Physical and clinical characterization of ambroxol SR matrix tablets containing melt-coated granules of ambroxol with compritol 888

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Abstract

Purpose: The physical and clinical characteristics of Ambroxol SR matrix tablets containing melt-coated granules of Ambroxol with Compritol 888 were evaluated.

Methods: Ambroxol SR matrix tablets containing melt-coated granules of Ambroxol with Compritol 888 were manufactured and their flow characteristics, bulk and tapped densities, and compressibility of the powder mixtures containing melted granules were measured. Dissolution was performed using a dissolution apparatus II method (USP 24) over a 24-h period. The pharmacokinetic studies in two cross-over design on 16 healthy male human subjects after oral administration with multiple doses of Amcosolv SR tablets with reference to PR-ABX capsules and Maxsolven capsules were evaluated.

Results: The powder mixtures of melted granules of ambroxol with Compritol 888 still exhibited acceptable flow characteristics for direct tabletting. In vitro dissolution studies showed that the drug release rate and amount were not affected by the particle size of the melted granules of ambroxol with Compritol 888 or by the tabletting speed. However, the hardness of the ambroxol SR tablets was increased by the particle size and tabletting speed. The pharmacokinetic study showed that Amcosolv tablets were able to reproduceably provide a slow and low-dose release of ambroxol.

Conclusions: The efficacy and safety of this ambroxol SR tablet (Amcosolv SR tablets) dosage form should provide optimum therapeutic efficacy and improve patient compliance.

Keywords: Compritol 888, Melt granulation, Matrix tablets, Ambroxol

1. Introduction

Cellulose ether derivatives, typically represented by hydroxypropylmethylcellulose (HPMC) of varying degrees of viscosity, have traditionally been used as matrix materials in sustained-release dosage forms due to their rapid hydration, and good compression and gelling characteristics, along with their ease of use, ready availability, and very low toxicity [1]. Since the controlling mechanism of HPMC drug release is dependent on its gelling characteristics, this is sometimes not optimal for providing highly water-soluble drugs with a desired sustained release rate.

Another problem with HPMC is that particles do not possess sufficient flowability for direct compression when producing matrix tablets. Furthermore, attempts at granulation to improve the flowability of formulations containing higher percentages of HPMC with aqueous solutions can result in fluffy particles, or rigid particles if alcoholic solutions are used. Both these particle forms are unsuitable for tablet compression.

Recently, a melt-coating granulation method has been widely used to obtain powdered agglomerates by the use of a meltable binder, which can be a molten liquid, a solid, or a solid that melts or softens during the solvent-free process [2]. When melted, the meltable binder acts like a binding liquid, similar to what occurs in a wet granulation process. Melt-coating granulation offers several advantages compared to conventional wet granulation in that it is cost-effective and safe since liquid addition and the subsequent drying phase required for the wet granulation process are not necessary. Moreover, melt-coating granulation is also well suited for water- or solvent-sensitive drugs. Granules prepared by melt-coating granulation exhibit better physical strength and have smoother surfaces than those obtained by wet granulation, and they are also suitable for further operations such as coating. Polyethylene glycols [3], waxes [4], stearic acid [5,6], fats, fatty acids, fatty alcohols [7,8], castor oil [9,10], and glycerides [11] are typical examples of meltable binders. Melt-coating granulation has been applied not only to the development of sustained-release formulations but also to the construction of fast-release dosage forms. The in vitro dissolution rates of ibuprofen and carbamazepine can be improved by melt-coating granulation using poloxamer 188 [12] and polyethylene glycol 4000 [13] as melting binders, respectively.

Compritol 888 has been used as a coating agent for oral sustained-release dosage forms [14,15], and increasing the amount or concentration of Compritol 888 leads to slower and more-prolonged drug-release profiles [16]. Compritol 888 has also been used as a lubricant to reduce interparticle friction during the densification phase and between the material and the compression die walls during the ejection phase of the compact [17]. We hypothesized that melt-coating granulation of highly water-soluble drugs with Compritol 888 might improve not only the overall flowability of the particle mixtures for direct compression but also the sustainability of drug release from matrix tablets. Ambroxol hydrochloride salt was selected as a model of a highly water-soluble drug.

