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The influence of viscosity-enhancing agents on oral absorption of drugs

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The objective of this study was to evaluate the influence of viscosity-enhancing agents on oral absorption of metoprolol (MPL) and bisoprolol (BPL). Although the viscosity values were similar for MPL and BPL in hydroxypropyl methylcellulose (HPMC, 1.2 % (w/w)) and polyvinyl alcohol (PVA, 8.8 % (w/w)) solutions, the order of diffusion rate constants of the drugs in media were phosphate buffer solution (reference) > HPMC solution > PVA solution. In *in vivo* rat intestinal absorption experiments showed that the C_{max} and AUC values of the drugs were lowest when they were administered into the rat jejunum in a PVA solution. *In vitro* binding studies showed that this may have been due to adsorption of the drugs to PVA molecules, resulting in decreased free fractions of the drugs. Our results indicated that intestinal absorption of the drugs in PVA solution was influenced both by decreased diffusion of the drugs and by interaction with PVA. Since various viscosity-enhancing agents are widely used as pharmaceutical and food additives, these findings may be of significance for understanding therapeutic efficacy and safety of oral drug products.

1. Introduction

Increased viscosity in the gastrointestinal (GI) tract can be induced by many factors. Abrahamsson et al. (2005) reported that viscosity in the human stomach increased to 10 to 2000 mPas after food ingestion. Furthermore, viscosity in the small intestinal contents of fed rats was reported in the range of 199 to 396 mPas (Gallaher et al. 1999). Other possible factors that elevate viscosity in the GI tract include intake of viscosity-enhancing agents such as water-soluble polymers, which are sometimes used as excipients in various pharmaceutical formulations, such as nano-suspensions to prevent aggregation of drug nano-particles (Oh et al. 2015; Xie et al. 2019; Jeong et al. 2018; Yang et al. 2018), and ingestion of dietary fiber supplements that are used to regulate glucose absorption (Dikeman et al. 2006a,b; Vaaler et al. 1980).

Intraluminal viscosity affects oral absorption of drugs through several mechanisms. Radwan et al. (2012 and 2013) reported that the disintegration rate of an immediate release tablet of trospium chloride was delayed in a viscous solution, resulting in delayed drug release. This effect occurred due to slow ingress of water into the tablets due to decreased water diffusivity (Radwan et al. 2013). A previous report showed that chitosan, a cationic dietary fiber, altered media pH, resulting in reduction of transport of losartan, an angiotensin II type 1 receptor blocker, across Caco-2 cell monolayers (Iwazaki et al. 2016). Furthermore, enhanced viscosity has been shown to delay gastric emptying in fed dogs (Russell et al. 1985; Ehrlein et al. 1982; Xu et al. 2005), likely resulting in delayed oral drug absorption.

To accurately evaluate and/or predict the effects of increased viscosity on oral absorption of drugs, each factor influencing drug absorption should be clearly elucidated, and critical factors should be reflected in any mathematical models or in vitro predictive tools. According to the Stokes-Einstein equation (Einstein 2011), increased media viscosity reduces drug diffusion. However, the relationship between diffusion of solubilized drug molecules in viscous media and intestinal permeation has not been characterized. Therefore, in this study, the effect of viscosity-enhancing agents on drug diffusion and intestinal permeation was evaluated in *in vitro* diffusion and *in vivo* absorption studies.

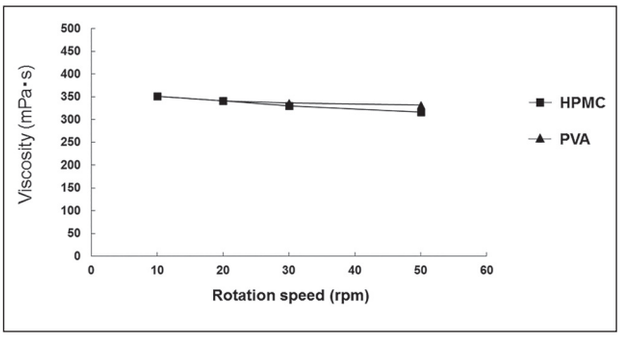

Fig. 1: Viscosities of various media at different rotation speed.

2. Investigations and results

2.1. Viscosity in various media

Fig. 1 shows the viscosity of the tested media at different spindle rotation speeds. The viscosities were 316.7-350.9 and 331.7-350.9 mPas in hydroxypropyl methylcellulose (HPMC, 1.2 % (w/w)) and polyvinyl alcohol (PVA, 8.8 % (w/w)) solutions, respectively. The viscosity values were similar in the two solutions.

