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# Influence of magnesium aluminium silicate on rheological, release and permeation characteristics of diclofenac sodium aqueous gels in-vitro

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## Abstract

The effect of magnesium aluminium silicate (MAS) on rheological, release and permeation characteristics of diclofenac sodium (DS) aqueous gels was investigated. DS aqueous gels were prepared using various gelling agents, such as 15% w/w poloxamer 407 (PM407), 1% w/w hydroxypropylmethylcellulose (HPMC), and 1% w/w high and low viscosity grades of sodium alginate (HV-SA and LV-SA, respectively). Different amounts of MAS (0.5, 1.0 and 1.5% w/w) were incorporated into the DS gels. Incorporation of MAS into the DS gels prepared using SA or PM407 caused a statistical increase in viscosity ($P < 0.05$) and a shift from Newtonian flow to pseudoplastic flow with thixotropic property. The DS release rates of these composite gels were significantly decreased ($P < 0.05$) when compared with the control gels. This was due to an interaction between MAS and PM407 or SA, and adsorption of DS onto MAS particles. Moreover, a longer lag time and no change in DS permeation flux were found when MAS was added to the gels. The findings suggest that the rheological characteristics of gels prepared using PM407 or SA could be improved by incorporating MAS. However, the use of MAS could retard the DS release and extend the lag time of DS permeation.

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## Introduction

Gelling agents for pharmaceuticals and cosmetics can be classified into inorganic and organic substances on the basis of the nature of the colloidal phase. Clay, an example of an inorganic gelling agent, possesses a lamellar structure that can be extensively hydrated. The flat surfaces of particles are negatively charged, while the edges are positively charged. The attraction of face to edge of these colloidal lamellae creates a three-dimensional network of particles throughout the gel. Organic gelling agents are obtained from natural and synthetic polymers. The long chains of polymer are extended in water due to hydrogen bond formation between water and hydroxyl groups of the polymers, leading to high viscosity and gel formation (Zatz & Kushla 1989).

Mixtures of polymers are commonly used to improve the rheological characteristics of food products. The nature of the synergy can be due to association of the different molecules of polymers or to non-association (Draget 2000). When two polymers associate, precipitation or gelation can occur. The viscosity synergism of some polymers has been reported by which an ionic and a non-ionic cellulose, such as sodium carboxymethylcellulose and hydroxypropylmethylcellulose (HPMC), produced an increase viscosity due to cross-linking. This led to the use of cellulose at reduced concentrations in formulated products (Walker & Wells 1982).

Magnesium aluminium silicate (MAS) has been used in oral and topical formulations as a suspending and stabilizing agent either alone or in combination with other suspending agents. The combination of MAS and anionic polymers, such as xanthan gum (Ciullo 1981) and carbomer (Ciullo & Braun 1991), resulted in viscosity synergism. The advantages of combining MAS with polymers in cosmetic products are: (i) the combination may be more economical than the use of either component alone; (ii) MAS can compensate for the loss of viscosity at elevated temperatures common to many polymers; and (iii) MAS can reduce the tacky, gummy or stringy nature of polymer dispersions (Veegum/Van Gel; R. T. Vanderbilt Company, Inc. Technical literature, 1999). However, the

incorporation of MAS in topical preparations may affect drug release and permeation across the skin because MAS could adsorb the drug, resulting in prolonged release (McGinity & Lach 1977; Martin et al 1981).

Non-ionic polymers, poloxamer 407 (PM407) and HPMC, and anionic polymers, high and low viscosity grades of sodium alginate (HV-SA and LV-SA, respectively), have been widely used as gelling agents in topical dosage forms. There are no previous reports about the effects of incorporation of MAS on the rheological properties of gels. Therefore, we investigated the effect of MAS on the rheological characteristics of diclofenac sodium (DS) aqueous gels prepared using these polymers. In addition, DS release from the composite gels and permeation across skin were also investigated.

## Materials and Methods

### Materials

DS, LV-SA (viscosity of 2% solution at 25°C: 250 cps), and HV-SA (viscosity of 2% solution at 25°C: 14 000 cps) were purchased from Sigma Chemical Company (MO, USA). PM407 was a gift from BASF (Thai) Ltd (Bangkok, Thailand). MAS (Veegum HV) and HPMC (viscosity of 2% solution at 25°C: 4000 mPa s) were obtained from R.T. Vanderbilt Company, Inc. (Norwalk, CT, USA) and Fluka (Buchs, Switzerland), respectively. Methanol and acetonitrile were of high-performance liquid chromatography (HPLC) grade. Other reagents used were of analytical grade and used as received.

