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Rheological characterization and in vivo evaluation of thermosensitive poloxamer-based hydrogel for intramuscular injection of piroxicam

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ABSTRACT

To develop an industrially practical thermosensitive injectable hydrogel that is easy to administer, gels quickly in the body and allows sustained release of the drug, poloxamer-based hydrogels containing piroxicam as a model drug were prepared with poloxamer, sodium hydroxide and sodium chloride using the cold method. Their rheological characterization, dissolution and pharmacokinetics after intramuscular administration to rabbits were evaluated. Among the ingredients tested, sodium hydroxide and piroxicam decreased the viscosity and retarded the gelation time of the injectable gel. However, sodium chloride did the opposite. The thermosensitive injectable gel composed of 2.5% piroxicam, 15% P 407, 17% P 188, 0.01% sodium hydroxide and 1.6% sodium chloride was instantly applied to practical industrial product, since it was easy to administer intramuscularly and gelled quickly in the body. The drug was dissolved out of the hydrogels by Fickian diffusion through the extramicellar aqueous channels of the gel matrix. Sodium chloride barely affected the dissolution mechanism or dissolution rate of the drug from the injectable gels. Furthermore, it maintained the plasma concentrations of drug for 4 days and gave a 150-fold higher AUC compared to piroxicam solution. Thus, it would be practically useful for delivering piroxicam in a pattern that allows sustained release for a long time, leading to better bioavailability.

1. Introduction

The use of a controlled release formulation for chronic pain management is the best way to improve the efficacy of the treatment, patient compliance and social rehabilitation (Negrin et al., 2004). Thermosensitive hydrogels that undergo a sol-to-gel transition in response to temperature changes are of great interest in long-acting therapeutic delivery and tissue engineering as an injectable depot system. Poloxamer, a copolymer of poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene), has been studied as a potential base for thermosensitive hydrogels (Cabana et al., 1997; Watanabe et al., 1990). It can carry sufficient drug, and shows good water-solubility, tolerability, biodegradability, non-toxicity and controlled release (Veyries et al., 1999). Furthermore, poloxamer solutions are known to exhibit the phenomenon of reverse thermal gelation, remaining as solutions at low temperatures and gelling following an increase in temperature (Choi et al., 1998a; Lenarets et al., 1987). There have been several attempts to modulate the gelation temperature of poloxamer-based liquids. The gelation temperature of poloxamer solutions can be adjusted by modifying cross-linking agents and monomers (Niu et al., 2009; Schmolka, 1972), by mixing different series of poloxamers (Abhaham, 1994), changing the weight of the poloxamers (Schmolka, 1985) and changing the pH and the ionic strength (Gilbert et al., 1987). However, for practical use of pharmaceutical preparations, the gelation temperature of poloxamer solutions has been controlled by mixing poloxamer series and adding the appropriate ingredients (Choi et al., 1998a, 1999). Such thermosensitive hydrogels have been used as a controlled release drug delivery system for injectable (Bhattarai et al., 2005; Blonder et al., 1999; Lee and Tae, 2007; Ricci et al., 2002, 2005), ocular (Raymond et al., 2004) and rectal administration (Choi et al., 1998b; Yong et al., 2004; Yun et al., 1999). However, most previous studies have focused only on rheological theory, and the in vitro and in vivo sustained release action of poloxamer-based thermosensitive hydrogels. There is a lack of knowledge on practical administration to the body such as syringe-ability and gelation time, although these two factors are crucial in the development of a desirable thermosensitive hydrogel that is easy to administer to the body and gels rapidly, enabling practical use in pharmaceutical preparations.

In this study, to get the information on rheological characterization suitable to practical administration for poloxamer-based thermosensitive hydrogels, the gels were prepared with poloxamer, sodium hydroxide and sodium chloride using the cold

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Table 1
Composition, viscosity and gelation time of piroxicam-loaded injectable hydrogel.