2.2. Diffusion of drugs across a dialysis membrane

The results of the *in vitro* diffusion study are summarized in Fig. 2. Regardless of medium, the drug concentrations in the acceptor side increased in a linear fashion with time, indicating that sink conditions were maintained in the acceptor side. Then, apparent first-order diffusion rate constants were calculated based on the drug concentration-time courses (Table 1).

In phosphate buffer (PB), the diffusion rate constant of MPL was 9.0±1.0 min^{-1}. When HPMC (1.2 % (w/w)) or PVA (8.8 % (w/w)) was added to the donor side, the constant significantly decreased to 6.5±0.8 min^{-1} and 5.2±0.7 min^{-1}, respectively. Similarly, the diffusion rate constant of BPL significantly decreased from 7.8±1.1 min^{-1} (PB) to 5.1±0.8 min^{-1} and 4.2±0.4 min^{-1} in HPMC and PVA, respectively.

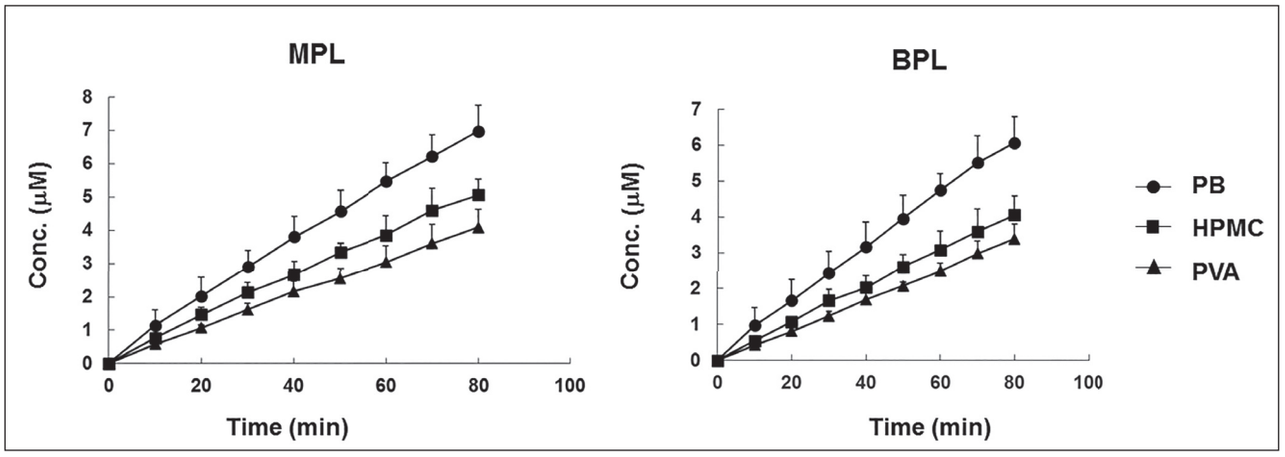

Fig. 2: Diffusion-time profiles of drugs in various media (n=4 for PB, n=3 for HPMC and PVA). The data are expressed as mean values with vertical bars showing the S.D. of each experiment.