### Preparation of DS gels

DS (1 g) was dissolved in 50 mL distilled water. Then, HPMC, HV-SA or LV-SA (1 g) was dispersed in the DS solution and stirred to obtain homogeneous gels at room temperature; PM407 (15 g) dispersion was performed at 4°C. MAS (0.5, 1.0 or 1.5 g), pre-hydrated using hot water for 15 min, was incorporated into the DS gel. The composite gels were obtained after final weight adjustment with water to 100 g. The gels were mixed with a homogenizer for 5 min and allowed to fully hydrate at room temperature overnight before use.

### Determination of DS content, density and pH of the gels

DS gels (0.5 g) were weighed and diluted with distilled water in a volumetric flask. The solution was filtered using 0.45-$\mu$m cellulose acetate membrane and the amount of DS was analysed using HPLC. The density of the gels was determined using a 25-mL pycnometer. The pH of the gels was measured using pH-meter (Ion Analyzer 250; Corning, USA).

### Rheological studies

The rheological properties of DS gels prepared using various polymers and the gels incorporating MAS were studied using a small sample adapter of a Brookfield digital rheometer (Model DV-III; Brookfield Engineering Laboratories, Inc., Middleboro, MA, USA). The sample temperature was controlled at $32 \pm 1$°C. A rheogram of the samples was obtained by plotting between shear rate and shear stress from various revolution rates when a spindle (no. 34) was used. The area of the hysteresis loop obtained from the rheograms (shear rate over the range 2.8–16.8 $s^{-1}$) was obtained from the difference between the areas under the up-curve and the down-curve, which was computed by using the trapezoidal rule. To compare the pseudoplastic flow of the DS gels, the following exponential formula was used (El-Gizawy & Aglan 2003):

$$F^K = \eta G \quad (1)$$

$$\text{Log } G = K \log F - \log \eta \quad (2)$$

where F, G, K, and $\eta$ are shear stress, shear rate, exponential constant and viscosity coefficient, respectively.

### Skin preparation

Cobra skin was used as a barrier membrane for the DS permeation studies because one snake skin provides enough material for a complete study, with low intraspecimen variation (Pongjanyakul et al 2000). The whole skin of a cobra (*Naja Naja Khaotia*) was obtained within 24 h after its natural death from the Snake Farm, Thai Red Cross, Bangkok, Thailand. The ventral portion of the cobra skin was removed and the dorsal portion was stored at −20°C. Before use, a piece of cobra skin was cut, rinsed several time with distilled water and hydrated with 0.01 M phosphate buffer at pH 7.4 for 30 min.

### In-vitro release and permeation studies

A 6-mL modified Franz-diffusion cell (diam. 1 cm) was used. The receptor medium, distilled water at 37°C, was stirred at 600 rev $min^{-1}$. A piece of 0.45-$\mu$m cellulose acetate (Schleicher & Schuell, Dassel, Germany) was used as a membrane. The membrane was soaked in distilled water overnight and then mounted on a diffusion cell. In the permeation study, 0.01 M phosphate buffer at pH 7.4 was used as a receptor compartment. The hydrated cobra skin was mounted on the diffusion cell with the stratum corneum surface facing the donor compartment. The DS gels or 1% w/w DS solution in distilled water (0.5 g) were placed in the donor compartment and the cells were then fixed and tightly fastened with a clamp. At appropriate intervals, 0.4-mL aliquots of the receptor medium were withdrawn and immediately replaced by fresh medium. The concentration of DS was analysed by HPLC. The release study was run for 6 h, while the skin permeation study was run for 48 h to achieve a steady-state permeation rate.

The release rate of DS from the gels was compared using the time to achieve release of 20% of DS content ($T_{20}$). Moreover, the mechanism of the DS released from the gels was investigated using a semi-empirical equation (Ritger & Peppas 1987) as follows:

$$M_t/M_\infty = kt^n \quad (3)$$

$$\text{Log } M_t/M_\infty = n \log t + \log k \quad (4)$$

where $M_t$ and $M_\infty$ are the cumulative amounts of DS released at time t and infinite time, respectively, k is the kinetic constant and n is the diffusional exponent, which is indicative of the transport mechanism.