Composition (%)	P 407	P 188	Sodium hydroxide	Piroxicam	Sodium chloride	Viscosity at 25 °C (mPa s)	Gelation time (min)
I	15	15	0	0	0	151–152	8.45
II	15	17	0	0	0	178–179	6.84
III	15	18	0	0	0	200–202	5.67
IV	15	20	0	0	0	232–235	4.89
V	15	17	0.01	0	0	151–153	7.94
VI	15	17	0.03	0	0	114–115	14.88
VII	15	17	0.05	0	0	78–79	19.47
VIII	15	17	0.01	1.0	0	130	10.41
IX	15	17	0.01	2.5	0	126–127	11.86
X	15	17	0.01	4.0	0	89–91	23.54
XI	15	17	0.01	2.5	0.4	128–129	13.28
XII	15	17	0.01	2.5	0.8	146–148	13.36
XIII	15	17	0.01	2.5	1.2	181–182	11.01
XIV	15	17	0.01	2.5	1.6	270–281	6.23
XV	15	17	0.01	2.5	2.0	330–334	3.38

method, and their syringe-ability and gelation time were evaluated. Furthermore, their pharmacokinetics was investigated after intramuscular administration to rabbits. The poorly water-soluble piroxicam was selected here as a model drug, since its use has been limited by the short duration of its effects in chronic pain management (Dadashzadeh et al., 2002; Piao et al., 2008).

2. Materials and methods

2.1. Materials

Piroxicam and sodium chloride were supplied by DC Chemicals (Seoul, South Korea). Poloxamer 407 (P 407) and poloxamer (P 188) were obtained from BASF (Ludwigshafen, Germany). Semipermeable membrane tubing (Spectra membrane tubing No. 1) was purchased from Spectrum Medical Industries Inc. (Los Angeles, CA, USA). All other chemicals were of reagent grade and were used without further purification.

2.2. Preparation of piroxicam-loaded injectable hydrogels

The poloxamer-based injectable gels were prepared with various ratios of piroxicam, P 407, P 188, sodium chloride and sodium hydroxide using the cold method (Choi et al., 1998a; Yong et al., 2004). The detailed composition each piroxicam-loaded poloxamer-based injectable gel is given in Table 1. In brief, P 188 and P 407 were dissolved in distilled water at 4 °C with gentle stirring. The poloxamer solution was left overnight in a refrigerator until a clear solution was formed. Various amounts of sodium hydroxide, piroxicam and sodium chloride were subsequently added to the poloxamer solution with gentle stirring, and then kept overnight at 4 °C.

2.3. Reological properties of piroxicam-loaded injectable hydrogel

The rheological behaviour of the piroxicam-loaded injectable hydrogels was investigated at 25 °C and 36.5 °C using a rheometer (Physica, Germany) (Ricci et al., 2002). Temperature was controlled by a circulating water bath (TC10, Germany) and the UDS 200 program was used to control and perform calculations in the rheometer. The instrument was set up with a parallel plate geometry using 25-mm diameter plates at two temperatures and samples of about 1 mm in thickness.

2.4. Dissolution

Each poloxamer-based hydorgel containing 100 mg of piroxicam was inserted into a semipermeable membrane tube. Both sides of the tube were tied with a thread to prevent leakage. The semipermeable membrane tube was then placed in a dissolution tester (DST-600, Fine Chemical, Korea). The dissolution test was performed at 36.5 °C using the paddle method at 100 rpm with 60 ml phosphate buffer (pH 7.2) as the dissolution medium. At 1-h intervals, 0.5 ml of the medium was sampled and filtered (Choi et al., 1998b; Yong et al., 2004). The resulting solution was then analysed by HPLC as described below.

2.5. Pharmacokinetics

2.5.1. In vivo experiments

Female New-Zealand rabbits weighing about 1.8 kg were fasted for 24 h prior to the experiments but allowed free access to water. Ten rabbits were divided into two groups. Each rabbit was administered piroxicam solution or injectable hydrogel (0.2 ml/kg, equivalent to 5 mg piroxicam/kg), respectively. All animal care and procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted in 1989 and revised in 1999 by the Society of Toxicology (SOT, 1999). Furthermore, the protocols for the animal studies were approved by the Institute of Laboratory Animal Resources of Yeungnam University.

2.5.2. Administration and blood-collecting

All rabbits were kept at 20 °C and 70%RH with a normal 12-h light/dark cycle starting 1 week before the experiment. The piroxicam solution and injectable hydrogel were administered intramuscularly to the hind leg of each rabbit. Then, 0.3 ml of blood samples were obtained at various intervals from the left or right ear vein into heparinized glass tubes and centrifuged at 3000 × *g* for 15 min using a 5415C centrifuge (Eppendorf, USA) (Blonder et al., 1999; Negrin et al., 2004).

