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DEVELOPMENT OF pH-INDEPENDENT ACRYLIC-WAX MATRIX TYPE SUSTAINED RELEASE DRUG DELIVERY SYSTEM OF ACEBROPHYLLINE

Kim Kang Min [1], Ko Chan Young [1] and Kang Jae Seon*[2]

Center for R&D, Hyundai Pharm [1], Seoul, Republic of Korea
Department of Pharmacy [2], Kyungsung University, Busan, Republic of Korea

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Correspondence to Author:

Kang Jae Seon

Department of pharmacy, Kyungsung University, Namgu, Suyoungro, 309, Busan, Republic of Korea

E-mail: kkij80@paran.com

ABSTRACT: The aim of the present study was to improve commercial twice-a-day Acebrophylline formulation to once-a-day new formulation to improve patient compliances. The double-layered tablet was composed of the fast release layer (Acebrophylline 50 mg) and sustained release layer (Acebrophylline 150 mg). To develop the double-layered tablet, the fast release and sustained release layers were prepared using polymer, wax, excipients and malic acid. The inclusion of malic acid in sustained release layer in double-layered tablet was showed to decrease release rates in pH 1.2 equal to dissolution rate of pH 6.8. The pharmacokinetic parameters such as AUC_t and C_{max} of double-layered tablet having fast release and sustained release layer were tested on mini pigs. These results showed similar pharmacokinetic parameters of AUC_t and C_{max} between Surfolase capsule and double-layered tablet. The 90% confidence intervals of the AUC_t ratio and the C_{max} ratio for double-layered tablet and Surfolase capsule were log 0.9402 ~ log 1.0245 and log 0.9983 ~ log 1.1542, respectively. This mean show that double-layered tablet using malic acid, Eudragit and carnauba wax is a promising approach for developing acebrophylline drug products.

INTRODUCTION: Acebrophylline is a compound synthesized by salifying the ambroxol base with theophylline-7-acetic acid. After administration, these two components are split on animals. Theophylline-7-acetic acid also acts as an ambroxol carrier [1].

It enhances the production and release of pulmonary surfactant. It protects mucosa and stabilizes alveoli. Acebrophylline was appeared that the presence of theophylline-7-acetic acid did not affect ambroxol plasma levels. However, Theophylline-7-acetic acid produces higher ambroxol lung tissue levels and higher tissue-to-plasma level than ambroxol alone [2]. Acebrophylline has been found to act both as a mucoregulations and a bronchodilating drug for the treatment of patients [2]. Ambroxol is a metabolite of bromhexine and described as Trans-4-[(2-Amino-3, 5-dibromobenzyl) amino]-cyclohexanol [3].

It is used as a mucolytic agent like bronchitis and bronchial asthma [4]. Absolute oral or rectal bioavailability is calculated to be approximately 70-80% [5]. Plasma protein binding is also approximately 90% [6]. Though ambroxol has been successfully used for decade in the form of its hydrochloride, it has a short plasma elimination half-life of 3-4 hours. According to short half-life, it is administrated in a dose of 30-60 mg 2-3 times a day.

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Ambroxol hydrochloride (75 mg of sustained release capsule) was developed to improve patient compliance for dose [7].

During the past few decades, various types of oral controlled release and sustained release formulations have been developed to improve the clinical efficacy of drugs such as coating and pelltization for ambroxol chloride [8-10]. The double-layer tablet has been used to develop controlled-release formulations. It is usually designed to release the drug at two different rates. The double-layered tablet is composed of a fast release layer with single or double sustained release layer [9-12]. The double-layered tablet offer a pharmacokinetic advantages which is controlled to release from the fast release layer followed by continuation of drug release from the sustained release layer [12].

In this study, we tried to change the acebrophylline sustained release release dosage form to the double layered tablet. The double-layer tablet was composed of fast release layer containing 50 mg of acebrophylline and sustained-release layer containing 150 mg of acebrophylline. Polymer and various ingredients were tested to reach the prefixed goal. Among them, Eudragit® L100-55, carnauba wax, Pearlitol 300 DC was selected for representative ingredients. Acrylic polymer (Eudragit L100-55) as a pH-dependent polymer used for our study is widely used for the sustained-release tablet, enteric coating and targeted delivery in the duodenum or jejunum [13].