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2. Experimental procedures

2.1. Materials

Ambroxol hydrochloride salt (100.6%; batch: 0600117) was purchased from Erregiere (San Paolo D’Argon, Italy). Compritol 888 was purchased from Gattefosse (Codex, France), Hydroxypropyl methylcellulose (Pharmacoat 645 W; labeled viscosity: 4.5 cp) and Metolose (60SH-4000; labeled viscosity: 4000 cp) were obtained from Shin-Etsu Chemical (Tokyo, Japan). Microcrystalline cellulose, PH 101 (MCC) was supplied by Ming-Tai Chemical (Taipei, Taiwan). Magnesium stearate was provided by Merek (Durnstadt, Germany). All materials were used as received, and all other chemicals were of reagent grade. Two commercial ambroxol products with sustained-release properties were used as references for comparison in the dissolution study. Prolonged-release ambroxol HCl 75-mg capsules (hereafter referred to as “PR-ABX” capsules; batch: L2823) were purchased from Malpharma (Rimini, Italy). Mucolvan SR capsules (containing 75 mg ambroxol HCl; batch: 104709; expiration date: 2004/07) were purchased from Boehringer Ingelheim (Biberach an der Riss, Germany).

2.2. Methods

Test formulations containing melted granules of ambroxol with Compritol 888 used in the preformulation studies of the sustained release of ambroxol are listed in Tables 1-3. The weight of tablets was set at 310 mg, with each containing 75 mg ambroxol HCl (24.2% weight per tablet). Except for Compritol 888, the excipients included in the preformulation studies were MCC, Pharmacoat, Metolose, and magnesium stearate. The final optimized formulation of ambroxol SR tablets consisted of 75 mg ambroxol HCl (24.2% weight per tablet), 37.5 mg Compritol 888 (12.1%), 178.6 mg MCC (57.6%), 17.35 mg Pharmacoat (5.6%), and 1.55 mg magnesium stearate (0.5%). Ambroxol was divided into two equal parts, one for instant release (referred to as ambroxol\textsubscript{IR}), while the other was granulated with melted Compritol 888 (referred to as ambroxol\textsubscript{SR}) for sustained release.

2.3. Melt-coating granulation

Compritol 888 was melted at 75-80°C in a container with heating. Then, an appropriate amount of ambroxol (ambroxol\textsubscript{IR}) according to the formula was added and thoroughly mixed. The ambroxol-Compritol 888 melted mixture was slowly poured onto a stainless plate and cooled to room temperature to allow it to solidify. The solidified mass was subsequently crushed into fine particles and the particles were sieved through 40-mesh (420-µm), 60-mesh (250-µm), and 120-mesh (125-µm) standard sieves to obtain three size fractions of <125, 125-250, and 250-420 µm. A fourth fraction was obtained just by passing through a 40-mesh (<420 µm) sieve. The melt-coated particles were then uniformly mixed with other ingredients, including an instant-release portion of ambroxol (ambroxol\textsubscript{SR}), microcrystalline cellulose (MCC), Pharmacoat, Metolose, and magnesium stearate, for 10 min in a plastic bag or a powder blender.

2.4. Physical characteristics of the melted granules

The flow characteristics, bulk and tapped densities, and compressibility of the powder mixtures containing melted granules were measured to verify the improvement in physical characteristics of those melted granules using Compritol 888 for tabletting. The freestanding cone method was employed to calculate the angle of repose as one indicator of the flow characteristics. The angle of repose, θ, is determined by tan θ = H/R, where H is the height and R is the radius in centimeters. For determination of the bulk and tapped densities, 100 ml of the powder mixture was gently sifted into a 100-ml graduated cylinder through a funnel. Then the weight (Wb) of 100 ml of powder mixture was determined, and the bulk density was calculated as(Db = Wb/100). The graduated cylinder was tapped from a height of 25 mm and the reduction in volume (VR) was measured after 100 taps, and then the tapped density (Dt = Wb/VR) was calculated as defined above. Carr’s compressibility index and the Hausner ratio were calculated from the following equations: Compressibility (%) = |(Dt - Db)| / Dt × 100% and the Hausner ratio = Dt / Db.