2.5.3. Blood sample analysis

Plasma (0.1 ml) was thoroughly mixed with 0.1 ml of acetonitrile, 0.01 ml of 60% perchloric acid and 25 μl of acetonitrile solution containing indomethacin (100 μg/ml) as an internal standard. It was centrifuged at 12,000 × *g* for 10 min to precipitate the proteins. The supernatant layer (0.2 ml) was evaporated under N_2 (g). The residue was reconstituted in 50 μl of mobile phase. The resulting solution (20 μl) was analysed by HPLC (Jasco UV-975, Japan) equipped with an Inertsil ODS-3C_{18} column (GL science, 0.5 μm, 25 cm × 0.46 cm i.d.) and UV detector (Model L-7450). The mobile phase consisted of 0.1 M sodium acetate, acetonitrile and triethanolamine (61:39:0.05, v/v) adjusted to pH 4 with glacial acetic acid. The eluent was monitored at 330 nm with a flow rate of 1.0 ml/min (Dadashzadeh et al., 2002; Piao et al., 2007, 2008).

2.5.4. Pharmacokinetic data analysis and statistical analysis

The area under the drug concentration–time curve from zero to infinity (AUC), the mean residence time (MRT), the elimination constant (K_{el}) and half-life ($t_{1/2}$) were calculated using a non-compartmental analysis (WinNonlin; professional edition, version 2.1; pharsiquit, Mountain View, CA, USA). The maximum plasma concentration of drug (C_{max}) and the time taken to reach the maximum plasma concentration (T_{max}) were obtained directly from the plasma data (Gibaldi and Perrier, 1982). Levels of statistical significance ($p < 0.05$) were assessed using the Student's *t*-test between two means for unpaired data. All data are expressed as mean ± standard deviation (S.D.) or as the median (ranges) for T_{max}.

3. Results and discussion

The gelation temperature is the temperature at which the liquid phase makes its transition to a gel. The gelation temperature range that would be suitable for an injectable gel is 30–36 °C (Choi et al., 1998a; Yong et al., 2004). If the gelation temperature of the injectable gel is lower than 30 °C, gelation occurs at room temperature, leading to difficulty in manufacturing, handling and administration. If the gelation temperature is higher than 36 °C, the injectable gel remains as a liquid at body temperature, and thus does not control the release of the drug in the body. Therefore, the injectable gel must have a suitable gelation temperature (30–36 °C) to be a liquid at room temperature and to form a gel phase instantly in the body.

As potential bases of injectable gel with suitable gelation temperatures (30–36 °C), poloxamer mixtures of P 407 and P 188 were selected due to their thermosensitive gelling properties. In addition, P 407 and P 188 are known to have low toxicity, relatively low levels of skin irritation, excellent water-solubility, high solubilizing capacity, good drug release characteristics and compatibility with other chemicals (Choi et al., 2008a; Veyries et al., 1999). It has previously been reported that mixtures of 15% P 407 and 15–20% P 188 form a liquid at room temperature and gel at body temperature (Choi et al., 2008a; Yun et al., 1999).

In the development of thermosensitive injectable gels, the syringe-ability is an important factor, influencing the ease of administration of the injectable gels to the body. In a preliminary study, the threshold of syringe-ability suitable for an injectable gel was investigated by administering injectable gels into the muscle of a rabbit using a syringe with a needle. Below the threshold of syringe ability, it was easy to administer without separating the needle from the syringe. However, above the upper threshold, it was difficult to administer intramuscularly and the needle became separated from the syringe. In the gels containing poloxamer, the threshold in syringe-ability was a viscosity of about 300 mPa s at 25 °C.