Carnauba wax was widely used as a matrix or as a coating polymer to sustain the release of drug. Both wax and Eudragit® formulation was used to release the drug [14]. We compare the pharmacokinetic of the newly developed acebrophylline-loaded the double-layered tablet with Surfolase capsule for once daily of dose.

MATERIALS AND METHODS: Acebrophylline was purchased from the Polichem Co., Ltd (Lugano-pazzallo, Switzerland). Surfolase capsules were provided from Hyundai Pharma Co., Ltd (Seoul, Korea). Microcrystalline cellulose (Avicel PH 102), Lactose (Pharmatose 200M), Carnauba wax and croscarmellose sodium (Ac-di-sol) were purchased from Whawon pharm Co., Ltd (Seoul, Korea). Magnesium stearate was provided by BASF Korea (Seoul, Korea). Mannitol (Pearlitol 300 DC) was purchased from Roquette (Lestrem, France). Eudragit L100-55 was purchased from Evonik degussa Ltd (Seoul, Korea). All other chemicals were obtained from Sigma-Aldrich (St. Louis, MO, USA).

Sustained release layer: Malic acid was firstly blended with magnesium stearate. Then, Acebrophylline, carnauba wax and Eudragit L100-55 were mixed for an additional 20 min. This powder blend was again added to magnesium stearate for lubricant. All of the prepared powder blends were compressed under constant pressure using IR press. The detailed composition of the sustained release tablet formulations are presented in **Table 1**.

TABLE 1: FORMULATIONS OF SUSTAINED RELEASE LAYER IN THE ACEBROPHYLLINE TABLETS

	Formulation 1	Formulation 2	Formulation 3	Formulation 4	Formulation 5
Tablet components (mg)					
Acebrophylline	150	150	150	150	150
Malic acid	60	60	60	40	80
Carnauba wax	100	80	100	100	100
Eudragit L100-55	100	100	80	100	100
Magnesium stearate	15	15	15	15	15
Tablet weight (mg)	425	405	405	405	445

Fast release layer: Table 2 presents the composition of the fast release tablet formulation. Acebrophylline was firstly blended with Avicel PH 102, lactose, and Ac-di-sol for diluent and superdisintegrant agent, respectively. Then, Pearlitol 300 DC was added to help for disintegrant and diluent to the powder blend and mixed for an additional 20 min. This mixture was lubricated using magnesium stearate and compressed on an IR press (Carver Laboratory Press FT15, Fred S. Carver, USA).

TABLE 2: A FORMULATION OF FAST RELEASE LAYER IN THE ACEBROPHYLLINE TABLET

	Formulation 6
Tablet components (mg)	
Acebrophylline	50
Lactose monohydrate	22.6
Microcrystalline cellulose 102	30
Mannitol 300DC	80
Croscarmellose sodium	13
Magnesium stearate	4.4
Tablet weight (mg)	**200**

Double-layered tablet: For double-layered tablets, sustained release layer blends were initially pre-compressed with low hardness. Then, fast release portion was added directly onto the obtained compressed tablet, and then recompressed together to combine the double-layered tablet until the desired hardness.

***In vitro* dissolution study of tablet:** Dissolution profiles of new tablets containing solid dispersion were determined at 37^{o}C, in 0.01N HCl buffer (pH 1.2) and phosphate buffer (pH 6.8), while in dissolution tester at 50 rpm using the basket method according to Korea Pharmacopoeia (KP) dissolution procedure. In addition, the drug release profile from a marketed product, Surfolase capsules, was examined for comparison purposes. In each dissolution test, a weighed quantity of all formulations was placed in 900 mL of the dissolution medium. Each of the 1 mL aliquots was withdrawn at each point through a filtering rod (10 mm).