2.5. Tablet manufacturing method

Tablets in the preliminary study were compressed using a Carver laboratory press using standard 9-mm concave punches at a compression force of 0.5 ton. A rising speed of 0.5 cm/s and a zero contact time were used to form the tablets. The weight of the tablet was set at 310 mg. Tablets for the clinical study were manufactured by a direct compression process using a 15-station rotary tabletting machine equipped with a 10-mm flat-face, bevelled-edge disk-shaped punch. The tabletting machine was adjusted to produce a consistent tablet weight of 310 mg containing 75 mg ambroxol. The tabletting speed was set at either 20 or 36 rpm.

2.6 Physical characteristics of ambroxol SR tablets

The weight variation was tested using the USP 24 method. Ten tablets from each sample were analyzed. The tablet hardness of ten tablets was determined by the load (N) required to diametrically break the tablet using a hardness tester (Pharma Test, model PTB 311, Hamburg, Germany). The friability study was conducted in a Roche friabilator (model AE-20, Aikho Engineering, Taipei, Taiwan). Pre-weighed 10-tablet samples were placed in the friabilator, which was then operated for 240 revolutions at a speed of 25 r/min. The tablets were dusted and reweighed. The friability was calculated from the following equation as Friability (%) = [Initial weight – Final weight] / Initial weight × 100%.

2.7. Disintegration testing

Disintegration was performed using a dissolution apparatus II method (USP 24) over a 24-h period. The dissolution media were 500 ml of pH 1.2 HCl solution, a pH 4.5 phosphate buffer solution (PBS), and a pH 6.8 PBS. For the pH-change dissolution method, the medium was a pH 1.2 HCl solution from 0 to 2 h, and then at 2 and 4 h, the pH of the medium was adjusted to pH 4.5 and 6.8, respectively, by adding appropriate amounts of trisodium phosphate. The temperature of the medium and the rotation speed
of the paddle were maintained at 37°C (± 0.5°C) and 100 rpm, respectively. Six tablets (or capsules) were used for each test. Samples (at 5 ml) were withdrawn at designated time points and passed through a membrane filter. The filtered sample was diluted to an appropriate volume with fresh medium and measured spectrophotometrically at 245 nm to determine the amount of released drug. The average percentage of drug dissolved at each sampling time was calculated after correction for the cumulative amount removed in previous samples. Throughout the study, similarity factors (t2) were used to compare the dissolution profiles.

2.8. Pharmacokinetic study

2.8.1. Subject and study design

Four healthy male volunteers participated in this pharmacokinetic pilot study. The study protocol was approved by the local Ethics Committee and all subjects gave their informed written consent prior to the start of the study. Subjects were at least 20 years of age and in good health following a comprehensive medical history, physical and routine laboratory screening tests (including fasting serum glucose). The body weight of each subject did not deviate from the ideal body weight by more than 20%.

2.8.2. Blood sample collection and processing

Heparinized venous blood samples (about 8 ml; except for blank samples, 16 ml) were collected via an indwelling venous cannula in the cubital vein on profile days according to the time schedule appended. This included blank samples prior to each dosing and 1, 2, 3, 5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 14, 24, 36, and 48 hours after the 5th drug administration on day 5. Any deviation from the stated sampling time was recorded on an appropriate form. Plasma samples were separated immediately by centrifugation at 3000 rpm for 10 minutes at 4°C, then transferred to suitably labeled tubes and stored at -80°C in a refrigerator until assayed.

2.8.3. Analytical methods and validation

Ambroxol concentrations in plasma were assayed using an LC/MS/MS method and fully validated with respect to its selectivity, sensitivity, linearity, recovery and accuracy, and precision (both within and between days). The calibration curves with a weighting factor of 1/x, were linear over the range 1 to 300 ng/ml (1, 2, 5, 10, 50, 100, 200 and 300 ng/ml) ambroxol and the correlation coefficient (R²) was better than 0.997.