The DS steady-state flux was obtained from the slope of the straight line portion of cumulative amount of DS permeated per surface area and time profile, and the lag time was obtained from the x-intercept.

### HPLC analysis of DS

The concentration of DS was determined using HPLC (Perkin Elmer, Norwalk, CT, USA). A reversed-phase HPLC using a C-18 column (HiQ Sil C18V, 4.6 × 250 mm) connected with a guard column was used. The mobile phase was 0.033 M potassium dihydrogen phosphate/methanol/acetonitrile (30:45:25 v/v) and the pH was adjusted to 6.7 with 5% w/v dipotassium hydrogen phosphate. The flow rate of the mobile phase was 1 mL $min^{-1}$, and the detector was a UV-vis detector set at a wavelength of 280 nm. The retention time of DS was approximately 6.5 min. Under these conditions, good linearity and reproducibility were shown over the range 0.1–400.0 $\mu g\,mL^{-1}$ DS.

### Statistical analysis

The differences between rheological, release and permeation data were analysed using a non-parametric multiple comparisons test (Kruskal–Wallis test) and individual differences were examined by a Mann–Whitney test. All statistical tests were run on the SPSS program for MS Windows, release 10.0 (SPSS Inc., Chicago, IL, USA). Statistically significant differences were defined as $P$ values of less than 0.05.

## Results and Discussion

The DS gels prepared using various hydrophilic polymers provided transparent gels, indicating that DS was completely dissolved. Incorporation of MAS gave opaque composite gels. The DS content in all gels was 0.95–1.05% w/w. This indicated good recovery of DS and reversible adsorption of DS onto the particle surface of MAS. The density of the gels was over the range 1.01–1.03 g $cm^{-3}$. The addition of MAS to the gels prepared using HPMC and SA caused a significant increase ($P < 0.05$) in the pH (Table 1), whereas the gels prepared using PM407 showed little change in pH. The increase in pH of the gels was observed because the OH groups associated with Si, Mg and Al in MAS provided a basic strength in the system and the 1.5% w/w MAS dispersion possessed a basic pH, which was found to be 8.36 ± 0.06, n = 3. Incorporating MAS did not affect the pH of the DS gels prepared using PM407 because the high quantity of gelling agent had a buffer capacity to maintain the pH of the system.

### Effect of MAS on rheological properties of DS gels

The flow curves of the DS gels are shown in Figure 1. The rheological parameters calculated using the shear rate and shear stress data of the up-curve are given in Table 1. The K value and viscosity coefficient were significantly increased ($P < 0.05$) when MAS was added to the DS gels prepared using SA and PM407. An increase in the K value indicated a change from Newtonian flow to pseudoplastic flow of the gels. The flow of the gels prepared using these polymers showed a hysteresis loop when MAS