Another factor to take into consideration is the gelation time, which is the time taken for injectable gels to change from a liquid state to a gel at 36.5 °C. Injectable gels with a relatively fast gelation time would show better control of the release of the drug in the body. In a preliminary study, the gelation threshold was investigated by tilting the injectable gels at 36.5 °C (Dumortier et al., 1991; Ricci et al., 2002). Below the gelation threshold during tilting, the injectable gels flowed like a liquid. However, above the threshold, the injectable gels maintained the gel state and did not flow. In the gels containing poloxamer, the threshold in syringe-ability was a viscosity of about 4000 mPa s at 36.5 °C. Therefore, in this study, the gelation time meant the time taken for the injectable gel to reach a viscosity of about 4000 mPa s in 36.5 °C. The gelation time was obtained directly from the viscosity data at 36.5 °C (see Figs. 1–4).

The thermosensitive gelation behaviour of the poloxamer-based injectable gels was studied by measuring the viscosity of the samples at 25 and 36.5 °C. The viscosity measurement was viewed as a quality control method in order to assess the behaviour of the gels at room temperature and biological temperature.

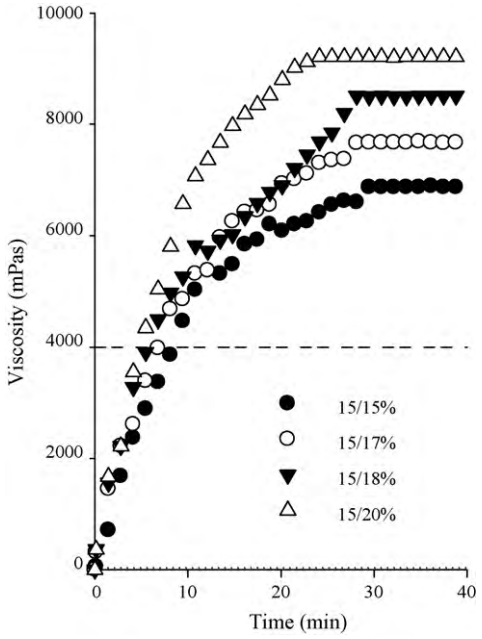

Fig. 1. Effect of P 188 on the viscosity of injectable gel at 36.5 °C. The injectable gels were composed of 15% P 407 and 15–20% P 188.

First, the effect of P 188 on the viscosity of the injectable gels at 25 and 36.5 °C was investigated. The injectable gels were prepared using the cold method with various ratios of P 407 and P 188, and their rheological characteristics were evaluated (Table 1, I–IV). As the P 188 concentration in the injectable gel increased, the viscosity increased at 25 °C (Table 1, I–IV). The injectable gel containing 15% P 407 and 15–20% P 188 was easy to administer intramuscularly due to a viscosity of 150–240 mPa s at 25 °C, which is below the viscosity threshold of 300 mPa s at 25 °C. As time elapsed, the viscosity of all

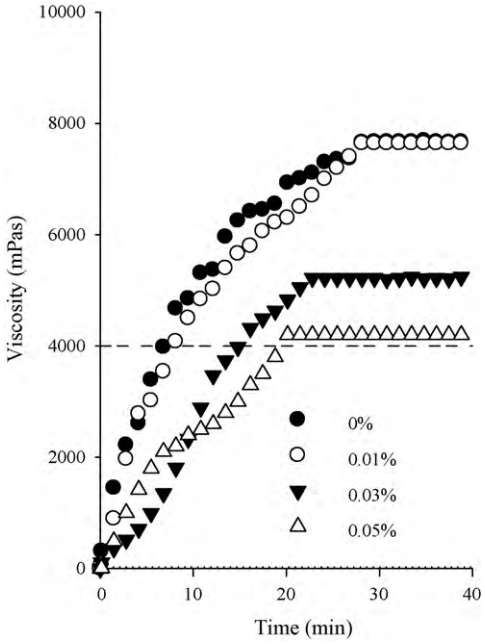

Fig. 2. Effect of sodium hydroxide on the viscosity of injectable gel at 36.5 °C. The injectable gels were composed of 15% P 407, 17% P 188 and 0–0.03% sodium hydroxide.