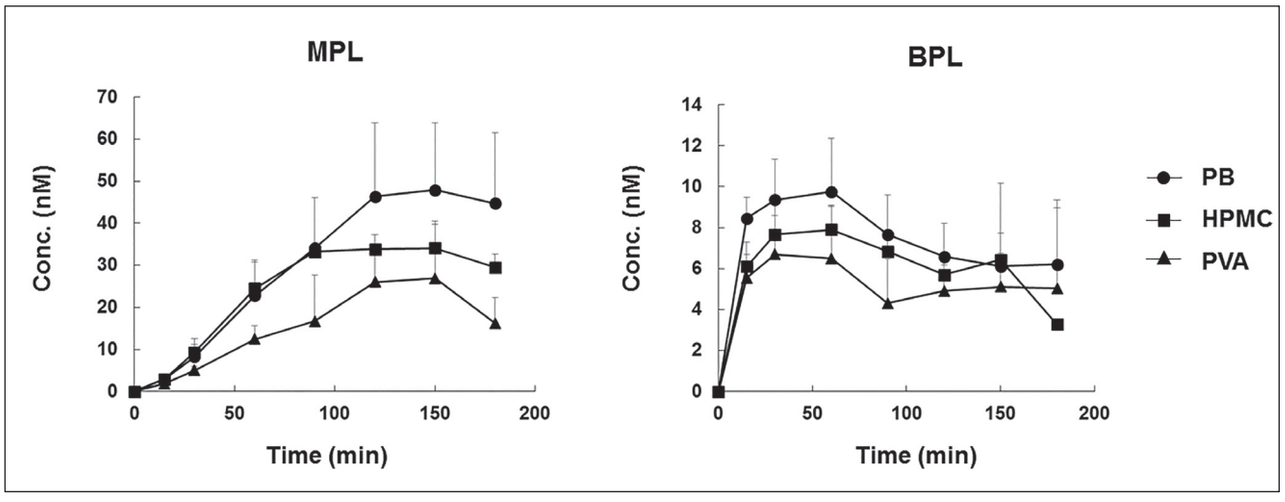

Fig. 3: Plasma concentration-time profiles after administration of drug solutions into the intestinal loop (n=6 for PB, n=4 for HPMC and PVA). The data are expressed as mean values with vertical bars showing the S.D. of each experiment.

Table 1: Apparent first-order diffusion rate constant (min^{-1}) of drugs in various media (n=3)

	Diffusion rate constant ($\times 10^{-4}$ min^{-1})	
	MPL	BPL
PB	9.0 ± 1.0	7.8 ± 1.1
HPMC	6.5 ± 0.8*	5.1 ± 0.8*
PVA	5.2 ± 0.7**	4.2 ± 0.4**

The data are expressed as mean values ± S.D.
*P<0.05,**P<0.01, significantly different from the data related to PB.

Table 2: Binding rate (%) of drugs to polymers (n=3)

	Binding rate (%)	
	MPL	BPL
PB	2.3 ± 9.6	3.8 ± 5.0
HPMC	-2.4 ± 5.5	-1.3 ± 12.2
PVA	44.9 ± 2.6**	41.7 ± 4.7**

The data are expressed as mean values ± S.D.
**P<0.01, significantly different from the data related to PB.

Table 3: Pharmacokinetic parameters

	MPL		BPL	
	C_{max} (nM)	$AUC_{0\text{-}180\ min}$ (nM*min)	C_{max} (nM)	$AUC_{0\text{-}180\ min}$ (nM*min)
PB	50.8 ± 16.9	5440 ± 1772	10.6 ± 1.3	1334 ± 307
HPMC	41.0 ± 8.8	4302 ± 468	9.6 ± 1.9	1078 ± 100
PVA	28.1 ± 10.9*	2632 ± 781**	7.30 ± 2.8	900 ± 352

The data are expressed as mean values ± S.D.
*P<0.05, **P<0.01, significantly different from the data related to PB.

2.3. Binding of drugs to viscous additives

Data from the binding study are shown in Table 2. In PB (without viscosity-enhancing agents), the binding rates were 2.3±9.6 % and 3.8±5.0 % for MPL and BPL, respectively, indicating that neither of the drugs adsorbed to the surface of the dialysis membrane or the inside of the diffusion chamber. In HPMC solutions the binding rates of both drugs were nearly 0, suggesting that neither of the drugs adsorbed to HPMC. In contrast, 44.9±2.6 % of MPL and 41.7±4.7 % of BPL were bound to PVA.