**Table 1** Characteristics of diclofenac sodium (DS) aqueous gels prepared using various hydrophilic polymers

| Component | pH | K | Viscosity coefficient ($Pa^K$ s) | n | $T_{20}$ (min) | Total DS released at 6 h (%) | Permeation flux ($\mu g\,cm^{-2}\,h^{-1}$) | Lag time (h) |
|---|---|---|---|---|---|---|---|---|
| 1% w/w LV-SA | 7.49 ± 0.04 | 0.76 ± 0.04 | 0.63 ± 0.07 | 1.18 ± 0.02 | 16.13 ± 0.47 | 88.42 ± 2.54 | 5.09 ± 0.51 | 18.95 ± 0.94[c] |
| + 0.5% w/w MAS | 8.91 ± 0.04[a] | 0.94 ± 0.02[a] | 2.15 ± 0.19[a] | 1.07 ± 0.03 | 30.38 ± 0.87[a] | 60.10 ± 3.14[a] | 4.33 ± 0.89 | 21.94 ± 1.60[a,c] |
| + 1.0% w/w MAS | 9.00 ± 0.02[a] | 1.36 ± 0.11[a] | 16.43 ± 5.96[a] | 0.92 ± 0.03 | 45.51 ± 0.45[a] | 46.75 ± 2.26[a] | 4.34 ± 0.57 | 26.58 ± 2.81[a,c] |
| + 1.5% w/w MAS | 9.11 ± 0.02[a] | 1.67 ± 0.03[a] | 94.13 ± 13.74[a] | 0.79 ± 0.05 | 56.97 ± 3.46[a] | 40.93 ± 0.83[a] | 6.08 ± 0.72 | 24.04 ± 0.68[a,c] |
| 1% w/w HV-SA | 7.59 ± 0.05 | 0.94 ± 0.03 | 9.04 ± 1.17 | 1.04 ± 0.10 | 43.75 ± 4.26 | 50.92 ± 3.59 | 4.37 ± 1.05 | 17.99 ± 1.53 |
| + 0.5% w/w MAS | 8.93 ± 0.06[a] | 1.05 ± 0.02[a] | 23.15 ± 2.01[a] | 0.98 ± 0.01 | 57.39 ± 2.77[a] | 45.40 ± 2.15[a] | 4.84 ± 0.67 | 25.02 ± 0.44[a,c] |
| + 1.0% w/w MAS | 8.90 ± 0.06[a] | 1.20 ± 0.06[a] | 77.80 ± 21.02[a] | 0.81 ± 0.06 | 114.93 ± 18.75[a] | 26.19 ± 3.08[a] | 3.84 ± 0.58 | 26.44 ± 0.60[a,c] |
| + 1.5% w/w MAS | 9.01 ± 0.04[a] | 1.39 ± 0.04[a] | 312.63 ± 75.39[a] | 0.98 ± 0.04 | 165.46 ± 27.58[a] | 23.39 ± 1.69[a] | 4.52 ± 0.76 | 24.01 ± 0.81[a,c] |
| 1% w/w HPMC | 7.19 ± 0.07 | 1.04 ± 0.07 | 20.02 ± 6.94 | 0.79 ± 0.01 | 29.27 ± 0.89 | 76.24 ± 6.33 | 4.43 ± 0.79 | 18.14 ± 0.21[c] |
| + 0.5% w/w MAS | 8.95 ± 0.01[a] | 0.93 ± 0.02 | 11.88 ± 1.59 | 0.79 ± 0.01 | 31.27 ± 1.31[a] | 65.99 ± 2.48[a] | 5.26 ± 1.37 | 23.04 ± 1.85[a,c] |
| + 1.0% w/w MAS | 9.02 ± 0.06[a] | 0.86 ± 0.02 | 9.02 ± 0.84 | 0.80 ± 0.01 | 33.73 ± 0.79[a] | 62.43 ± 1.54[a] | 4.38 ± 2.00 | 25.24 ± 0.76[a,c] |
| + 1.5% w/w MAS | 8.95 ± 0.03[a] | 1.09 ± 0.09 | 43.14 ± 18.74 | 0.71 ± 0.01 | 37.51 ± 2.05[a] | 53.43 ± 1.55[a] | 3.89 ± 1.00 | 25.11 ± 0.44[a,c] |
| 15% w/w PM407 | 7.94 ± 0.04 | 0.83 ± 0.08 | 3.61 ± 1.27 | 1.19 ± 0.02 | 43.17 ± 1.24 | 78.39 ± 1.23 | 1.12 ± 0.38[b] | 22.67 ± 1.59[c] |
| + 0.5% w/w MAS | 8.06 ± 0.05 | 0.89 ± 0.04 | 6.65 ± 1.55[b] | 0.94 ± 0.04 | 60.16 ± 1.03[a] | 59.29 ± 1.01[a] | 2.11 ± 0.29[b] | 25.38 ± 0.83[a,c] |
| + 1.0% w/w MAS | 8.09 ± 0.02 | 1.09 ± 0.02[a] | 28.67 ± 4.17[b] | 0.83 ± 0.03 | 89.62 ± 2.29[a] | 45.29 ± 3.99[a] | 1.82 ± 0.22[b] | 26.65 ± 0.11[a,c] |
| + 1.5% w/w MAS | 8.08 ± 0.01 | 1.51 ± 0.04[a] | 738.65 ± 169.79[b] | 0.99 ± 0.06 | 130.18 ± 17.28[a] | 34.66 ± 3.31[a] | 1.64 ± 0.44[b] | 24.60 ± 1.12[a,c] |

MAS, magnesium aluminium silicate; K, exponential constant; n, diffusional exponent; $T_{20}$, time to achieve release of 20% of DS content in donor compartment. Data are mean ± s.d., n = 3. [a] $P < 0.05$, compared with the gel without MAS. [b] $P < 0.05$, compared with permeation flux of DS solution (5.27 ± 0.76 $\mu g\,cm^{-2}\,h^{-1}$). [c] $P < 0.05$, compared with lag time of DS solution (16.62 ± 0.68 h).