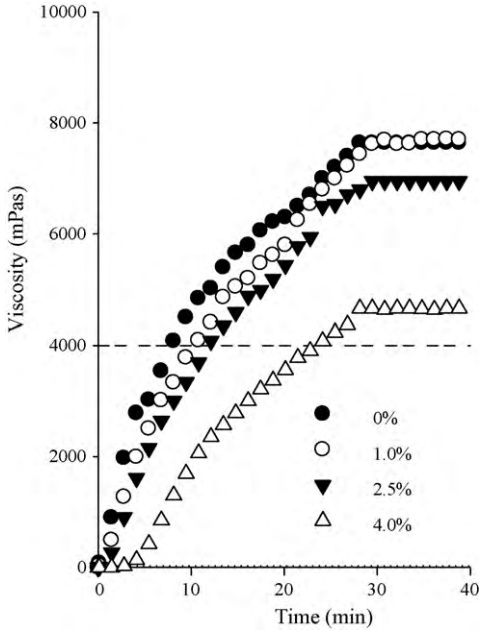

Fig. 3. Effect of piroxicam on the viscosity of injectable gel at 36.5 °C. The injectable gels were composed of 15% P 407, 17% P 188, 0.01% sodium hydroxide and 0–4% piroxicam.

injectable gels rapidly increased, and then maintained a constant intrinsic viscosity (Fig. 1). The higher the P 188 concentration was in the injectable gel, the higher the constant intrinsic viscosity was. Similarly, P 188 shortened the gelation time of the injectable gels, that is, the time taken to reach a viscosity of about 4000 mPa s at 36.5 °C (Fig. 1).

To investigate the effect of sodium hydroxide on the viscosity of the injectable gels, the gels were prepared with 15% P 407, 17% P 188 and 0–0.03% sodium hydroxide, and their rheological characteristics were evaluated (Table 1, II, V–VII). Sodium hydroxide was used as a solubilizer of piroxicam in this study (Piao et al., 2007, 2008). As

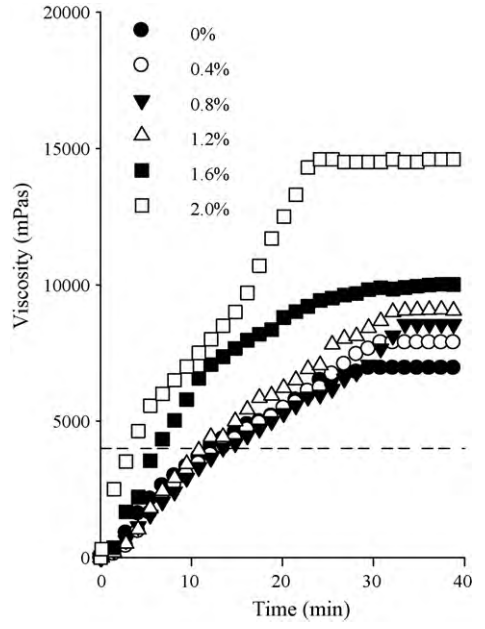

Fig. 4. Effect of sodium chloride on the viscosity of injectable gel at 36.5 °C. The injectable gels were composed of 15% P 407, 17% P 188, 0.01% sodium hydroxide, 2.5% piroxicam and 0–2% sodium chloride.

Table 2
Release kinetic parameters.

Injectable gel	Release exponent, n	Kinetic constant, k (%/h^n)	Correlation coefficient, r
IX	0.54	0.91	0.95
XIV	0.55	0.95	0.96
XV	0.52	0.95	0.95

the sodium hydroxide concentration increased, the viscosity of the injectable gels decreased at 25 °C and 36.5 °C (Table 1, II, V–VII; Fig. 2). Furthermore, sodium hydroxide lengthened the gelation time of the injectable gels (Fig. 2; Table 1, II, V–VII). These injectable gels were easy to administer intramuscularly due to their viscosity of 80–180 mPa s at 25 °C, which is below the viscosity threshold of 300 mPa s at 25 °C.

To investigate the effect of piroxicam on the viscosity of the injectable gels, the rheological characteristics of injectable gels prepared with 15% P 407, 17% P 188, 0.01% sodium hydroxide and 0–4% piroxicam were evaluated (Table 1, V. VIII–X). These injectable gels were clear and homogeneous, since the drug is soluble in alkali poloxamer solution. The higher the piroxicam concentration was, the lower the viscosity of the injectable gels was at 25 °C and 36.5 °C (Table 1, V, VIII–X; Fig. 3). The drug lengthened the gelation time of the injectable gels (Fig. 3; Table 1, V, VIII–X). These injectable gels were easy to administer intramuscularly, with a viscosity threshold below 300 mPa s at 25 °C. However, all piroxicam-loaded injectable gels had relatively low gelation times (Table 1, V, VIII–X).