Filtered samples were assayed by a high pressure liquid chromatography (HPLC) method for ambroxol concentrations. The optimal conditions of ambroxol detection were achieved using an HPLC (Agilent Technologies, 1100 series, USA) column (Inertsil ODS-3, 150 mm x 4.6 mm, 5 µm) and detection at 244 nm using a UV monitor (Agilent Technologies, 1100 series, Photo-Diode Array UV/Vis detector, USA). The column was held at 40^{o} and the mobile phase consisted of 0.1% ammonium carbonate in water – acetonitrile (43:57, v/v).

Chromatography was performed isocratically at a flow rate of 1 mL/min. Drug concentrations were expressed as the percentage of ambroxol released over time (n = 8 each).

***In vivo* experiments for administration and blood-collecting:** Mini pigs (13.5 ± 1.2 kg) were used in the pharmacokinetic studies, and all animals were treated in accordance with guidelines offered by Guide for the Care and Use of Laboratory Animals from the National Institutes of Health. Prior to each experiment, the animals were fasted overnight with free access to water. All animals were kept in a temperature-controlled environment (20 ± 2) with a 12 h light-dark cycle. Food and water were also freely available. Six pigs were divided into two groups. Six male pigs were used where one tablet or capsule per pig was administered.

The Surfolase capsule (Acebrophylline 100 mg) is administrated twice daily. The double-layered tablet is administrated once daily. According to a randomized crossover, each pig received prepared batches of either the double-layered tablet of formulation 1 (sustained release layer) and formulation 6 (fast release layer) or Surfolase capsules with a washout period of 2 weeks (**Tables 1 & 2**). For evaluation of the ambroxol following oral administration of mini pigs, blood samples (1 mL) of Surfolase capsule were collected from the jugular vein immediately before administration, and at 0.33, 0.66, 1, 1.5, 2, 4, 8, 12, 12.33, 12.66, 13, 13.5, 14, 16, 20, 24, 30 and 36 h after administration.

Blood samples of double-layered tablet were collected at 0, 0.33, 0.66, 1, 1.5, 2, 4, 8, 12, 16, 20, 24, 30 and 36 h after administration. All heparinized blood samples were immediately cooled on ice and then centrifuged at 3,000 rpm (4) for 10 min. The plasma was stored at -70 until analysis was performed. Each mini pigs an oral dose of Surfolase capsule and double-layered tablet in a standard 2 x 2 crossover method in a randomized order.

Pharmacokinetic parameters such as AUC_t and C_{max} were calculated from total serum concentration-time curves of ambroxol. C_{max} was recorded as actual measurement values and AUC_t was calculated by trapezoidal formula in 0-36 h. Their test/reference ratios using log-transformed data, together with their means and 90% confidence intervals, were analyzed with the two-way analysis

of variance (ANOVA) that performed with the equiv test and K-BE test (2007) program at a significant level of 0.05. The bioequivalence of Surfolase capsule and double-layered tablet were estimated by AUC_t and C_{max} used as a reference value.

Plasma sample preparation: 200 µL of plasma samples were added into microcentrifuge tubes. To each sample, 20 µL of internal standard solution (5,000 ng/mL) was added, as well as 400 µL acetonitrile. Then the tubes were capped and vortexed for 10 min. Samples were centrifuged at 3,000 rpm and -4^{o}C for 10 min. The upper organic layer (Acetonitrile layer) was injected into the LC-MS/MS for mass spectral analysis.

Ambroxol standard, QC and IS preparation: Primary stock solution of ambroxol (1 mg/mL) and domperidone [Internal standard (IS); 500 µg/mL] were prepared in 80% MeOH. Working standard solutions of ambroxol were prepared by combining aliquots of primary stock solution and diluting with 80% MeOH. The working solution for the internal standard (5,000 ng/mL) was prepared by diluting with 80% MeOH. Plasma calibration standards of ambroxol at seven concentrations (10, 50, 100, 200, 500, 1,000 and 1,500 ng/mL) were prepared and analyzed by spiking the working standard solutions. For the plasma quality control (QC) samples, 20 µL of the QC working solution (100, 2,000 and 15,000 ng/mL) was added to microcentrifuge tubes containing 180 µL control plasma to yield final QC concentrations of 10, 200 and 1,500 ng/mL). QCs were stored at -20^{o}C.