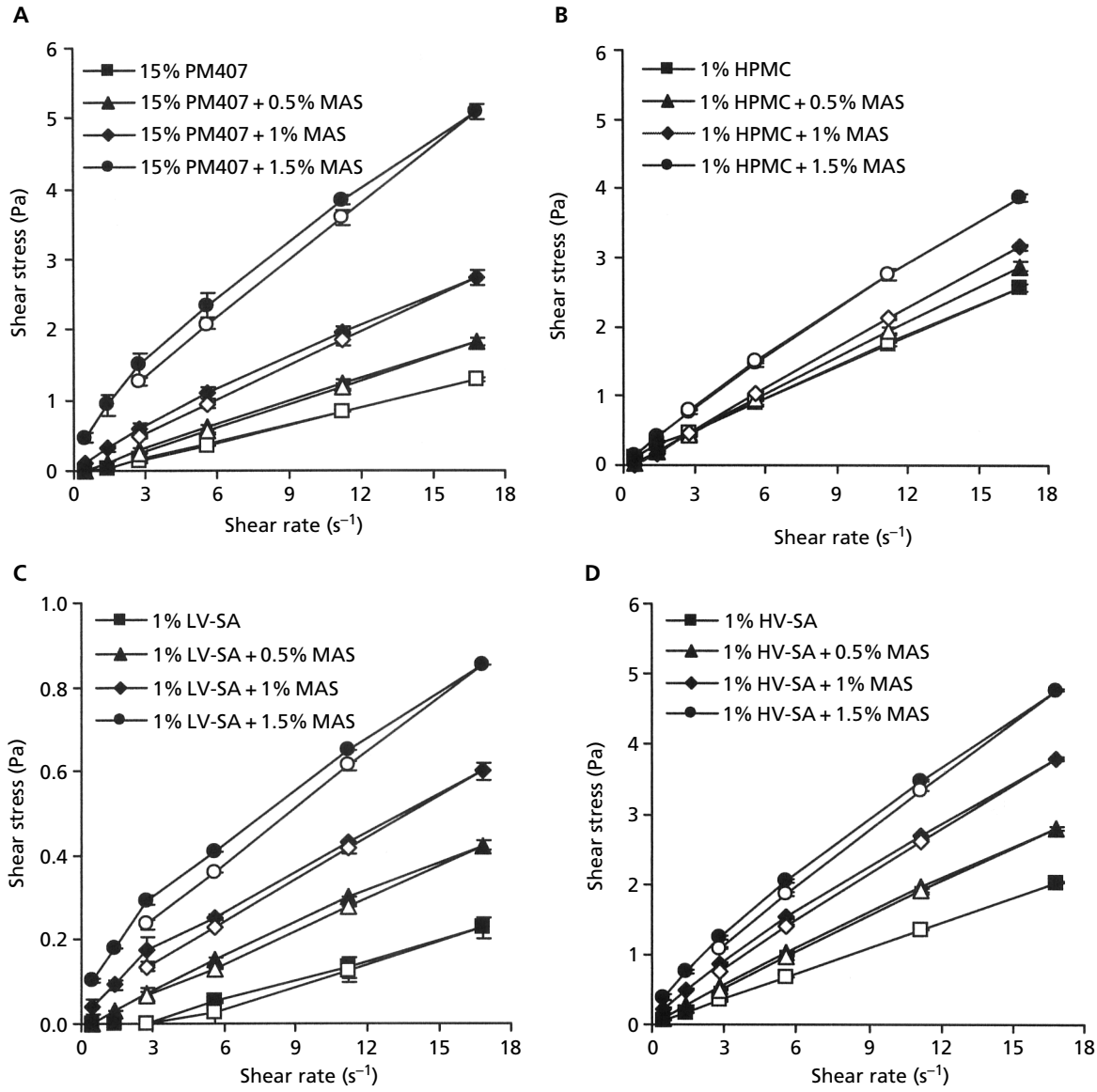


**Figure 1** Effect of magnesium aluminium silicate (MAS) on flow curves of diclofenac sodium aqueous gels prepared using 15% w/w PM407 (A), 1% w/w HPMC (B), 1% w/w LV-SA (C), and 1% w/w HV-SA (D). Closed symbols represent the up-curve; open symbols represent the down-curve. Each point is the mean ± s.d., n = 3.