Thus, injectable gels with relatively high gelation times were prepared by adding 0.4–2% sodium chloride to 15% P 407, 17% P 188, 0.01% sodium hydroxide and 2.5% piroxicam (Table 1, IX, XI–XV). Sodium hydroxide was used to control gelation in this study (Choi et al., 1999). As the sodium chloride concentration in the poloxamer solution increased, the viscosity of the injectable gels increased at 25 °C and 36.5 °C (Table 1, IX, XI–XV; Fig. 4). The injectable gels containing less than 1.6% sodium chloride were easy to administer intramuscularly, with a viscosity of 90–190 mPa s at 25 °C, below the viscosity threshold of 300 mPa s at 25 °C. However, the injectable gel containing 2.0% sodium chloride was difficult to administer intramuscularly since it had a viscosity of about 330 mPa s at 25 °C. Sodium chloride shortened the gelation time of the injectable gels (Fig. 4; Table 2, IX, XI–XV). Among the injectable gel easy to administer intramuscularly, the injectable gels containing 1.6% sodium chloride had the fastest gelation time of about 6 min.

The multivariate analysis of the rheological behaviour of injectable gels indicated that the drug and ingredients generally had significant effects on the rheological characteristics of the poloxamer hydrogels. All the injectable gels underwent an apparent sol-to-gel transition with a poloxamer concentration ranging from 30 to 35% (Figs. 1–4). At room temperature, the solutions were viscous liquids that flowed easily. With the exception of formulation XV, these injectable gels were easy to inject intramuscularly through a 20-gauge needle, since they had a viscosity below the threshold of 300 mPa s at 25 °C. As the solutions were heated to biological temperature, they transformed into gels. The gels reverted back to solutions when the temperature dropped to 25 °C. The temperature-dependent gelation of poloxamer solutions could be explained by a configuration change (Choi et al., 1998a, 1999). Poloxamer molecules exhibit a well-arranged zigzag configuration. With increasing temperature, the zigzag configuration of poloxamer may be transformed into a close-packed meander configuration, forming a more closely-packed and more viscous gel (Choi et al., 1998a; Kim et al., 1998; Watanabe et al., 1990). Sodium hydroxide and piroxicam decreased the viscosity of injectable gels

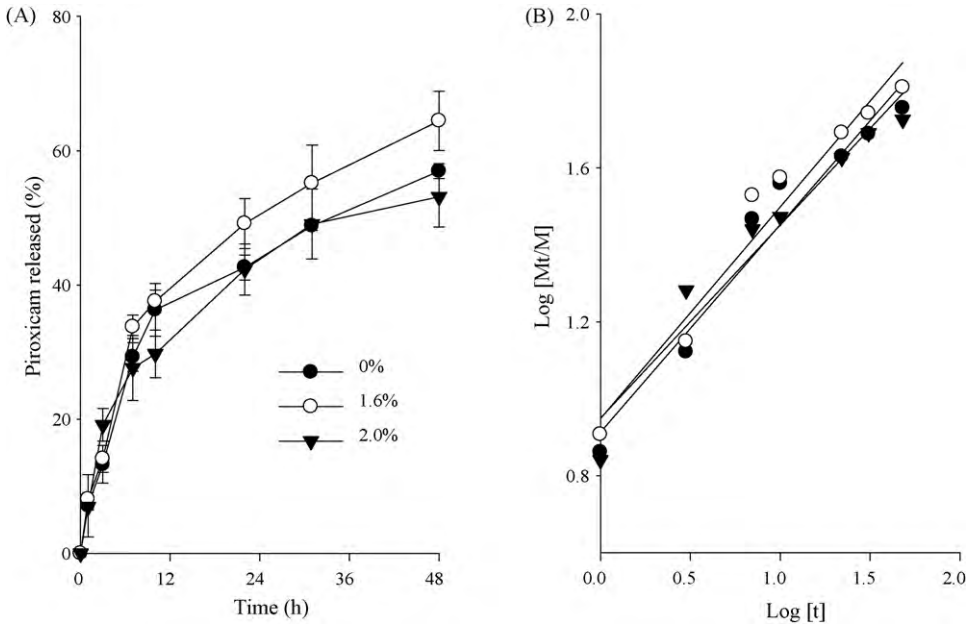

Fig. 5. Effect of sodium chloride on drug release (A) and release kinetics (B). The injectable hydrogels were composed of 15% P 407, 17% P 188, 0.01% sodium hydroxide, 2.5% piroxicam and 0–2.0% sodium chloride. Each value represents the mean ± SD ($n = 6$).