The pharmacokinetic variables of ambroxol in healthy male human subjects were calculated using a non-compartmental model. The maximum plasma concentration (Cmax, ss) and the time to reach Cmax, ss (Tmax, ss) at steady-state were obtained directly from the observed concentration-time curve data. The terminal rate constant, Kd, was calculated by applying a log-linear regression analysis to at least the last three time points. The apparent elimination half-life (T1/2) was calculated as 0.693/Kd. The area under the plasma concentration-time curve (AUC0-t, ss), the area under the moment versus time curve (AUMC0-t, ss), the mean residence time (MRT0-t, ss), and the relative total clearance (CL/F) of ambroxol at steady-state were calculated from the following equations:

\[ \text{AUC}_{0-t, \text{ss}} = (C_t + C_{t+1}) \times (t_{t+1} - t_t) / 2 \]

\[ \text{AUMC}_{0-t, \text{ss}} = (C_t + C_{t+1}) \times (t_{t+1} - t_t) / 2 \]

\[ \text{MRT}_{0-t, \text{ss}} = \text{AUMC}_{0-t, \text{ss}} / \text{AUC}_{0-t, \text{ss}} \]

\[ \text{CL/F} = \text{Dose} / \text{AUC}_{0-t, \text{ss}} \]

3. Results and discussion

All ambroxol (75 mg, 24.2%) preparations were used in melted form; the dissolution profiles of ambroxol for formulations A1 to A4 (Table 1) were obtained in a pH 1.2 HCl solution, and the plots are shown in Fig. 1 along with a comparison with PR-ABX capsules. The dissolution rate and amount (except formula A2) of these formulas were all lower than those of PR-ABX capsules. Among these formulas, although dissolution could be sustained for 24 h, the initial release rates were insufficient, so an appropriate amount of instantly released ambroxol was needed.

Ambroxol was then divided into equal amounts of 37.5 mg (ambroxolins, instantly released and ambroxolmelt, melt-coated with Compriol 888 at a ratio of 1:1.5). The dissolution rates of these formulations of B1 B7 (Table 2) containing ambroxol in such a composition were determined in a pH 1.2 HCl solution, and the results compared with PR-ABX capsules in Fig. 2. The results demonstrate that the dissolution profile of B1 tablets was the closest to that of PR-ABX capsules (t2 = 63.2). However, the dissolution rate of ambroxol from this B series of formulations was still not fast enough during the initial time period.

Keeping the two parts of ambroxol and ambroxolmelt the same in the formulation, the C series (Table 3) was melt-granulated with smaller amounts of Compritol 888 and MCC, and a low-viscosity grade of HPMC (Pharmacut) was used to enhance the dissolution rate. The dissolution profiles in pH 1.2 HCl solution for C1 to C4 tablets were examined and compared with those of PR-ABX capsules in Fig. 3. Although, the dissolution profiles of C1 and C2 tablets during the initial time period (0-4 h) were very similar to those of PR-ABX capsules in pH 1.2 HCl solution, no dissolution.
profile of tablets for this series of formulations had f2 values higher than 50 in any of the dissolution media.

By appropriate adjustment of the relative fraction of excipients and manufacturing parameters, such as tabletting force and speed, an optimized formulation was developed which exhibited sustained drug release for up to 24 h, designated as Ambroxol SR matrix tablets (75 mg ambroxol). The tablets contained both ambroxol and ambroxolmelt at 12.1%, MCC at 57.6%, Pharmacoat at 5.6%, and Compritol 888 at 12.1%. The flow properties of these tablets formulations containing melted granules of ambroxol with Compritol 888 in different size fractions (< 125, 125-250, 250-420, and < 420 μm) were measured and compared. The results showed that the effect of the size of melted granules on all flow properties measured was minimal. However, variations in flow properties measured for formulations containing melted granules in each size fraction of < 420 μm seemed to be smaller among the four different size fractions examined. The mean repose angle was 38.0 ± 0.5°, the bulk density was 0.39 ± 0.02 g/ml, the tapped density was 0.50 ± 0.01 g/ml, and Carr’s compressibility index was 21.41% ± 2.11%, and the Hausner ratio was 1.27 ± 0.03. These data show that the powder mixture including melted granules of ambroxol with Compritol 888 indeed possessed reasonable flow properties to allow direct tabletting [18].