was incorporated (Figure 1), suggesting a higher thixotropic property of the flow. On the other hand, MAS incorporation did not affect the flow of the HPMC gels. The areas of the hysteresis loops of the DS gels (2.8–16.8 Pa $s^{-1}$) are shown in Figure 2. The area of the hysteresis loop of the DS gels using PM407 and HV-SA was significantly increased ($P < 0.05$) with increasing content of MAS. LV-SA gels incorporating 1.5% w/w MAS had a significantly greater ($P < 0.05$) hysteresis area than those incorporating a lesser amount of MAS.

The surfaces of MAS particles contain many silanol groups, which have hydrogen bonding potential with carboxyl groups of some drugs (Gupta et al 2003). SA consists of the sodium salt of alginic acid, a linear glycuronan polymer consisting of a mixture of β-D-mannosyluronic acid and α-L-gulosyluronic acid residues (Draget 2000). Thus, silanol groups of MAS could form hydrogen bonds with carboxyl groups of SA. In addition, a partial cross-linking of homopolymeric blocks of guluronic acid with a small quantity of divalent cations in the MAS dispersion, such as aluminium and calcium ions, could occur (Vauthier et al 1994). This led to viscosity synergism. MAS also caused an increase in the thixotropic property of the mixture because the interaction between MAS and SA may provide numerous points of contact to produce a loose three-dimensional structure and so the mixture was gel-like in structure. The mixture underwent a gel-to-sol transformation and exhibited shear thinning when shear

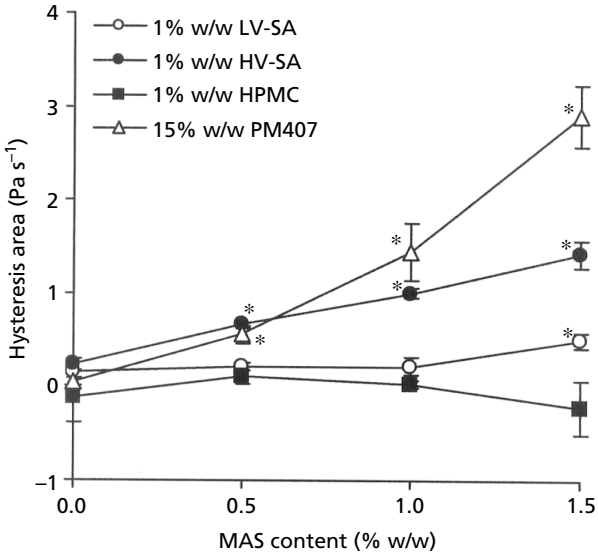


**Figure 2** Effect of magnesium aluminium silicate (MAS) on the hysteresis area obtained from flow curves of diclofenac sodium aqueous gels prepared using various hydrophilic polymers. Each point is the mean ± s.d., n = 3. *$P < 0.05$, compared with the gel without MAS.

stress was applied. The structure started to reform slowly to the original state after the shear stress was eventually removed.

PM407 is a triblock copolymer with a central hydrophobic chain of polyoxypropylene and two identical lateral hydrophilic chains of polyoxyethylene. HPMC is a partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose. The viscosity synergism between these polymers and MAS may be due to hydrogen bond formation of the hydroxyl and ether groups of these polymers with the silanol groups of MAS. It was observed that incorporating MAS into PM407 gels caused a greater increase in viscosity and hysteresis area than HPMC because a higher quantity of PM407 was used to form the gel. Moreover, the effect of MAS on the rheology of HPMC was obviously less than that of SA because the carboxyl groups of SA could form a strong hydrogen bond with MAS and a partial cross-linking with divalent cations in MAS.

## Effect of MAS on release of DS gels

The DS release profiles of the gels did not form straight lines and incomplete release of DS was found. The total DS released from the gels at 6 h is shown in Table 1. The greater the content of MAS in the gels, the less the total DS released. On the other hand, the gels with MAS had a longer $T_{20}$ than those without MAS (Table 1). The $T_{20}$ significantly increased ($P < 0.05$) with increasing content of MAS in the gels. It was observed that in gels composed of PM407 or SA, the addition of 1.5% w/w MAS provided 3.0–3.8-times longer $T_{20}$ than the control gels, while the $T_{20}$ of the HPMC gel with 1.5% w/w MAS was 1.3-times longer than that of the HPMC gel alone. This was possibly due to the interaction of MAS with PM407 or SA. Moreover, the adsorption of DS onto the high surface area of MAS particles obviously affected the total amount of DS released and this may also retard the release of DS.

