Preparation and evaluation of double-phased mucoadhesive suppositories of lidocaine utilizing Carbopol® and white beeswax

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Abstract

In an attempt to restrict drug absorption from suppositories to only the lower rectum, mucoadhesive lidocaine (LID) suppositories were prepared using Witepsol® H-15 as a base, and Carbopol® 934P (CP) and white beeswax (WAX) as additives. CP has a mucoadhesive property and WAX gives the suppositories stiffness. The suppositories containing 10% CP and 20% WAX stayed in the lower recta of rats for at least 2 h. Double-phased suppositories consisting of a front layer containing 10% CP and 20% WAX and a terminal layer containing LID and various amounts of CP were prepared. In vitro release profiles of LID from double-phased suppositories were similar to conventional single-phased suppositories containing CP alone. Values of AUCo–6 h and MRT of LID after administration of double-phased suppositories to rabbits were larger than those for single-phased suppositories with or without CP. On the other hand, the initial plasma metabolites concentrations after administration of double-phased suppositories were significantly lower and tended to exhibit delayed Tmax compared to single-phased suppositories. These results suggest that the double-phased mucoadhesive suppositories suppress initial metabolism of LID, and may be useful for improving bioavailabilities of drugs, like LID, which accept first-pass effect considerably. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Double-phased suppository; Mucoadhesive; First-pass effect; Carbopol®; White beeswax

1. Introduction

Drugs released from suppositories and absorbed into the lower rectum can avoid first-pass effect. Usually, suppositories move to the upper rectum after administration while dissolving or melting, and this is disadvantageous for the drugs which accept first-pass effect considerably. Huang et al. designed double-layered suppositories using Unilubu®, Hiviswako® and polyethylene glycol to aid lower rectal absorption, but their results were not sufficient [1].

In this study, we attempted to restrict drug absorption from suppositories to the lower rectum. Mucoadhesive double-phased suppositories were prepared using Witepsol® H-15 (H-15) as a base, and Carbopol® 934P (CP) and white beeswax (WAX) as additives. CP is a carboxyvinyl polymer with a mucoadhesive property and has been reported to be mucoadhesive material [2–5]. WAX was added to
rise the melting point of the base [6] which helps the suppository to keep its shape and prevents it from melting and extending over a wide area. Lidocaine (LID) was selected as a model drug which undergoes first-pass effect [7], and plasma concentrations of LID and its metabolites, monoethylglycine xylidide (MEGX) and glycine xylidide (GX), were measured.

2. Materials and methods

2.1. Materials

Lidocaine was purchased from Wako Pure Chemical Industries (Japan) and used after passing through a 100 mesh sieve. Witepsol® H-15 and Carbopol® 934P were supplied by Mitsuba Trading (Japan) and B.F. Goodrich (USA), respectively. Metabolite samples of LID, monoethylglycine xylidide hydrochloride and glycine xylidide hydrochloride were supplied by Astra Japan. All other chemicals used were of reagent grade.

2.2. Preparation of suppositories

Suppositories were prepared by the fusion method. H-15 and WAX were melted and mixed at about 60°C, CP was then mixed by ultrasonication for 10 min. LID was mixed into the base mixture and the mixture was poured into a suppository mold (for 2 g, Erbo, Germany) and cooled at room temperature. Suppositories containing LID and CP alone were prepared by the same method. Double-phased suppositories were prepared as follows: first, a base mixture for the front layer was poured into the mold, cooled, removed from the mold, and the top of 20 mm of the base (1.4 g) was cut off and used. The front layer was put into the mold again and the terminal layer was poured next to it at approximately 60°C and cooled at room temperature. Suppositories were stored at 10°C and used within 1 week.

2.3. Measurement of the hardness of base

Melted base mixture was poured into a teflon mold and cut into plates of 5×5×20 mm after solidifying. The peak value of the shearing stress at breaking under pressure of 30 cm/min using tooth press stick B was measured at approximately 20°C using a Rheometer (Fudoh Kogyo, Japan) and used to indicate base hardness.

2.4. Measurement of the melting point of base

Base melting point was measured by a differential scanning calorimeter (TAS200 DSC8230D, Rigaku Denki, Japan). Base was crushed using mortar and pestle made of agate and 5 mg was used as the test sample. Alumina powder (5 mg) was used as a standard sample and measured at a heating speed of 3°C/min. The temperature of the DSC curve peak was regarded as the melting point of the base.