The hardness values of ambroxol SR tablets at different tabletting speeds (20 and 36 r/min) and particle sizes (< 125, 125-250, and 250-420 μm) are shown in Fig. 4. Values for the hardness of tablets prepared with different particle size fractions at tabletting speeds of 20 and 36 rpm were 58.8 ± 8.8 and 45.2 ± 7.1 N for < 125 μm, 59.2 ± 16.6 and 49.6 ± 4.0 N for 125-250 μm, and 62.4 ± 4.8 and 63.8 ± 9.9 N for 250-420 μm, respectively. At the low tabletting speed (20 r/min), hardness was not affected by particle size, while at the high tabletting speed (36 r/min), the larger particle size may have made the tablets more compact. For particle sizes smaller than 125 μm or in the range 125-250 μm, the hardness of tablets compressed at a tabletting speed of 20 r/min was significantly higher than that at 36 r/min, while in the case of large particle sizes (250-420 μm), there was no significant difference between these tabletting speeds. This phenomenon can be rationalized by the plastic deformation characteristics of the tablet materials.

MCC and Pharmacoat are well known for their plastic deformation properties. At a low tabletting speed, these materials have sufficient time to deform plastically which results in more-compact tablets. Another reason is the bonding-masking effect of melted granules. Compritol 888 is a type of wax, and may mask the bonding formation of other excipients, such as MCC and HPMC. Melted granules with a large particle size have smaller surface areas and result in a small masking effect on tablet bonding formation, while melted granules with a small particle size have large surface areas and can mask the tablet bonding formation more effectively, resulting in tablets with a reduced hardness.

Fig. 5 shows that the dissolution profiles of ambroxol SR tablets are similar in a pH 1.2 HCl solution regardless of the size fraction used to prepare the tablets (< 125, 125-250, and 250-420 μm) and the tabletting speed (20 or 36 r/min chosen. However, at a low tabletting speed (20 r/min), the hardness of the matrix tablets was not affected by the size fraction used, while at a high tabletting speed (36 r/min), tablets produced with the larger particle size may be more compact. Therefore, it was concluded that it was only necessary to keep the size of the melt-coated particles below 420 μm and to use the lower speed to manufacture Ambroxol SR tablets.

According to the dissolution studies, drug release rates were not affected by tabletting speed or particle size, and a low tabletting speed produced more-compact tablets. Finally, a particle size < 420 μm of ambroxol-Compritol 888 melted particles was selected because of the higher production yield. The selected melted particles were thoroughly mixed with other excipients and tabletted at 20 r/min. Fig. 5 also shows the dissolution profiles of ambroxol SR tablets prepared with this size fraction in a pH 1.2 solution. The dissolution rate was slightly faster with the selected particle size of < 420 μm than for the other range of particle sizes at 0-8 h, while it decreased slightly at 8-24 h. The f2 values were 62.0, 58.3, and 56.1 for Ambroxol SR tablets (< 420 μm) and the other particle size fractions (< 125, 125-250, and 250-420 μm), respectively. These data show that the dissolution rates were only significantly influenced by particle size.

Since almost 34 min was required to produce a batch of 10,000 tablets, 10 tablets at 1, 16 and 31 min as the initial, medium, and final stages after production were respectively sampled to evaluate the flow characteristics indicated by the weight variation of the tablet and the content uniformity of ambroxol. The mean and standard deviation were calculated for each tablet stage. Weight variations (mean ± SD) of Ambroxol SR tablets were 310.3 ± 3.3, 310.4 ± 3.3, and 310.9 ± 3.2 mg at 1, 16, and 31 min of production, respectively. The Ambroxol content (mean ± SD) of Ambroxol SR tablets was 75.13 ± 0.37, 75.30 ± 0.95, and 75.18 ± 0.76 mg at 1, 16, and 31 min of production, respectively. The mean values showed that the tablets manufactured at the beginning, middle and final stages of tabletting production had similar weights and ambroxol content. The weights and ambroxol content of the samples did not differ significantly (p = 0.9316 and 0.8651, respectively) as tested by one-way ANOVA. These data also confirmed that the powder flowability was sufficiently good to produce uniform tablets.

Fig. 6 shows the dissolution profiles of Ambroxol SR tablets, PR-ABX capsules, and Mucosolvan capsules in three dissolution media (pH 1.2 HCl solution, pH 4.5 PBS, and pH 6.8 PBS). The release rate and the amount of the two commercial products, PR-ABX and Mucosolvan capsules, were dependent on the pH of the dissolution medium, while the release of ambroxol from Ambroxol SR tablets was not. Even in a pH-changing medium, the release profile was also found to be independent of the pH value (Fig. 7).