Using Equation 4, a good relationship between log $M_t/M_\infty$ and log t was found, with $R^2$ greater than 0.99. The n values of the gels obtained were greater than 0.5 (Table 1), suggesting an anomalous transport of DS in the gels. This indicated that not only the diffusion process of DS, but also the swelling process of the polymers controlled the release of DS from the gels. Moreover, the DS release may be controlled by the desorption process of DS from the suspended MAS particles. This may lead to a deviation of DS release from the diffusion-controlled mechanism. However, the n values tended to decrease when MAS was added to the gels prepared using PM407 and SA, whereas the HPMC gels with MAS provided similar n values. This may be because the interaction of MAS with PM407 or SA caused a more rigid structure of the composite gels, which might decrease the swelling of the gels during the release testing.

## Effect of MAS on permeation of DS gels

The permeation profiles of DS from the gels across cobra skin showed zero-order kinetics with a lag time. The relationship between the amount of DS permeated and time gave a good correlation ($R^2 > 0.97$) when investigated using linear regression analysis. The DS permeation flux and lag time of the gels are shown in Table 1. A significantly longer lag time of the DS gels was found ($P < 0.05$) when MAS was incorporated into the gels but this did not correlate with the amount of MAS added. Moreover, MAS incorporation caused no significant change in DS permeation flux. It was found that the DS permeation flux from the DS gel with PM407 was significantly less ($P < 0.05$) than that from other gelling agents. The permeation flux and lag time of the gels were also compared with those of 1% w/w DS solution in distilled water (pH = 7.06 ± 0.11, n = 3). The permeation flux and lag time of 1% w/w DS solution were 5.27 ± 0.76 $\mu g\,cm^{-2}\,h^{-1}$ and 16.62 ± 0.86 h (n = 3), respectively. The lag time of DS solution was significantly shorter ($P < 0.05$) than that of the gels using LV-SA, HPMC and PM407, whereas the permeation flux of the DS solution was comparable with that of SA and HPMC, and significantly greater ($P < 0.05$) than that of PM407.

DS, a non-steroidal anti-inflammatory drug, is a weak acid compound with a $pK_a$ value of 4 (Adeyeye & Li 1990). The logarithm of the octanol/water partition coefficient of DS is −0.962 (Morimoto et al 1992). At pH above 7, 99.9% of DS is the ionized form of diclofenac acid. It is known that the permeation across skin of the ionized form of drugs is less than that of the un-ionized form (Swarbrick et al 1984; Kushla & Zatz 1991). However, the ionized form of DS could form an ion pair, which has greater hydrophobicity (Fini et al 1999). Thus, the ion pairs of DS could permeate across the skin by the lipid pathway (Maitani et al 1994).

The permeation profiles of the gels followed zero-order kinetics, indicating that the DS released from the gels caused an excess concentration of DS on the surface of the skin before permeation and that the skin was a rate-limiting step. For this reason, the permeation rate of DS from the gels using SA and HPMC was not significantly different when compared with DS solution. However, a slower release of DS from the gels with or without MAS affected the time required to establish a uniform concentration gradient in the skin. Thus, a longer lag time was obtained. In the case of PM407, the permeation rate of DS was less than other gelling agents and DS solution. This indicated that the DS release onto the skin was controlled by the polymer matrix of PM407. The viscosity of PM407 may have been increased because it was incubated at the skin surface temperature (37°C) for a long time. This is due to micellization of PM407 at higher temperatures (Bohorquez et al 1999). This phenomenon was more dominant at higher temperatures because of dehydration and poor solubility of the polyoxypropylene core. The increase in viscosity was attributed to the proximity of micelles and micelle entanglements (Cabana et al 1997). Moreover, the ion pairs of DS could be entrapped in the micelle as a drug reservoir. Therefore, the slow release of DS from PM407 gels with or without MAS on the skin surface was obtained, which led to the lower permeation flux of DS.

## Conclusion

Incorporation of MAS into DS gels prepared using PM407 or SA caused a change in the rheological characteristics and decreased the release rate of DS. Moreover, a longer lag time and no change in DS permeation flux were found. Thus, the use of MAS to improve the rheological properties of aqueous gels could retard the drug release and extend the lag time of drug permeation.

