Sustained-Release Phenylpropanolamine Hydrochloride Bilayer Caplets Containing the Hydroxypropylmethylcellulose 2208 Matrix.

I. Formulation and Dissolution Characteristics

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The purpose of this study was to develop a new sustained-release phenylpropanolamine hydrochloride (PPA) bilayer caplets that consists of an immediate-release portion and a prolonged-release portion containing a hydroxypropylmethylcellulose 2208 (HPMC2208) matrix. Since PPA is a highly water-soluble drug, incorporation of 60% HPMC2208 level in the matrix was required for giving the product a PPA-slow releasing property. Difference in the viscosity grade of HPMC2208 in the matrices did not greatly influence the PPA dissolution characteristics from the matrices. Therefore, we formulated the prolonged-release portion consisting of 10% PPA, 30% excipients, and 60% HPMC2208 (Metolose 90SH4000) into the sustained-release PPA bilayer caplets. The PPA dissolution characteristics from the formulated bilayer caplets showed the prolonged dissolution profile after rapid dissolution and was close to the targeted profile calculated from PPA pharmacokinetics study. The manufacturing methods of the prolonged-release portion and the filling order of the prolonged-release portion in bilayer compression did not significantly affect the PPA dissolution characteristics from the bilayer caplets. The PPA dissolution characteristics from the bilayer caplets was pH independent. Moreover, the PPA dissolution characteristics from the bilayer caplets was not affected by mechanical shear. The sustained-release PPA bilayer caplets is expected to present constant prolonged-release of PPA after rapid dissolution in vivo without dissolution change due to pH and mechanical shear.

Key words bilayer caplet; phenylpropanolamine hydrochloride; hydroxypropylmethylcellulose; dissolution; formulation; hydrophilic matrix

Phenylpropanolamine hydrochloride (PPA), a sympathomimetic drug, is widely used as a nasal decongestant. Although PPA is rapidly and completely absorbed from the gastrointestinal tract after oral administration in humans, its plasma half-life in humans is short, 3.9 h, requiring that the drug be administered three times daily. It is therefore important and desirable to prolong the effective plasma level in order to maintain the clinical efficacy of the drug. Alderman and Hashem et al. suggested that hydrophilic polymer matrices incorporated in the drug is an adequate method to maintain a prolonged plasma drug level.2,3) The application of an immediate-release portion to a prolonged-release system can produce the rapid onset of plasma levels for those drugs that are required to show the prompt appearance of the therapeutic effect, followed by a prolonged-release phase at a constant rate. Typical forms containing both an immediate-release portion and a prolonged-release portion are spansule capsules4) and bilayer tablets what is termed spantabs.5)

Since it was reported that multiple unit was superior in reliability in prolonged gastric emptying time to single unit,6) multiple unit, such as spansule capsules, was widely chosen as a sustained-release dosage form. However, in the case that the sustained active ingredient is PPA, single unit is the same utility, such as plasma levels in humans, as reported with respect to multiple unit.7)

Bilayer caplets are excellent in two respects; firstly, single unit, such as bilayer caplets, excel in unit size than multiple unit, such as spansule capsules, and secondly, tablet shape changes from flat to capsule-like, namely caplets, that improve easiness in swallowing as compared with flat tablets.

Highly water-soluble drugs, such as PPA, play an important role in polymer swelling and contribute to the matrix integrity in hydrophilic polymer matrices as compared with slightly or poorly water-soluble drugs.8) Therefore, it was technologically difficult to slow PPA dissolution from hydrophilic polymer matrices. Thus, there were several reports concerning formulation and dissolution characteristics of prolonged-release PPA granules coated with wax or ethylcellulose.9,10) In contrast, there have been few reports concerning formulation and dissolution characteristics of sustained-release PPA bilayer caplets containing a hydrophilic polymer matrix.

Alderman2) suggested that hydroxypropylmethylcellulose 2208 (HPMC2208) can hydrate rapidly enough to protect the tablets from fast disintegration and dissolution in the matrices than in the cases of HPMC2906, HPMC2910, hydroxypropylcellulose (HPC), and methylcellulose. Hence, HPMC2208 was chosen as a hydrophilic polymer constituting the prolonged-release matrix in bilayer caplets.

The purpose of this study was to develop a new long-acting nasal decongestant oral product (BENZA®AL), having bilayer consists of an immediate-release layer and a prolonged-release layer containing a HPMC2208 matrix, to deliver the PPA at controlled rate. In this study, formulation and dissolution characteristics of sustained-release PPA bilayer caplets containing a hydrophilic polymer matrix were investigated.