Fig. 8 shows the influence of the pH value of the dissolution medium on the percentage of ambroxol released at 8 and 24 h from Ambroxol SR tablets, Mucosolvan capsules, and PR-ABX capsules. The percentage of ambroxol released from Ambroxol SR tablets was not affected by a pH change between pH 1.2 and 6.8 at either 8 or 24 h. For PR-ABX capsules at 8 h, the percentage of ambroxol released slightly increased when the pH value was changed from 1.2 to 4.5, but decreased significantly from pH 4.5 to 6.8. At 24 h, the amount released decreased on increasing the pH value from 1.2 to 6.8. The percentage ambroxol released from Mucosolvan capsules increased on increasing the pH value from 1.2 to 6.8 both at 8 and 24 h. These results are in agreement with
Table 1
Formulations of ambroxol SR tablets in the preformulation study (I)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>A1 (mg)</th>
<th>A2 (mg)</th>
<th>A3 (mg)</th>
<th>A4 (mg)</th>
</tr>
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<tbody>
<tr>
<td>MCC</td>
<td>116.7</td>
<td>70.0</td>
<td>70.0</td>
<td>46.7</td>
</tr>
<tr>
<td>Pharmacoat</td>
<td>0</td>
<td>46.7</td>
<td>23.4</td>
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<tr>
<td>Metolose</td>
<td>0</td>
<td>0</td>
<td>23.3</td>
<td>23.3</td>
</tr>
<tr>
<td>Ambroxolact</td>
<td>75.0</td>
<td>24.2</td>
<td>16.7</td>
<td>16.7</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>116.7</td>
<td>37.6</td>
<td>16.6</td>
<td>16.6</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>16.0</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Weight of one tablet (mg)</td>
<td>310.0</td>
<td>100.0*</td>
<td></td>
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</tbody>
</table>

Figures in parentheses represent the percent weight of each tablet.

Table 2
Formulations of ambroxol SR tablets in the preformulation study (II)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>B1 (mg)</th>
<th>B2 (mg)</th>
<th>B3 (mg)</th>
<th>B4 (mg)</th>
<th>B5 (mg)</th>
<th>B6 (mg)</th>
<th>B7 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC</td>
<td>174.7</td>
<td>0</td>
<td>0</td>
<td>87.4</td>
<td>0</td>
<td>166.0</td>
<td>139.8</td>
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<tr>
<td>Pharmacoat</td>
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<td>0</td>
<td>87.3</td>
<td>87.4</td>
<td>8.7</td>
<td>34.9</td>
</tr>
<tr>
<td>Metolose</td>
<td>0</td>
<td>0</td>
<td>174.7</td>
<td>0</td>
<td>87.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ambroxolact</td>
<td>37.5</td>
<td>12.1</td>
<td>37.5</td>
<td>12.1</td>
<td>58.7</td>
<td>19.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>58.7</td>
<td>19.0</td>
<td>58.7</td>
<td>19.0</td>
<td>58.7</td>
<td>19.0</td>
<td>58.7</td>
</tr>
<tr>
<td>Magnesium stearate</td>
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<td>0.5</td>
<td>1.6</td>
<td>0.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Weight of one tablet (mg)</td>
<td>310.0</td>
<td>100.0*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures in parentheses represent the percent weight of each tablet.

Table 3
Formulations of ambroxol SR tablets in the preformulation study (III)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>C1 (mg)</th>
<th>C2 (mg)</th>
<th>C3 (mg)</th>
<th>C4 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC</td>
<td>196 (63.2)</td>
<td>194 (62.6)</td>
<td>192 (61.9)</td>
<td>186.2 (60.0)</td>
</tr>
<tr>
<td>Pharmacoat</td>
<td>0</td>
<td>2 (0.6)</td>
<td>4 (1.3)</td>
<td>9.8 (3.2)</td>
</tr>
<tr>
<td>Ambroxolact</td>
<td>37.5</td>
<td>12.1</td>
<td>37.5</td>
<td>12.1</td>
</tr>
<tr>
<td>Compritol 888</td>
<td>37.5</td>
<td>12.1</td>
<td>37.5</td>
<td>12.1</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.6</td>
<td>0.5</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Weight of one tablet (mg)</td>
<td>310.0</td>
<td>100.0*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures in parentheses represent the percent weight of each tablet.