Extraction recovery and stability: The recovery of ambroxol was determined by comparing the peak area obtained for QC samples (10, 200 and 1,500 ng/mL). All samples were followed by Wen *et al* [15] for the stability of ambroxol.

LC-MS/MS conditions: Tandem mass spectrometry (MS/MS) was performed using a Sciex API 3200 triple quadruple mass spectrometer equipped with turbo electrospray ion source (Foster City, CA USA). The conditions were modified from the method described by Kumar *et al* [16]. 10 µL of sample were delivered into the ESI source using the micro-LC (Foster City, CA USA) and auto sampler (Agilent Technologies, 1200 series, USA) with Zorbox Eclipse XDB-C18 column (2.1 x 50 mm, 5 µm particle size). The isocratic mobile used after degassing was composed of 25% solvent A (0.1% formic acid in water) and 75% solvent B (0.1% formic acid in acetonitrile), with a total running time of 2 min and flow rate of 250 µL/min. In detecting ambroxol using the multiple reaction monitoring (MRM) scan mode with positive ion detection, the following parameter settings were used: declustering potential (DP), 56 V; collision energy (CE), 31 eV; collision cell exit potential (CXP), 4 V; spray voltage, 4500 V; and ion temperature, 500^o. Ion source gas 1 (GS1), Ion source gas 2 (GS2), curtain gas (CUR) and collision gas (CAD) were 50, 50, 20 and 4 psi, respectively. The monitoring ions were set as *m/z* 376.9 → 262.0 for ambroxol and *m/z* 426.1 → 175.1 for domperidone. The scan dwell time was set at 150 ms for every channel.

RESULTS AND DISCUSSION:

***In vitro* dissolution studies:** To test whether ambroxol or not affect analysis of drug from double-layered tablets made by several ingredients, we performed analysis of new double-layered tablets. Ambroxol was found to be stable under the current condition. There was no change in the retention time after the extrusion process.

The commercial surfolase capsule (Acebrophylline 100 mg) is administrated twice daily. The object of double-layered tablet (Acebrophylline 200 mg) is administrated once daily for convenience of patients. Accordingly, we performed the object in vivo correlation double-layered formulation having about 50% the disintegration rate of 2 h in pH 1.2 for fast release effect and about 80% the dissolution rate of 12 h in pH 6.8 for sustained release effect.

The profile in **Figure 1** demonstrates that drug release was slow significantly released to depend on malic acid, carnauba wax and eudragit L100-55 when dissolution of Surfolase capsule (**Figure 2**) was compared with the sustained release formulations having differentiated ingredients under acebrophylline. The release rates of ambroxol were also influenced according to amount of malic acid (**Figure 1**).

The release rates of Surfolase capsule is more highly released in pH 1.2 than release rate in pH 6.8 (**Figure 2**). This mean can be having fast dissolution and pharmacokinetic in sustained release layer of double layered tablet. The double-layered tablet should have decreased for release rate in dissolution test of pH 1.2 as a whole. The inclusion of malic acid in sustained release layer in tablet was showed to decrease release rates in pH 1.2 equal to dissolution rate of pH 6.8 (**Figure 1**).

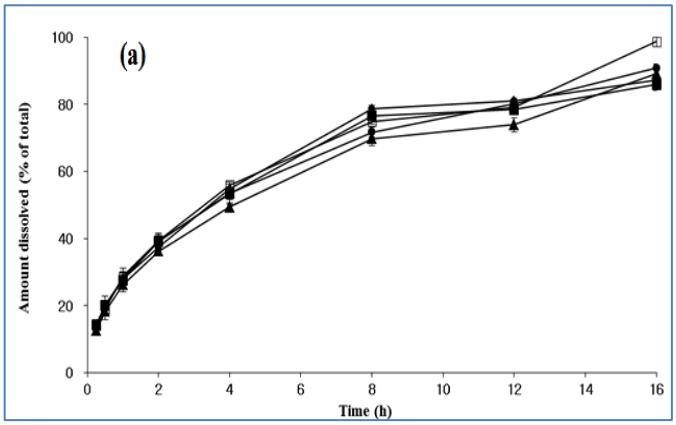

FIGURE 1: DISSOLUTION PROFILES OF SUSTAINED RELEASE LAYERS TREATED IN (a) pH 1.2 and (b) pH 6.8. ● FORMULATION 1; ◆ FORMULATION 2; ■ FORMULATION 3; ▲ FORMULATION 4; □ FORMULATION 5. (MEAN ± S.E., N=8)