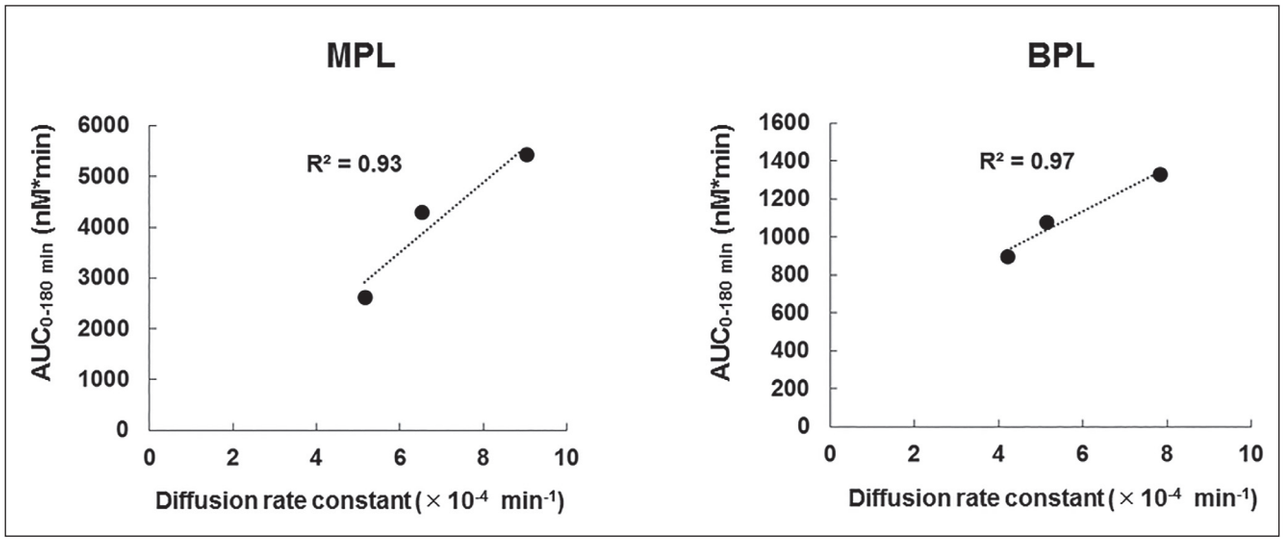

Fig. 4: *In vitro-in vivo* correlation of diffusion rate constant and $AUC_{0\text{-}180\ min}$.

2.4. Drug absorption across the intestinal membrane

Plasma concentration-time profiles and pharmacokinetic parameters determined after injection of drug solutions into the rat intestinal loop are shown in Fig. 3 and Table 3. For both drugs, the C_{max} and $AUC_{0\text{-}180\ min}$ were highest in the PB group. Both values were lower when the drugs were administered with viscosity-enhancing agents compared to control, and the reduction was more pronounced in the PVA group than in the HPMC group, although significant differences in the C_{max} and $AUC_{0\text{-}180\ min}$ values were observed only in the MPL in PVA groups.

3. Discussion

Various viscosity-enhancing agents are widely utilized in the pharmaceutical and food industries (Smith et al. 2012; Yuminoki et al. 2016). Co-administration of viscosity-enhancing agents with a drug may decrease diffusion of drug molecules within the GI tract, resulting in decreased oral drug absorption. However, understanding of the effects of viscosity on diffusion is limited. To better understand the therapeutic efficacy and safety of oral drug products, it is important to characterize the influence of viscosity-enhancing agents on oral drug absorption.

Although the viscosities in HPMC (1.2 % (w/w)) and PVA (8.8 % (w/w)) solutions were similar (Fig. 1), *in vitro* diffusion and *in vivo* intestinal absorption of the model drugs was markedly reduced in PVA compared with HPMC (Table 1 and 3). These results suggested that the diffusion and intestinal absorption of the drugs in PVA was reduced not only by increased viscosity (Fig. 1) but also adsorption of the drugs to PVA (Table 2). In HPMC, only enhanced viscosity may influence drug diffusion and absorption. Nishida et al. (2000) reported that absorption of phenol red from the rat liver surface was decreased in viscous formulations, and the reduction was more pronounced in 15 % PVA compared to 1 % carboxymethylcellulose sodium salt (CMC-Na), although the viscosity of 15 % PVA (53 mPas) was similar to that of 1 % CMC-Na (53 mPas). These findings agreed with the results of our study. Since PVA has various functional groups, interactions may occur between PVA and phenol red, resulting in reduced absorption (Nishida et al. 2000).

Figure 4 shows the correlation between the *in-vitro* diffusion rate constant and *in-vivo* oral AUC. The oral AUC values of the drugs seems to be dependent on diffusion rate constants (R^2=0.93 for MPL and R^2=0.97 for BPL). Therefore, the effect of viscous additives on intestinal permeation may be explained by reduced diffusion and/or binding of drugs to polymers. However, since data points are low, further investigation will be necessary to evaluate this effect more accurately.

Use of generic oral products has become common in health care systems worldwide. Water-soluble polymers are often used as excipients in various oral products such as suspensions and supersaturable formulations (Kumar et al. 2015; Knopp et al. 2016). Since different types of pharmaceutical excipients are generally used in original and generic products (Shibata et al. 2012; Cristofoletti et al. 2013; Shohin et al. 2014), selection of water-soluble polymers for development of generics is very important for achieving bioequivalence between the original and generic oral products. Furthermore, viscosity in the GI tract is enhanced after ingestion of some of food additives and supplementary dietary fibers (Bak et al. 2018; Rebello et al. 2014), so attention should be paid to the effects of viscosity-enhancing agents on oral absorption of drugs to aid in evaluation of therapeutic efficacy and safety.

4. Experimental

4.1. Materials

Metoprolol tartrate and bisoprolol hemifumarate were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Antipyrine (APR) and PVA (polymerization degree=1500-1800) were obtained from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). HPMC (NE-4000) was kindly donated by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). All other reagents were analytical grade commercial products.

