm for AMT and CPP, respectively. The flow rate of the mobile phase was 1.0 and 0.8 mL/min for AMT and CPP, respectively. The injected volume was 10 µL.

Results

Figure 1A shows that the concentration of AMT did not change when suspended alone in the simple suspension method. The pH of the suspension was 6.0. On the other hand, the concentration of AMT in the presence of MgO decreased to 55.5% and 38.9% at 30 min and 60 min, respectively. The active metabolite of AMT, IMT, was found to

\[ \text{Fig. 1} \quad \text{Time profiles of AMT without and with MgO (A), and time profiles of IMT without and with MgO (B)} \]

Data are shown as the Mean ± SD (n = 3) in the units of %. SD bars are not shown when the values of SD fall within the symbols.
increase in the simple suspension method, indicating that the hydrolysis of AMT was proceeding (Fig. 1B). The pH of the suspension was 9.5 when AMT and MgO were suspended together but changed to 6.0 after the addition of methanol and phosphate buffer.

Figure 2 shows that CPP was not hydrolyzed in the simple suspension method without MgO, but it was hydrolyzed in the presence of MgO. The CPP concentrations with MgO were 47.9, 28.5, 20.8 and 12.7% at 30, 60, 90 and 120 min, respectively.

Discussion

The increased use of the simple suspension method is considered to be advantageous for administering tablets and capsules to patients that cannot intake them safely. Although there is a general notion that ester prodrugs could be hydrolyzed under alkaline conditions, there has been little information on the quantitative stability of ester prodrugs when applied to the simple suspension method together with alkaline agents. Especially, theoretical drug interactions may not necessarily happen in the real cases of the simple suspension method, considering that all the suspended drugs cannot be completely dissolved in 20 mL warm water and that dug tablets contain many additives including agents for pH adjustment. MgO is frequently prescribed as an antacid or laxative, and combinations of MgO and other medicines are often observed in clinical practice. Therefore, this study was undertaken to evaluate whether the ester prodrugs tested are stable or not, in the presence of MgO, under the clinical situation employing the simple suspension method.

The decreases in the stability of drugs with MgO in the simple suspension method observed in this study should be of clinical notice, as well as the previous reports on L-dopa with MgO and aspirin with MgO or LiCO3. In some previous studies, the suspension was preliminarily separated into the dissolved and undissolved drugs by centrifugation for the determination of drugs. In this study, however, we did not differentiate the dissolved and undissolved drugs, since the extraction procedure using methanol was performed after sampling from the dispersed suspension at designated times and determined the concentrations of the suspensions. Although the water solubility of AMT and CPP are known to be low, the hydrolysis reaction could be proceeding on the surface of small particles in suspensions. Moreover, since the generated product is water soluble, the above reaction can be accelerated even if the prodrug itself is not well dissolved in water. In any case, the suspended water-insoluble drugs will be absorbed from the intestine with the aid of bile acids, after administration via a tube.

The AMT concentration decreased, and its active form, IMT, was generated in a time-dependent manner when suspended with MgO, indicat-
ing that AMT was hydrolyzed to IMT. AMT was developed to avoid the gastrointestinal side effects of IMT,\textsuperscript{12} thus the application of the simple suspension method to AMT and MgO in patients may cause gastrointestinal injury including peptic ulcers. On the other hand, AMT was not hydrolyzed at pH 6.0 without MgO, indicating that AMT can be administered alone by the simple suspension method. The initial concentrations of AMT were 81.6\% and 82.5\% for control and concomitant groups, respectively. Although methanol can dissolve AMT at 10-30 mg/mL,\textsuperscript{18} some drug-contained small particles could exist in the suspension and these particles were thought to be removed at the filtration process before injection into HPLC, resulting in the initial concentration of AMT to be lower than 100\%.

The present results showed that the concentration of AMT, suspended with MgO in warm water, decreased to 55.5 and 38.9\% (832 and 584 \(\mu\)g/mL) at 30 min and 60 min, respectively. This amount of AMT degraded was different from the amount of IMT formed. Based on the fact that there were several peaks beside IMT peaks in the HPLC chromatogram (not shown), the above difference may have occurred partly because AMT was decomposed not only to IMT but also to other compounds. Another reason for the above difference is the possibility that IMT can also be decomposed in alkaline conditions, as suggested in a previous report.\textsuperscript{20}

These results indicated that AMT is stable at neutral pH, but decomposed under alkaline conditions. The proposed mechanism for the decomposition of N-acyl derivatives of indoles involves the initial OH\textsuperscript{-} attack to the amide, followed by base-catalyzed decomposition of the tetrahedral intermediate.\textsuperscript{20}

The CPP concentration without MgO at 5, 10, 15, 30, 60, 90, and 120 min, was stable while CPP concentration with MgO at 30, 60, 90 and 120 min was decreased to 47.9, 28.5, 20.8 and 12.7\% at 30, 60, 90 and 120 min, respectively. Therefore, CPP was hydrolyzed in the presence of MgO, indicating that CPP cannot be administered with drugs that can increase the pH of the suspension. Although CPP is highly soluble in methanol (1.43 g/mL),\textsuperscript{19} the initial concentrations of CPP were slightly less than 100\% (Fig. 2), probably due to the removal of small particles in methanol solution at the filtration process, similar to AMT as mentioned above. The generated CP was not measured since CP was not separated with either of the water soluble components in the CPP tablet. The suspension pH with MgO was 9.0, but the suspension pH decreased to 5.5 after the addition of methanol and phosphate buffer. This result is consistent with a previous study that found CPP is slightly degraded at pH 6.0 but is degraded at pH 7.0 and 8.0.\textsuperscript{16} A proposed mechanism for the ester hydrolysis of CPP is the transfer of the double bond in the cephalosporin structure under neutral and alkaline conditions.\textsuperscript{16}

Moreover, the application of the simple suspension method to CPP with MgO in patients may cause some reduction of therapeutic effects of CPP, since CPP was developed to increase the intestinal absorption of CP. Therefore, it is highly recommended for ester prodrugs and MgO to be suspended and administered separately. Prodrugs may preferably be administered prior to MgO. Other alkaline agents should be administered separately for the same reason. The present study clearly showed that the two prodrugs are converted to their active compounds when concomitantly suspended with an alkaline agent, MgO. Ester hydrolysis of the prodrugs in the simple suspension method may result in the reduction of therapeutic
effects due to decreased drug absorption or an increased risk of gastrointestinal side effects. Therefore, ester prodrugs should not be suspended with alkaline agents in warm water, rather they should be suspended and administered separately.

This study demonstrated that AMT and CPP can be markedly hydrolyzed when applied to the simple suspension method in combination with an alkaline drug, MgO, which can increase the suspension pH. This information should be of clinical notice for the simple suspension method.

References


2) Ishida S, Okano Y, Simple suspension method up to date (6), Yakugaku, 2006, 48, 905-910.


11) Pina AEC, Favari L, Hernandez GC, Pharmacokinetics of acemetacin and its active metabolite indomethacin in rats during acute hepatic damage and liver regeneration, Ann Hepatol, 2009, 8, 141-147.


19) Interview Form of Banan® tablets 100 mg, revised 7th ed., ed. by Daiichi Sankyo Co., Ltd., Tokyo, February 2013.