2.5. Measurement of rectal residence of suppositories in rats

To facilitate observation, brilliant blue FCF was added to the base 12.5 mg/g. The melted base mixture was drawn into a 1 ml disposable syringe with a cut off tip. After solidification at room temperature, suppositories of 4 mm diameter were extruded and cut into 20 mm long sections. After rectal administration of suppositories to Wistar male rats (130.8~177.9 g) fasted for 48 h, the recta were excised and the distances suppositories moved were estimated by measuring the distance from a point 20 mm past the anus to the front of the colored region.

2.6. In vitro drug release tests

The release tests were carried out according to the method reported by Iwata et al. [8]. A membrane filter SS (pore size 3.0 μm, Millipore, USA) was fixed at the bottom of a stainless steel cell (40 mm I.D., 20 mm high). A suppository containing 5 mg LID was put into the cell and the cell was attached to a JP XIII dissolution tester (Toyama Sangyo, Japan). A hole (2 mm diameter) on the cell cover was firmly filled with cotton. The cell was rotated at 120 rpm in 500 ml of JP XIII second fluid (pH 6.8, 37±0.5°C). At a predetermined time, 5 ml of dissolution test fluid was collected and the absorption at 205 nm was measured using a UV spectrophotometer (Beckman, Japan). Each sampling was compensated immedi-
ately by the test fluid of same temperature and same amount.

2.7. Absorption studies using rabbits

Japanese white male rabbits (2.1~3.1 kg) were used after fasting for 24 h. At predetermined intervals after rectal administration of 50 mg LID suppository to the rabbit, 2 ml blood samples were withdrawn from ear veins and centrifuged at 3000 rpm for 10 min. Plasma samples were frozen and stored at −15°C until assayed. Plasma drug concentrations were measured by high-performance liquid chromatography according to the method reported by Satoh et al. [9]. Briefly, 1 ml plasma was mixed with 2 μg procainamide hydrochloride as an internal standard. After addition of 5 ml of benzene:chloroform (4:1) and 400 μl of 5 N NaOH and vortexing for 30 s, the mixture was centrifuged at 3000 rpm for 30 min. The upper organic phase was transferred and evaporated to dryness under a stream of dry nitrogen. The residue was dissolved in 100 μl of mobile phase (pH 4.0 phosphate buffer:acetonitrile (9:1)) and 25 μl of solution was injected into the HPLC column (μBondapak C₁₈, 3.9×150 mm, Japan Waters) at 60°C. The HPLC system was equipped with a pump (LC-6AD, Shimadzu, Japan) which was set at a flow rate of 0.9 ml/min and a UV detector (SPD10-AV, Shimadzu, Japan). UV absorption at 214 nm was monitored and plasma concentrations of LID and metabolites were estimated using a Chromatopac C-R7A Plus (Shimadzu, Japan) by the internal standard method.

2.8. Pharmacokinetic data analysis

Values of AUC₀⁻₆ h and MRT were calculated using the Program MULTI (moment calculation, PRG5-1) by the normal trapezoidal method.

2.9. Statistical analysis

Significant differences between the observed data were assessed by Student’s t-test. The data were considered to be significantly different when the P value was less than 0.05.

3. Results and discussion

3.1. The hardness of base

Considering the practical use of suppositories, the effects of CP and WAX on base hardness were examined. As shown in Table 1, base hardness was not decreased by addition of CP and WAX, suggesting that addition of 10% CP and 10~30% WAX to H-15 does not spoil the mechanical strength of the suppository required for clinical usage.

3.2. The melting point of base

Endothermic curves of bases containing CP and WAX obtained using DSC are shown in Fig. 1. The DSC peak due to fusion of H-15 was at about 34°C. The peak due to fusion of WAX appeared at about 58°C and it became larger with increasing amounts of WAX. Addition of WAX may raise the melting point of the suppository and may enable the suppository to maintain its shape longer. The DSC peak of H-15 was not changed by addition of CP and WAX. The DSC peak of CP was not found in the measured range (28~100°C), so that the CP dispersed in the suppository should not influence the fusion of the suppository.

3.3. Rectal residence of suppositories

Suppository movement after rectal administration to rats is shown in Fig. 2. Suppositories containing 10% CP and 20~30% WAX were retained in the lower rectum for at least 2 h. However, as it was reported that addition of WAX decreased drug release remarkably [10], results of the dissolution test in this study suggested that release of LID from the suppository containing 10% CP and 10% WAX

<table>
<thead>
<tr>
<th>Carbopol w/w %</th>
<th>White beeswax w/w %</th>
<th>Hardness (kg)</th>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1.46±0.48</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>1.86±0.17</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>2.22±0.09</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>1.63±0.40</td>
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* Each value represents the mean±SD of five experiments.
at 8 h was only 12.15%. These results indicate that addition of WAX is advantageous for the rectal residence of the suppository but is not adequate from a viewpoint of drug release. Therefore, as shown in Fig. 3, double-phased suppositories composed of a mucoadhesive front layer containing 10% CP and 20% WAX as the anchoring phase and a terminal layer containing CP and LID as the drug releasing phase were designed. These double-phased suppositories have a larger front layer than the double-layered suppositories used by Huang et al. [1].