4.2. Measurement of viscosity in various media

HPMC and PVA were dissolved in 50 mM PB (pH 6.5) at 1.2 and 8.8 % (w/w), respectively. The viscosity in each medium was measured using a viscometer with an S62 spindle (LVDV-I Prime, Brookfield Engineering Laboratories, Inc., Massachusetts, USA) at 37 °C at various rotation speeds.

4.3. In vitro diffusion study

In vitro diffusion was evaluated using a diffusion chamber (9 mm diameter, 3.4 mL volumes; PermeGear, Inc., Pennsylvania, USA). A dialysis membrane with a molecular weight cut-off of > 1000 Da (Spectrum Laboratories, Inc., California, USA) was placed between the chambers. PB, HPMC (1.2 % (w/w)) and PVA (8.8 % (w/w)) solutions (3 g) containing 100 mM MPL or BPL were added to the donor side. Blank PB (3 g) was used as an acceptor solution. Both side of the dialysis membrane were stirred at 300 rpm using magnetic stirrers. Samples (50 mL) were taken periodically from the acceptor side. Diffusion rates were estimated from the slope of the regression line of the concentration-time courses. The diffusion rate constants were calculated as follows:

$$\text{Dissolution rate constant} = \frac{\text{Diffusion rate}}{\text{Initial drug concentration in donor side}}$$

4.4. In vitro binding study

Adsorption of drugs to polymers was assessed using a diffusion chamber with dialysis membranes under the same conditions as described in Section 4.3. Both the donor and acceptor sides were stirred for 24 h (PB) or 48 h (HPMC and PVA) to allow for binding equilibration. After equilibration, a sample (50 mL) was taken from the acceptor side. The binding rates (%) of the drugs to the polymers were calculated as follows:

$$\text{Total drug concentration in donor side} = \frac{\text{Total drug mass in chamber} - \text{drug mass in acceptor side}}{\text{Volume in donor side}}$$

Drug concentration bound to polymer =
Total drug concentration in donor side - drug concentration in acceptor side

$$\text{Binding rate (\%)} = \frac{\text{Drug concentration bound to polymer}}{\text{Total drug concentration in donor side}} \times 100$$

4.5. In vivo absorption study

The animal study was performed in compliance with the Guidelines for the Care and Use of Laboratory Animals of the Committee for Animal Experiments of Hiroshima International University. Male Wistar rats (229-263 g) were purchased from Japan SLC (Hamamatsu, Japan). The rats were fasted overnight prior to experiments. Pentobarbital (5 mg/100 g body weight; Kyoritsu Seiyaku Corporation, Tokyo, Japan) was intraperitoneally administered to induce anesthesia. A cannula was made by insertion of a polyethylene tube (0.96 mm outer diameter) into the femoral artery. Next, the abdomen was opened, and a 10-cm intestinal loop was made in the proximal jejunum. Isosmotic phosphate buffers (mixture of 2.54 % $NaH_2PO_4 \cdot 2H_2O$ and 4.41 % $Na_2HPO_4 \cdot 12H_2O$, pH 6.5) with or without viscosity-enhancing agents containing 100 mM MPL or BPL (1 mL) were injected into the intestinal loop. Blood samples were collected at 0, 15, 30, 60, 90 120 150, and 180 min from the femoral artery cannula. Blood samples were centrifuged, and the resulting plasma was mixed with 1 mM APR in methanol (internal standard) and methanol at a ratio of 1:1:1 for deproteinization. After centrifugation, the drug content in the resulting supernatant was quantified by LC-MS/MS. When rats awoke during experiments, pentobarbital (2.5 mg/100 g body weight) was administered.

4.6. Quantification of drugs in samples

MPL and BPL in various samples were analyzed using an LC-MS/MS system comprised of an LCMS-8040 triple quadrupole mass spectrometer (Shimadzu, Kyoto, Japan) and an LC-20AD binary pump. The drugs were chromatographically separated using a Phenomenex Kinetex C18 column (50 × 2.1 mm, 2.6 µm, CA, USA) maintained at 40 °C. The mobile phase (mixture of 0.1% formic acid in Milli-Q water and methanol at 55:45 (v/v)) flow rate was maintained at 0.2 mL/min. MPL, BPL, and APR were detected in positive ion mode. The precursor-to-product ion transitions used for multiple reaction monitoring were m/z 268.2>116.1 for MPL, 326>116.1 for BPL, and 189>56.1 for APR.

4.7. Statistical analysis

The statistical software ystat 2000.xls. (Igakutosho-Shuppan Ltd., Japan) was used to determine statistical significance using unpaired Student's t-tests. P-values less than 0.05 were regarded as statistically significant.

Conflict of interest: None declared.

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