Those of a previous report [19]. Mucosolv capsules are based on pellets composed of fatty acids. In medium with a higher pH value, fatty acids are ionized and can act as surfactants that markedly promote drug release. PR-ABX capsules are based on pellets with a dialyzing membrane for controlled release. The lower release from PR-ABX capsules in higher-pH medium could be due to the lower solubility of such a basic drug as ambroxol in a medium with a pH value close to neutral.

The mean and standard deviation of the ambroxol plasma concentration-time profiles in 16 subjects after multiple dosing of Amsolvon SR tablets in comparison with PR-ABX capsules (A) and Mucosolv capsules (B) in a cross-over study are shown in Fig. 9. The pharmacokinetic (PK) parameters were calculated for each formulation and are summarized in Table 4. The results show that the PK parameters obtained for Amsolvon tablets in these two cross-over studies using PR-ABX capsules or Mucosolv capsules as the respective reference did not differ in a statistically significant manner. The reproducibility of the Amsolvon tablets in terms of their quality is indicated. Based on the pivotal PK parameters, AUC0-24, Cmax, tmax, Cmin, tmin, C0, t0, and the variability in two one-sided t-tests, the Amsolvon tablets and Mucosolvan capsules are bioequivalent, whereas the Amsolvon tablets and
Fig. 1. Dissolution profiles of ambroxol tablets of formulae A1 to A4, and PR-ABX capsules in pH 1.2 HCl solution.

Fig. 2. Dissolution profiles of ambroxol tablets of formulae B1 to B7, and PR-ABX capsules in pH 1.2 HCl solution.

Fig. 3. Dissolution profiles of ambroxol tablets of formulae C1 to C4, and PR-ABX capsules in pH 1.2 HCl solution.

Fig. 4. Hardness of ambroxol tablets at different tabletting speeds (20 and 36 rpm) and particle sizes (<125, 125-250, and 250-420 μm).

Fig. 5. Effect of size and tabletting speed (20 or 36 rpm) on dissolution of ambroxol in pH 1.2 HCl solution.

Fig. 6. Dissolution profiles of Amsolvon SR tablets, PR-ABX, and Mucosolvan capsules in various dissolution media.

PR-ABX capsules are not. Obviously, this was due to the higher $C_{\text{max,ss}}$ and lower $C_{\text{min,ss}}$ which also result in larger fluctuations, so that PR-ABX capsules are not statistically bioequivalent to Amsolvon tablets. Since the relative bioavailability ($F$), $C_{\text{max,ss}}$, $T_{\text{max}}$, and MRT$_{ss}$ after oral administration of PR-ABX capsule were found not to be statistically significantly different from those of Amsolvon tablets, it is reasonable to attribute the non-bioequivalence to the difference in the in vivo dissolution rate or absorption rate. A smaller $T_{\text{max}}$ after oral administration of
Fig. 7. Dissolution profiles of Amsolvent SR tablets, Mucoisolvan capsules, and PR-ABX capsules in dissolution medium in which the pH changed (pH 1.2 HCl solution for 0–2 h, pH 4.5 phosphate buffer for 2–4 h, and pH 6.8 phosphate buffer for 4–24 h).

PR-ABX capsules also indicates that the in vivo dissolution of ambroxol from PR-ABX capsules is faster leading to a faster rate of absorption than that from Amsolvent tablets.

The dissolution characteristics shown in Fig. 8 demonstrate that the amount and release rate of drug from PR-ABX capsules were greater than those from Amsolvent tablets under both acidic conditions (pH 1.2 and 4.5), and then reversibly became smaller and slower than those of Amsolvent tablets in medium with a neutral pH. Expectedly, the in vivo dissolution of ambroxol from PR-ABX capsules was faster in the upper part of the GI tract and slower in the distal part of the small intestine compared with that from Amsolvent tablets. This resulted in more abrupt increases in the plasma concentrations of ambroxol followed by a rapid decline in the systemic appearance of ambroxol after oral administration of PR-ABX capsules. Compared with that for PR-ABX capsules, the pH independence of the in vitro dissolution rate of ambroxol from Amsolvent tablets led to a smooth rise and decline in the plasma concentration of ambroxol. Therefore, a higher C_{max,m} (149.3 ± 43.7 vs. 99.4 ± 30.9), a lower C_{min,m} (18.6 ± 10.5 vs. 38.2 ± 17.1), and a larger fluctuation (2.23 ± 0.48 vs. 1.09 ± 0.30) were observed after oral administration of PR-ABX capsules than after Amsolvent tablets. This correlation between in vitro dissolution and in vivo absorption used to rationalize the relationship between the dissolution and plasma profiles of PR-ABX capsules and Amsolvent tablets should involve a mechanism for activating drug release from both which is physiologically irrelevant.