The overall dissolution rates in pH 1.2 and 6.8 were decreased when formulation 1 was compared to formulation 4. The dissolution rates of formulation 4 were also significant differences objected the dissolution rates in between pH 1.2 and 6.8 at each time. However, the increased malic acid (formulation 5) was not affected the dissolution rates.

The formulation 2 and 3 having decreased Eudragit and carnauba wax were similar to the dissolution rates compared to the formulation 1 (**Figure 1**). The dissolution rates of fast release layer were similar at dissolution media with Surfolase capsule for 2 hours (**Figure 2**).

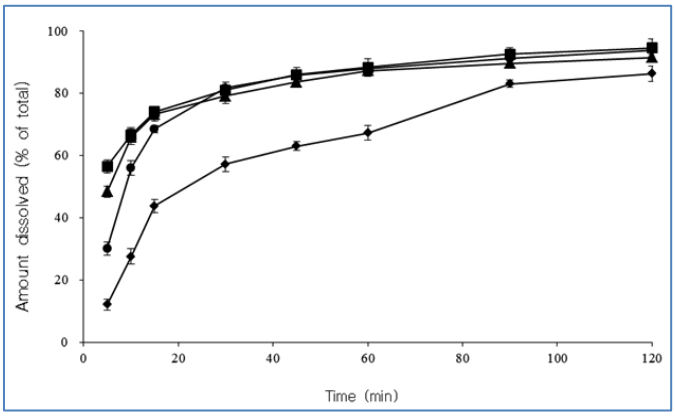

FIGURE 2: DISSOLUTION PROFILES OF SURFOLASE CAPSULE AND FORMULATION 6 (FAST RELEASE LAYER), TREATED IN pH 1.2 AND pH 6.8. ● SURFOLASE CAPSULE (pH 1.2); ◆ SURFOLASE CAPSULE (pH 6.8); ■ FORMULATION 6 (pH 1.2); ▲ FORMULATION 6 (pH 6.8). (MEAN ± S.E., N=8)

The total volume of acebrophylline (double-layered tablet) was also moderated by each of 50 and 150 mg in fast release and sustained release layers. The double-layered tablet of formulation 1 (sustained release layer) and formulation 6 (fast release layer) was released about 80% the dissolution rate of 12 h in pH 6.8 for sustained release effect (**Figure 3**).

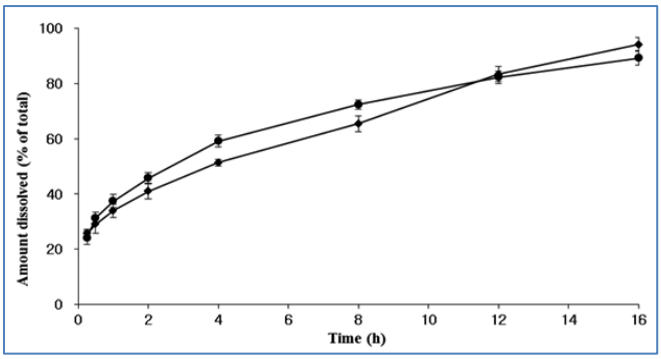

FIGURE 3: DISSOLUTION PROFILES OF DOUBLE-LAYERED TABLETS HAVING FORMULATION 1 (SUSTAINED RELEASE LAYER) AND FORMULATION 6 (FAST RELEASE LAYER), TREATED IN pH 1.2 AND pH 6.8. ● DOUBLE-LAYERED TABLETS (pH 1.2); ◆ DOUBLE-LAYERED TABLETS (pH 6.8). (MEAN ± S.E., N=8)

The double-layered tablet had also decreasing dissolved ambroxol compared to the Surfolase capsule at each time in pH 1.2. According to results of dissolution in pH 1.2 and 6.8, pharmacokinetic profiles in mini pigs of acebrophylline also showed effect of slow release in the profile (**Figure 4**).