Experimental

Materials

PPA (Alps Pharmaceutical Ind. Co.) was used as a sustained-release drug. d-Chlorpheniramine maleate (d-CP, Kongo Chemical Co.), beladonna total alkaloids (BEA, Alps Pharmaceutical Ind. Co.), anhydrous caffeine (CAF, Shiratori Pharmaceutical Co.), and tranexamic acid (TRA, Daiichi Pharmaceutical Co.) were used as immediate-release drugs.

HPMC 2208 (Metolose 90SH4000, Metolose 90SH15000, Metolose

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Preparation of HPMCC2208 Matrix Tablets In the experiment in which the effect of HPMCC2208 level in the matrices was investigated, PPA 20mg, HPMCC2208, Fujicalin SG were directly compacted with a compression instrument (Autograph AG-5000B, Shimadzu Corporation) using a 8 mm diameter flat-faced punch. The HPMCC2208 level was varied from 40 to 120 mg. The quantity of Fujicalin SG was adjusted to maintain a consistent tablet weight of 200 mg. The compression speed was 10 mm/min. The ejection speed was 100 mm/min. The compression pressure was 98 MPa. In the experiments in which the effect of HPMCC2208 viscosity grade in the matrices was investigated, PPA 20 mg and HPMCC2208 120 mg were directly compacted with the compression instrument using a 7 mm diameter flat-faced punch. The compression speed, the ejection speed, and the compression pressure were the same as that described above.

Manufacturing of the Immediate-Release Portion by Wet Granulation PPA, CE, CAF, TRA, Cornstarch, and Sylysia 320 were granulated with BEA ethanol solution and HPC-L aqueous solution using an agitation granulator (vertical granulator FM-VG-25, Powrex Co.). The immediate-release portion was colored with Yellow No. 5. The granules were vacuum dried at 40 °C for 16 h and were size-reduced with a screening mill (power mill, Showa Kagaku Kikai Co.). The size-reduced granules were mixed with LH31 and Mg-St by a diffusion mixer (tumbler mixer, Showa Kagaku Kikai Co.).

Physical properties of the immediate-release portion are as follows: particle size distribution is that 16 mesh on 1%, 16—30 mesh 14%, 30—60 mesh 22%, 60—100 mesh 36%, 100 mesh pass 27%, median particle size is 214 μm, loose specific volume is 1.8 ml/g, dense specific volume is 1.4 ml/g.

Manufacturing of the Prolonged-Release Portion by Dry Granulation The prolonged-release portion consisting of PPA, Ceolus KG-801, Fujicalin SG, and Metolose 90SH4000 were granulated by a roller compactor (rotor compactor mini, Freund Ind. Co.). The compactor was equipped with a conical screw roller pair with serration, type DPS. The diameter and width of the roller were 100 and 35 mm, respectively. The roller compaction pressure was 46.7 kN. The compacts were size-reduced with a screening mill (power mill, Showa Kagaku Kikai Co.). The size-reduced granules were mixed with Mg-St and Sylysia 320 by a diffusion mixer (tumbler mixer, Showa Kagaku Kikai Co.). Physical properties of the prolonged-release portion by dry granulation are as follows: particle size distribution is that 16 mesh on 1%, 16—30 mesh 23%, 30—60 mesh 20%, 60—100 mesh 24%, 100 mesh pass 32%, median particle size is 225 μm, loose specific volume is 2.1 ml/g, dense specific volume is 1.5 ml/g.

Manufacturing of the Prolonged-Release Portion by Direct Compression The prolonged-release portion consisting of PPA, Ceolus KG-801, Fujicalin SG, and Metolose 90SH4000 were directly mixed with Mg-St and Sylysia 320 by a diffusion mixer (tumbler mixer, Showa Kagaku Kikai Co.). Physical properties of the prolonged-release portion by direct compression are as follows: particle size distribution is that 16 mesh on 1%, 16—30 mesh 23%, 30—60 mesh 20%, 60—100 mesh 24%, 100 mesh pass 32%, median particle size is 225 μm, loose specific volume is 2.1 ml/g, dense specific volume is 1.5 ml/g.