and lengthened the gelation time of the injectable gel. However, sodium chloride did the opposite. As a possible mechanism by which sodium hydroxide and piroxicam affected the rheological characteristics of the injectable gel base, it is speculated that they could reduce the hydrogen bonding in the cross-linked reticular poloxamer gel (injectable gel base) as a result of their placement between the poloxamer molecules in the gel matrix (Choi et al., 1998a; Kim et al., 1998; Schmolka, 1972). However, sodium chloride could strengthen the bonding of the cross-linked reticular injectable gel base due to the very strong cross-linking bonding of sodium salts obtained by placing sodium chloride between the poloxamer molecules in the gel matrix (Choi et al., 1999; Yong et al., 2001).

The dissolution profiles of drug from the formulations with different ratios of sodium chloride (0, 1.6 and 2% (w/v) ratio), which had different viscosities and gelation times, are plotted in Fig. 5A. This part of the study was carried out to determine the effect of sodium chloride content on the dissolution of formulations. The cumulative percentage of the drug dissolved in the dissolution medium was plotted versus time. Our results showed that the drug dissolution profile of the poloxamer-based injectable gels that had different weight ratios of sodium chloride did not vary significantly (Fig. 5A). Thus, the dissolution profile of the drug was barely affected by the formulation, even though sodium chloride had an effect on the gelation time and viscous properties of the formulation.

To understand the mechanism of dissolution of drugs from hydrogels, we described the dissolution rate using the following equations:

$$\frac{M_t}{M} = kt^n$$

$$\log\left[\frac{M_t}{M}\right] = \log k + n\log[t]$$

where M_t/M is the fraction of dissolved drug at time t, k is a characteristic constant of the hydrogel and n is an indication of the dissolution mechanism.

As the k value increases, dissolution becomes faster. The n value of 1 corresponds to zero-order dissolution kinetics, $0.5 < n < 1$ means a non-Fickian dissolution model and $n = 0.5$ indicates Fickian diffusion (Higuchi model) (Choi et al., 1998a). From the plot of log (M_t/M) versus log (t) (Fig. 5B), the kinetic parameters n and k were calculated. Table 3 shows that most n values were close to 0.5, suggesting that the drug was dissolved from hydrogels by Fickian diffusion through the extramicellar aqueous channels of the gel matrix (Choi et al., 1998a; Yong et al., 2004). Furthermore, their similar n and k values indicated that sodium chloride barely affected the dissolution mechanism or dissolution rate.

From these findings, among the hydrogels tested, the injectable hydrogel composed of 2.5% piroxicam, 15% P 407, 17% P 188, 0.01% sodium hydroxide and 1.6% sodium chloride, which was easiest to administer intramuscularly and gelled most rapidly in the body, was selected for further study.

Its pharmacokinetic study was carried out to investigate if it could control the release of drug like other poloxamer-based injectable gels (Bhattarai et al., 2005; Blonder et al., 1999; Lee and Tae, 2007; Ricci et al., 2002, 2005). Fig. 6 shows the mean plasma concentration–time profiles of piroxicam after intramuscular administration of piroxicam solution and injectable gel to rabbits at the dose of 5 mg/kg piroxicam. The piroxicam solution gave maximum plasma concentrations of drug at 0.25 h followed by a gradual decrease up to 7 h. However, after intramuscular administration of the injectable gel to rabbits, the drug was observed to achieve plasma levels of about 1.5 μg/ml at 7 h. The plasma concentrations of piroxicam remained at 1.5–2.2 μg/ml for 4 days and finally fell to less than 20 μg/ml at the end of 7 days. The plasma

Table 3
Pharmacokinetic parameters of piroxicam delivered by piroxicam solution and injectable hydrogel.