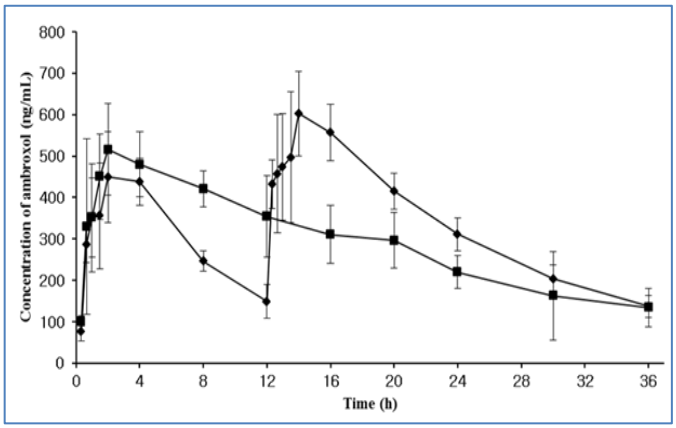

FIGURE 4: PLASMA CONCENTRATION OF AMBROXOL IN MINI PIGS PLASMA TIME CURVE (MEAN ± S.E., N=12). ◆, SURFOLASE® CAPSULE; ■, DOUBLE-LAYERED TABLETS

Standard curve: The retention time of ambroxol and IS of MS/MS was about 0.54 and 0.51 min, respectively. Standard calibration curves were constructed on different working days using the same mini pig plasma.

A validation was performed to assess the performance of the method. Seven-point calibration standard curve of ambroxol ranging from 10 to 1,500 ng/mL in mini-pig plasma was used in triplicate in each analytical run. For ambroxol, the regression equation was y = 0.0332 x – 0.0102 (r = 0.9992, n = 5) over the range of 10 – 1,500 ng/mL. Thus, the calibration curve did not exhibit any non-linearity within the chosen range. The limit of quantification (LOQ) of ambroxol was established at 10 ng/mL, and the coefficient of variation (CV) was less than 20%. Based on the standard data presented here, it was concluded that the calibration curves used in this method were precise and accurate for the measurement of ambroxol in mini pig plasma.

Accuracy and precision: The intra- and inter-day accuracy and precision of the assay were characterized by the four levels of QCs run in five replicates. The results, which were summarized in **Table 3**, demonstrated that the accuracy and precision values were within the acceptable range and the method was accurate and precise. Accuracy was assessed by calculating the percent deviation from the theoretical concentration. Precision was determined by calculating the coefficient of variation for intra- and inter-day replicates.

TABLE 3: INTRA- AND INTER- DAY ACCURACY AND PRECISION OF AMBROXOL IN MINI PIG

	Low (10 ng/mL)	Middle (200 ng/mL)	High (1,500 ng/mL)
	Intra-day accuracy and precision		
Mean	10.08	202.02	1494.00
S.D.	0.09	4.08	29.66
% CV	0.91	2.02	1.99
% Deviation	0.07	0.05	0.04
	Inter-day accuracy and precision		
Mean	10.13	202.28	1570.00
S.D.	0.21	2.07	46.90
% CV	2.10	1.03	2.99
% Deviation	0.15	0.04	0.72

Extraction recovery: The extraction recoveries of ambroxol were 27.3±0.02%, 28.6±0.01%, 30.1± 0.01% and 29.1±0.03% at the concentrations of 20, 200, 1,000 and 2,000 ng/mL, respectively (data not shown). The sensitivity is good enough for the detection of the drug concentration [17].

Pharmacokinetic study: The pharmacokinetic parameters of double-layered tablet in ambroxol were determined after oral administration of double-layered tablet of formulation 1 (sustained release layer) and formulation 6 (fast release layer) having ambroxol decreased by malic acid in dissolution test of pH 1.2 and Surfolase capsules, respectively. This double-layered tablet and Surfolase capsules were also tested for pharmacokinetic studies in mini pigs.