Bilayer Compression The rotary bilayer tablets press (aquarius 0512LD2AX, Kikusui Seisakusho Co.) was utilized for bilayer compression. A schematic representation of bilayer compression is illustrated in Fig. 1. We termed the method A: a prolonged-release portion was fed as the first layer and an immediate-release portion was fed as the second layer in bilayer compression, and termed the method B: an immediate-release portion was fed as the first layer and a prolonged-release portion was fed as the second layer in bilayer compression. A pre-compression pressure and main compression pressure were 6.5 and 91 MPa, respectively. Dies were of 13.5×6.2 mm size in an oblong shape, and concave punches of 3.8 mm radius of curvature were used. Each of the layer weighed 200 mg. Thickness of bilayer caplets is 5.5 mm±6%. Hardness of bilayer caplets is 100—140 N. Unless otherwise specified, bilayer caplets by method B was used in the experiments.

Dissolution Study on the Paddle Method The matrix tablets and bilayer caplets were subjected to the dissolution test using a JP XIII paddle apparatus (dissolution tester, Toyobo Sango Co.) in 900 ml of water maintained at 37±0.5 °C, with the paddle rotating at 100 rpm.

In the experiments in which the effect of paddle rotating speed was investigated, the paddle rotating speed was varied from 50 to 200 rpm. In the experiments in which the effect of dissolution medium was investigated, the dissolution medium was changed from water to the JP XIII 1st fluid (pH 1.2) or the JP XIII 2nd fluid (pH 6.8). Measurement of PPA release was performed by HPLC (LC-9A instrument, Shimadzu Corporation) with UV detection at 210 nm. The mobile phase was 0.013 M sodium lauryl sulfate aqueous solution (pH 2.0): methanol (1 : 2) at a flow rate of 1.0 ml/min through a C18 column (Wakosil 5C18 AR 6 mm φ×150 mm). The column temperature was 40 °C.

Dissolution Study on the Paddle-Beads Method On the paddle-beads method, the apparatus used was the same as that described above. The dissolution medium was water maintained at 37±0.5 °C. The medium volume was 250 ml. A total of 2500 polystyrene beads (diameter 6.5 mm, Wako Pure Chemical Co.) was added to the medium. The paddle rotating speed was 25 rpm. Measurement of released PPA was performed as described above.

Similarity Assessment of Dissolution Profiles Moore and Flanner suggested a simple model independent approach uses a similarity factor to compare dissolution profiles. The similarity factor (f2) was calculated using the following Eq. 1.

\[ f_2(\%) = 100 \left( 1 - \frac{1}{n} \sum_{i=1}^{n} \left( \frac{R_i - T_i}{R_i + T_i} \right)^2 \right)^{0.5} \]
were similar and the Metolose 90SH15000 matrix tablets and 80.8% for Metolose ces. PP A dissolution characteristics from the HPMC2208 matri-
we confirmed that viscosity grades did not significantly affect files. This is shown in Fig. 3. The HPMC2208 viscosity grade showed similar dissolution pro-
dissolution characteristics from matrices with differing viscosity grade shows a greater swelling volume. However, PP A order 90SH100000 boflavin. The extent of swelling of Metolose 90SH is in the drug release from matrices. He reported the case of ri-
Therefore, increases in polymer viscosity will generally slow
the strength of gels, the resulting gelatinous diffusion layer
in a matrix formulation increases the gel layer viscosity and
required for giving the matrix the prolonged PP A dissolution
characteristics. It was due to highly water-soluble property of
PP A. Maximally, 405 mg of PP A can be dissolved in 1 ml
solution Characteristics (Fig. 3). The time to release 90% of PP A from Metolose
Metolose 90SH4000 matrices decreased. This is shown in Fig. 2. The time to release 90% of PP A from Metolose 90SH4000 matrices were about 3, 5, and 7 h for PP: Metolose 90SH4000 ratio were 1:2, 1:4, and 1:6, respectively. The ratio of 1:6 was most suitable for the prolonged-release characteristics of PP A. On the ratio of 1:6, the Metolose 90SH4000 level in the matrix with suitable weight was 60%. High Metolose 90SH4000 level in the matrix was required for giving the matrix the prolonged PP A dissolution characteristics. It was due to highly water-soluble property of PP A. Maximally, 405 mg of PP A can be dissolved in 1 ml water at 37 °C.

Alderman suggested that increasing viscosity of polymer in a matrix formulation increases the gel layer viscosity and the strength of gels, the resulting gelatinous diffusion layer becomes stronger and more resistant to diffusion or erosion. Therefore, increases in polymer viscosity will generally slow drug release from matrices. He reported the case of riboflavin. The extent of swelling of Metolose 90SH is in the order 90SH100000 > 90SH15000 > 90SH4000. Higher viscosity grade shows a greater swelling volume. However, PP A dissolution characteristics from matrices with differing HPMC2208 viscosity grade showed similar dissolution profiles. This is shown in Fig. 3. The f2 values were 75.2% for Metolose 90SH15000 matrix tablets and 80.8% for Metolose 90SH100000 matrix tablets. Since overall dissolution profiles were similar and the f2 values were between 50% and 100%, we confirmed that viscosity grades did not significantly affect PP A dissolution characteristics from the HPMC2208 matrices.