Although the in vitro dissolution of Mucoisolvan capsules was characterized by a slower release rate and lower amount of ambroxol released under both acidic conditions (pH 1.2 and 4.5) followed by a very marked increase at pH 6.8, the plasma profiles after oral administration were found to be bioequivalent to those of Amsolvent tablets from which the rate and amount of drug released were unaffected by the pH change. The irrelevant correlation between the dissolution and plasma concentration profiles of Mucoisolvan capsule can perhaps be due to the fact that the conditions employed in the in vitro dissolution study differed from the in vivo conditions in that enzymes present in the GI tract could degrade the lipid material used to encapsulate the drug for sustained release. Alternatively, although a slower release rate and lower amount of ambroxol released from Mucoisolvan capsules were observed compared with Amsolvent tablets under both acidic conditions, enzymatic degradation of the lipids after oral administration of Mucoisolvan capsules should facilitate the in vivo release rate, thus releasing an amount of ambroxol which results in plasma profiles similar to those of Amsolvent tablets.
Table 4
Mean pharmacokinetic parameters after multiple-dose administration of amssolvor SR tablets, PR-ABX, and mucosolvan capsules at steady-state

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Amssolvor vs. PR-ABX</th>
<th>Amssolvor vs. Mucosolvan</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-24h} (ng·h/ml)</td>
<td>1446 ± 590</td>
<td>1527 ± 423</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>99.4 ± 30.9</td>
<td>149.3 ± 43.7</td>
</tr>
<tr>
<td>C_{min} (ng/ml)</td>
<td>38.2 ± 17.1</td>
<td>18.6 ± 10.5</td>
</tr>
<tr>
<td>C_{cmax} (ng/ml)</td>
<td>60.2 ± 24.6</td>
<td>60.7 ± 20.0</td>
</tr>
<tr>
<td>Fluctuation</td>
<td>1.09 ± 0.30</td>
<td>2.23 ± 0.48</td>
</tr>
<tr>
<td>MRTw (h)</td>
<td>10.4 ± 0.6</td>
<td>9.0 ± 0.7</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>6.88 ± 2.23</td>
<td>4.75 ± 1.31</td>
</tr>
<tr>
<td>T_{1/2} (h)</td>
<td>10.56 ± 2.01</td>
<td>9.54 ± 1.76</td>
</tr>
<tr>
<td>Relative Bioavailability (F)</td>
<td>1.02 ± 0.31</td>
<td>—</td>
</tr>
</tbody>
</table>

*Mean = SD; T = (AUC_{0-24h} of the test drug) / (AUC_{0-24h} of the reference drug).

4. Conclusions

The present study showed that the half amount of ambroxol in ambroxol SR tablets made by melt-coating granulation with an equal amount of Compritol 888 could prolong the drug release without adversely affecting the granule and tablet properties. In vitro dissolution studies showed that the rate and amount of drug released were not significantly affected by the mean particle size of the ambroxol-Compritol 888 melted granules or tabletting speeds. However, the hardness of the ambroxol SR tablets was influenced by the particle size and tabletting speed. The higher yield of melted particles (< 420 μm) and a tabletting speed of 20 mm/min were selected for Amssolvor SR tablets. The dissolution profile of Amssolvor SR tablets was characterized by the pH independence and was more similar to that of PR-ABX capsules than to Mucosolvan capsules in three different dissolution media or pH-changing medium. However, the pharmacokinetic study in two cross-over design on 16 healthy male human subjects after oral administration with multiple doses of Amssolvor SR tablets with reference to PR-ABX capsules and Mucosolvan capsules showed that Amssolvor tablets were able to reproducibly provide a slower and less variable release of ambroxol. The efficacy and safety of this ambroxol SR tablet (Amssolvor SR tablet) dosage form are expected to offer optimum therapeutic efficacy and improved patient compliance.

References