There have the fast release layer and the sustained release layer by several ingredients for fast and slow release under the volume of fixed total acebrophylline (200 mg). **Figure 4** represented the change of mean plasma concentration of ambroxol after oral administration in mini-pigs. There are all values of parameters in **Table 4**. The double-layered tablet of formulation 1 (sustained release layer) and formulation 6 (fast release layer) and Surfolase capsules were similar to the maximum plasma concentration (C_{max}), the mean residence time (MRT), $AUC_{(0-36)}$ (the area under the plasma concentration-time curve from 0 to 36 h) and $AUC_{(0-\infty)}$ (the area under the plasma concentration-time curve from 0 to infinity) in mini pigs (**Table 4**).

The 90% confidence intervals of the AUC_t ratio and the C_{max} ratio for double-layered tablet and Surfolase capsule were log 0.9402 ~ log 1.0245 and log 0.9983 ~ log 1.1542, respectively. These values were within the acceptable bioequivalence intervals of log 0.80 ~ log 1.25, recommended by the guidelines of Korea Food and Drug Administration. The results also showed that the differences between double-layered tablet and Surfolase capsule based on the reference drug, -6.5 and 12.62 % for AUC_t and the C_{max}, respectively (**Table 5**). These results indicated that ambroxol of fast release layer from Pearlitol DC 300 was fast released and ambroxol of sustained-release layer from carnauba wax and Eudragit L100-55 were slow released in mini pigs.

TABLE 4: PHARMACOKINETICS OF AMBROXOL IN DOUBLE-LAYERED TABLETS OF FORMULATION 1 (SUSTAINED RELEASE LAYER) AND FORMULATION 6 (FAST RELEASE LAYER) AND SURFOLASE CAPSULES IN MINI PIGS (MEAN ± S.E., N=12)

Parameters	Double-layered tablet	Surfolase capsule
C_{max} (ng/mL)	537.33 ± 137.91	477.1 ± 133.86
T_{max} (h)	2.01 ± 0.14	2.15 ± 0.65
MRT (h)	14.09 ± 1.10	13.86 ± 1.54
$t_{1/2}$ (h)	22.47 ± 0.5	8.54 ± 0.19
$AUC_{(0-36)}$ (h·ng/mL)	12352.15 ± 1002.71	13721.12 ± 1051.99
$AUC_{(0-\infty)}$ (h·ng/mL)	14766.12 ± 1325.89	15792.67 ± 1372.40

All values are expressed as mean ± standard deviation.

TABLE 5: STATISTICAL RESULTS OF BIOEQUIVALENCE EVALUATION BETWEEN DOUBLE-LAYERED TABLET AND SURFOLASE CAPSULE IN MINI PIGS[#] (MEAN ± S.E., N=12)

	Parameters	
	AUC_t	C_{max}
Difference (%)	-6.5	12.62
Test/Ref point estimate	0.96	1.07
Confidence interval (δ)[a]	$0.9042 \leq \delta \leq 1.0245$	$0.9983 \leq \delta \leq 1.1542$

[#]The AUCt and Cmax values were calculated on the basis of logarithmically transformed data. [a]α=0.05

This result suggested that malic acid, carnauba wax and Eudragit L100-55 would be useful to deliver ambroxol in a pattern that allows improved dissolution rate, leading to be double-layered tablet. We demonstrated the potential of malic acid, carnauba wax and Eudragit L100-55 processed by double-layered tablet for improving oral delivery.

Our results also indicate that the proposed method has been successfully applied to pharmacokinetic studies to determine the concentration of ambroxol in human plasma.

CONCLUSION: From these observations of double-layered tablet and pharmacokinetic behaviors, the malic acid, carnauba wax and Eudragit L100-55 could be efficacious in leading the sustained release profile of pharmacokinetic behaviors in mini pigs. According to the pharmacokinetic profiles, there was significantly equal to C_{max} and AUC. In addition, the double-layered tablet of acebrophylline has simplified the dosage regimen and may help to improve patient compliance. These results will also be useful for further pharmacokinetic studies of acebrophylline during clinical trial.

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