Although riboflavin is a water-insoluble drug, PP A is a highly water-soluble drug. Accordingly, it was suggested that PPA can easily diffuse through hard gelatinous layer in the matrix. Therefore, viscosity grades did not significantly af-

PPA pharmacokinetics study had previously been con-
ducted for the purpose of the formulation of the bilayer caplets having the most suitable sustained-release characteristics of PPA in humans. The most suitable sustained-release characteristics of PPA from the bilayer caplets, that is a twice daily medicine, have the same maximum plasma concentra-
tion (Cmax), the prolonged mean residence time (MRT), and 1.5 fold area under the plasma concentration–time curve (AUC) as compared with an immediate-release dosage form that is a three times daily medicine. The study was performed using 3 different PPA release formulations that are one immediate-release formulation whose PPA is completely dis-
solved within 0.5 h, and two prolonged-release formulations (T50 = 0.9 h and T50 = 2.3 h). The 3 different formulations were orally administered in humans in a crossover design. The most suitable sustained-release characteristics of PPA was calculated from the individual PPA plasma concentration data of each formulation in the study. As a result, the targeted PPA dissolution profile in vitro was obtained through the calculation of the most suitable sustained-release characteristics of PPA in vivo. From the targeted PPA dissolution profile, we decided that PPA content in the immediate-release portion was 5 mg and PPA content in the prolonged-release portion was 20 mg in a bilayer caplet. Therefore, we formulated the prolonged-release portion consisting of 10% PPA, 30% excipients (the diluents, the lubricant, and the glidant), and 60% Metolose 90SH4000 into the sustained-release PPA bi-
layer caplets.

Effect of Manufacturing Method of the Prolonged-Re-
lease Portion on PPA Dissolution Characteristics The specific volume of the prolonged-release portion manufac-
tured by wet granulation became high as compared with the physical mixture because of swelling property of Metolose 90SH4000 and 60% Metolose 90SH 4000 level in the pro-
longed-release portion. We found that the prolonged-release portion manufactured by wet granulation is unsuitable for compression using the rotary bilayer tablets press. Accord-
ingly, dry granulation and direct compression were chosen for manufacturing methods of the prolonged-release portion. PPA dissolution characteristics from two types of bilayer caplets, whose prolonged-release portion was manufactured by dry granulation and direct compression, were investi-
gated. This is shown in Fig. 4. The targeted PPA dissolution profile is also shown in Fig. 4. The PPA dissolution charac-
teristics from two types of the formulated bilayer caplets showed the prolonged dissolution profile after rapid dissolution and was close to the targeted profile. The f2 values were 68.1% for bilayer caplets having the prolonged-release por-
tion manufactured by direct compression and 58.6% for bi-
layer caplets having the prolonged-release portion manufac-
tured by dry granulation. We confirmed that the dissolution profiles from two types of the formulated bilayer caplets were similar to the targeted profile. Moreover, we confirmed that manufacturing methods of the prolonged-release portion

![Fig. 2. Effect of PPA : Metolose 90SH4000 Ratio in the Matrices on PPA Dissolution Characteristics (n = 3)](image)

<table>
<thead>
<tr>
<th>PPA: Metolose 90SH4000 ratio</th>
<th>1:2</th>
<th>1:4</th>
<th>1:6</th>
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![Fig. 3. Effect of HPMC2208 Viscosity Grade in the Matrices on PPA Dissolution Characteristics (n = 6)](image)

- Metolose 90SH40000
- Metolose 90SH150000
- Metolose 90SH1000000
did not significantly affect the PPA dissolution characteristics from the bilayer caplets. It was suggested that the swelling ability of Metolose 90SH4000 is not significantly changed by the mechanical force that is the roller compaction pressure. This result confirms the findings by Sheskey et al.\(^{16}\) that no significant difference in drug release on HPMC matrices was observed regardless of the manufacturing methods in the case that drug is niacinamide which is a highly water-soluble drug and HPMC level is 30%.