Parameters	Piroxicam solution	Injectable hydrogel
AUC (h μg/ml)	1.37 ± 0.14	228.46 ± 25.83*
MRT (h)	1.92 ± 0.35	72.43 ± 5.68*
Kel (h^{-1})	0.48 ± 0.10	0.015 ± 0.005*
$t_{1/2}$ (h)	1.49 ± 0.28	49.29 ± 14.53*

* $P < 0.05$ compared with piroxicam solution.
** Each value represents the mean ± S.E. ($n = 5$).

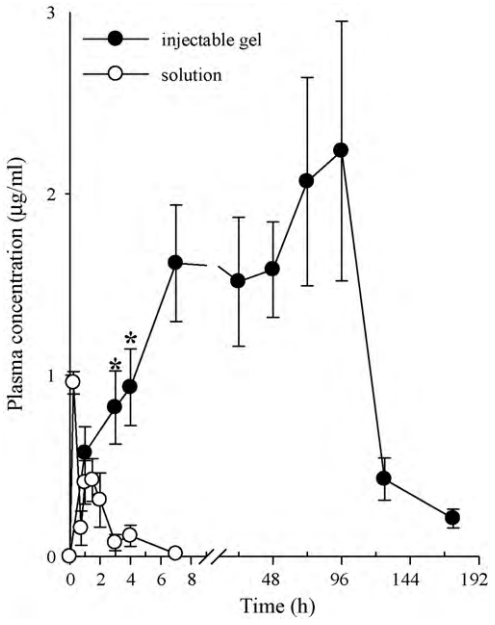

Fig. 6. Blood concentration–time profiles of piroxicam after intramuscular administration of piroxicam solution and injectable hydrogel to rabbits. The injectable hydrogel was composed of 2.5% piroxicam, 15% P 407, 17% P 188, 0.01% sodium hydroxide and 1.6% sodium chloride. Each value represents the mean ± S.D. ($n = 5$). *$p < 0.05$ compared with piroxicam powder.

concentration of piroxicam in the injectable gel was significantly higher than that in the piroxicam solution. The corresponding pharmacokinetic parameters are listed in Table 2. The injectable gel gave a significantly higher AUC and hence 150-fold better bioavailability compared to the piroxicam solution. Moreover, the MRT, $t_{1/2}$ and K_{el} value of piroxicam from the injectable gel were significantly ($p < 0.05$) different from those of the piroxicam solution. Our results suggest that a piroxicam-loaded injectable gel would be useful for delivering piroxicam in a pattern that allows sustained release for a long time, leading to better bioavailability. Our results also showed that it gels rapidly in the body, comes into contact with a very small amount of body fluid in the muscle and very slowly releases the drug by Fickian diffusion (Bhattarai et al., 2005; Lee and Tae, 2007; Ricci et al., 2005).

In summary, the injectable hydrogel composed of 2.5% piroxicam, 15% P 407, 17% P 188, 0.01% sodium hydroxide and 1.6% sodium chloride was easy to administer intramuscularly, gelled rapidly in the body and sustained the release of drug for a long time. In addition, this injectable gel can be easily administered without the need for surgical procedures. Since water can be used as a solvent, it can freely diffuse in the surrounding tissue, allowing network arrangement and implant hardening in the body. After finishing the release of drug, this injectable gel was very slowly degraded, since ploxamer was biocompatible and biodegradable (Veyries et al., 1999). Thus, this thermosensitive injectable gel contains no toxic additives so there is no need to remove it after treatment.

4. Conclusion

The thermosensitive injectable gel composed of 2.5% piroxicam, 15% P 407, 17% P 188, 0.01% sodium hydroxide and 1.6% sodium chloride was instantly applied to practical industrial product, since it was easy to administer intramuscularly and gelled quickly in the body. The drug was dissolved from hydrogels by Fickian diffusion through the extramicellar aqueous channels of the gel matrix. Moreover, it maintained the plasma concentrations of drug for 4 days and gave a 150-fold higher AUC compared to piroxicam solution. Thus, it would be practically useful for delivering piroxicam in a pattern that allows sustained release for a long time, leading to better bioavailability.

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