3.4. Drug release properties of suppositories

As shown in Fig. 4, release profiles of LID from double-phased suppositories were not affected by WAX in the front layer, and they were similar to the
single-phased suppositories containing CP alone. Both single- and double-phased suppositories exhibited increased LID release rates with addition of 2% CP and decreased rates with addition of 10% CP. This phenomenon may be due to the water soluble property of CP, i.e. addition of a small amount of CP improved the water absorbability of the base and facilitated the release of lipophilic LID, but large amounts of CP formed a highly viscous gel layer and suppressed the release of LID.

3.5. Animal studies

Fig. 5(a) shows the plasma concentration profiles of LID after rectal administration of single- and double-phased suppositories to rabbits. Both suppository types exhibited better absorption compared with the H-15 suppository, especially the double-phased suppository containing 5% CP, which had the highest $C_{\text{max}}$. Double-phased suppositories had remarkably prolonged plasma concentration profiles compared with single-phased suppositories with a concentration of LID of 0.1 $\mu$g/ml at 4 h after administration.

Plasma concentration profiles of metabolites, MEGX and GX, are shown in Fig. 5(b) and (c). MEGX is mono-desethylated LID and GX is di-desethylated LID. Generally, in humans, plasma MEGX concentrations are higher than GX [11] but GX concentrations exceeded MEGX in the present study in rabbits. However, both inter species differences in LID metabolism [12] and the administration route [13] might effect the MEGX/GX ratio. Both single- and double-phased suppositories had $T_{\text{max}}$ that were delayed compared with the H-15 suppository. The $T_{\text{max}}$ delay for double-phased suppositories was especially remarkable and a flat profile was observed for suppositories with 2% CP. These results suggest that double-phased suppositories are retained in the lower rectum, which suppresses metabolism of LID for longer periods and results in high plasma concentrations of LID, compared with single-phased suppositories containing CP alone.

3.6. Pharmacokinetic data analysis

3.6.1. Single-phased suppositories

Fig. 6 shows the AUC values of LID and the AUC ratios of metabolites/LID for different suppositories. It has been reported that an optimum concentration of CP exists [14], but in this study, the AUC of LID became larger with increasing amounts of CP in single-phased suppositories, and the AUC ratios of metabolites/LID decreased compared with H-15
Fig. 5. Plasma concentration profiles of lidocaine (a), monoethylglycine xylidide (b), and glycine xylidide (c) after rectal administration of suppositories to rabbits. ●: H-15 alone, ○: CP 2%, △: CP 5%, □: CP 10% (*P<0.05, **P<0.01, ***P<0.001 vs. H-15 alone). Each point represents the mean±SE of three to five rabbits.
suppositories. These results suggest that even with addition of CP alone, the absorption region of LID is limited in some extent. However, addition of 2% CP may be also influenced by an improvement of release rate of LID as already described in Section 3.4. Fig. 7 shows the effect of CP content on MRT values of LID and its metabolites. In single-phased suppositories, no MRT effects were found, suggesting suppression of first-pass effect improved AUC, rather than sustained release. LID used as a model drug in this study accepts significant first-pass effect, so most LID released from single-phased suppositories in the upper rectum underwent hepatic metabolism and did not increase the MRT.

### 3.6.2. Double-phased suppositories

On the other hand, in double-phased suppositories, the AUC of LID increased the most with the addition of 5% CP and exhibited the lowest metabolites/LID AUC ratio as shown in Fig. 6. These results indicate that the optimum concentration of CP for the drug releasing phase of this double-phased suppository is around 5%. The absorption region of LID in the double-phased suppository was strictly limited, and therefore the drug release property greatly influenced absorption. Moreover, as Fig. 7 shows, all MRT values for LID and metabolites were prolonged for an average of 0.31 h compared with single-phased suppositories containing identical amounts of CP. These results also suggest the mucoadhesive front layer containing WAX prevents movement of the terminal layer containing the drug toward the upper rectum and limits the absorption region of LID to the lower rectum.
4. Conclusion

The results suggest that this double-phased suppository with both rectal stagnation and moderate drug release property facilitates drug absorption in the lower rectum effectively. This double-phased suppository may be useful for improving bioavailability of drugs with significant first-pass effect like LID.

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References