**Effect of Filling Order of the Prolonged-Release Portion in Bilayer Compression on PPA Dissolution Characteristics** The bilayer caplets by method A and method B were chosen in this experiment. Different filling order of the prolonged-release portion in bilayer compression gave different shape of the prolonged-release portion in bilayer caplets. Shape is an important factor for dissolution from matrices. Ford et al. investigated the influences of tablet shape on the release rates of promethazine hydrochloride tablets.\(^{17}\) They concluded that the release rate is proportional to the surface area of tablet since release rates decreased as the tablet surface area decreased. However, PPA dissolution profiles from two types of bilayer caplets showed similar curves. This is shown in Fig. 5. The \(f_2\) value was 71.8%. The filling order of the prolonged-release portion in bilayer compression related to the compressed shape did not significantly affect the PPA dissolution characteristics from bilayer caplets. Since the shape of prolonged-release portion readily changed by swelling of Metolose 90SH4000 in the dissolution test, the shape of prolonged-release portion in the bilayer caplets did not significantly affect PPA dissolution characteristics in this case.

**Effect of Dissolution Medium on PPA Dissolution Characteristics** It is important for the sustained-release product to have pH independent drug release characteristics owing to reliable absorption in the digestive organ. Therefore, the effect of dissolution medium on the PPA dissolution characteristics from the bilayer caplets was investigated. This is shown in Fig. 6. The \(f_2\) values were 74.8% for the JP XIII 1st fluid and 98.7% for the JP XIII 2nd fluid. The dissolution medium did not significantly affect PPA dissolution characteristics from the bilayer caplets. The PPA dissolution characteristic from bilayer caplets was pH independent, because Metolose 90SH4000 is pH independent swelling polymer\(^2\) and PPA can be highly dissolved regardless of pH. PPA, 412 and 88 mg, can be dissolved in 1 ml of the JP XIII 1st fluid and the JP XIII 2nd fluid at 37 °C, respectively.

**Effect of Paddle Rotating Speed on PPA Dissolution Characteristics** The significance of mechanical shear in terms of the in vivo drug release has been demonstrated on hydrophilic polymer matrices.\(^{18}\) Abrahamsson et al. suggested that investigation of the effect of paddle rotating speed is meaningful in the test for investigation of prandial effects on hydrophilic matrix tablets.\(^{19}\) Figure 7 shows that effect of paddle rotating speed on PPA dissolution characteristics from the bilayer caplets. The \(f_2\) values were 71.5% for 50 rpm and 74.8% for 200 rpm. It was found that the dissolution characteristics is not significantly affected by the paddle rotating speed.

**PPA Dissolution Characteristics on the Paddle-Beads Method** Aoki et al. proposed the paddle-beads method to introduce a mechanical impact force into the paddle method for the purpose of simulating the in vivo dissolution.\(^{12,13}\) Therefore, the paddle-beads method was performed to examine the effect of mechanical shear on the PPA dissolution characteristics. Figure 8 shows the PPA dissolution characteristics on the paddle-beads method. The \(f_2\) value was 67.7%.
The PPA dissolution characteristics was not significantly different from those on the paddle method. We found that the PPA dissolution characteristics from the bilayer caplets containing the Metolose 90SH4000 matrix is not significantly affected by mechanical shear that is the combination of the paddle rotating and the beads. This is due to the fact that Metolose 90SH4000 has excellent hydro-gel strength and Metolose 90SH4000 level in the prolonged-release portion is 60%. It was suggested that the PPA dissolution from the formulated bilayer caplets was less susceptible to the influence of mechanical shear arising from digestive actions or friction force between the bilayer caplets and the gastrointestinal mucus.

Conclusions

PPA is a highly water-soluble drug that can easily diffuse through hard gelatinous layer in the matrices. Therefore, we formulated the prolonged-release portion consisting of 10% PPA, 30% excipients, and 60% Metolose 90SH4000 into the sustained-release PPA bilayer caplets. The PPA dissolution characteristics from the formulated bilayer caplets showed the prolonged dissolution profile after rapid dissolution and was close to the targeted profile calculated from PPA pharmacokinetics study. The PPA dissolution characteristics from the formulated bilayer caplets was not significantly affected by manufacturing methods of the bilayer caplets. The PPA dissolution characteristics from the bilayer caplets was pH independent. Moreover, the PPA dissolution characteristics from the bilayer caplets was not significantly affected by the mechanical shear, such as paddle rotating speed and the beads in the medium. Similarity of dissolution profiles was confirmed by overall profiles and the similarity factor ($f_2$).

The sustained-release PPA bilayer caplets is expected to present constant prolonged-release of PPA after rapid dissolution in vivo without dissolution change due to pH and mechanical shear during the transition in gastrointestinal tract.

References and Notes