## References


Adeyeye, C. M., Li, P. K. (1990) Diclofenac sodium. In: Florey, K. (ed.) *Analytical profiles of drug substances*, Vol. 19. Academic Press, New York, pp 123–144

Bohorquez, M., Koch, C., Trygstad, T., Pandit, N. (1999) A study of the temperature-dependent micellization of pluronic F127. *J. Colloid Interface Sci.* **216**: 34–40

Cabana, A., Aït-Kadi, A., Juhász, J. (1997) Study of the gelation process of polyethylene $oxide_a$-polypropylene $oxide_b$-polyethylene $oxide_a$ copolymer (poloxamer 407) aqueous solutions. *J. Colloid Interface Sci.* **190**: 307–312

Ciullo, P. A. (1981) Rheological properties of magnesium aluminum silicate/xanthan gum dispersions. *J. Soc. Cosmet. Chem.* **32**: 275–285

Ciullo, P. A., Braun, D. B. (1991) Clay/carbomer mixtures enhance emulsion stability. *Cosmet. Toilet.* **106**: 89–95

Draget, K. I. (2000) Alginates. In: Philips, G. O., Williams, P. A. (eds) *Handbook of hydrocolloids*. Woodhead Publishing, Cambridge, pp 379–395

El-Gizawy, S. A., Aglan, N. I. (2003) Formulation and evaluation of metronidazole acid gel for vaginal contraception. *J. Pharm. Pharmacol.* **55**: 903–909

Fini, A., Fazio, G., Gonzalez-Rodriguez, M., Cavallari, C., Passerini, N., Rodriguez, L. (1999) Formation of ion-pair in aqueous solutions of diclofenac salts. *Int. J. Pharm.* **187**: 163–173

Gupta, M. K., Vanwert, A., Bogner, R. H. (2003) Formation of physical stable amorphous drugs by milling with Neusilin. *J. Pharm. Sci.* **92**: 536–551

Kushla, G. P., Zatz, J. L. (1991) Influence of pH on lidocaine penetration through human and hairless mouse skin in vitro. *Int. J. Pharm.* **71**: 167–173

Maitani, Y., Kugo, M., Nagai, T. (1994) Permeation of diclofenac salts through silicone membrane: a mechanistic study of percutaneous absorption of ionizable drugs. *Chem. Pharm. Bull.* **42**: 1297–1301

Martin, M. J. S., Camazano, M. S., Hernandez, M. T. V., Dominguez-Gil, A. (1981) Interaction of propranolol hydrochloride with montmorillonite. *J. Pharm. Pharmacol.* **33**: 408–410

McGinity, J. W., Lach, J. L. (1977) Sustained-release application of montmorillonite interaction with amphetamine sulfate. *J. Pharm. Sci.* **66**: 63–66

Morimoto, Y., Hatanaka, T., Sugibayashi, K., Omiya, H. (1992) Prediction of skin permeability of drugs: comparison of human and hairless rat skin. *J. Pharm. Pharmacol.* **44**: 634–639

Pongjanyakul, T., Prakongpan, S., Priprem, A. (2000) Permeation studies comparing cobra skin with human skin using nicotine transdermal patches. *Drug Dev. Ind. Pharm.* **26**: 635–642

Ritger, P. L., Peppas, N. A. (1987) A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. *J. Control. Release* **5**: 37–42

Swarbrick, J., Lee, G., Brom, J., Gensmantel, N. P. (1984) Drug permeation through human skin II: permeability of ionizable compounds. *J. Pharm. Sci.* **73**: 1352–1355

Vauthier, C., Rajaonarivony, M., Couarraze G., Couvreur, P., Puisieux, F. (1994) Characterization of alginate pregel by rheological investigation. *Eur. J. Pharm. Biopharm.* **40**: 218–222

Walker, C. V., Wells, J. I. (1982) Rheological synergism between ionic and non-ionic cellulose gums. *Int. J. Pharm.* **11**: 309–322

Zatz, J. L., Kushla, G. P. (1989) Gels. In: Lieberman, H. A., Rieger, M. M., Banker, G. S. (eds) *Pharmaceutical dosage forms: disperse systems*, Vol. 19. Marcel Dekker, Inc., New York and Basel, pp 495–510