Rheological characterization of Poloxamer 407 nimesulide gels

Freitas, M.N.1; Farah, M.2; Bretas, R.E.S.2; Ricci-Júnior. E.1; Marchetti, J.M.1

1Departamento de Ciências Farmacêuticas, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, USP, Ribeirão Preto, SP, Brasil.  
2Departamento de Engenharia de Materiais, Universidade Federal de São Carlos, São Carlos, SP, Brasil.

Received 22/05/06 / Accepted 30/11/06

ABSTRACT

The thermal gelling property of Poloxamer 407-nimesulide gels was characterized by rheological studies. Nimesulide, a local anti-inflammatory and anesthetic drug used for the treatment of acute and chronic pain, has a short duration of action and a long-acting single-dose injection would be of clinical importance. Thus a poloxamer 407 gel applied intramuscularly could prolong the release and action of nimesulide. In this study, aqueous gels with nimesulide, containing three different concentrations of Poloxamer 407, were prepared. Viscosity measurements were performed by rheological studies to obtain the optimal sol-gel transition temperature. Poloxamer 407 gels are pseudoplastic and viscoelastic materials, which have an elastic modulus (G’), characteristic of the solid, and a viscous modulus (G’’), characteristic of the liquid material. Moreover, being pseudoplastic gels, when they are deformed by shearing, their viscosity decreases. Increase of the polymer concentration increased the viscosity of the gels, which could affect the releasing process of nimesulide. Furthermore, the presence of nimesulide led to a lowering of the sol-gel transition temperature. 

Keywords: Poloxamer 407 gels; nimesulide; rheological characterization; viscosity; sol-gel transition temperature.

INTRODUCTION

The study of the rheological behavior of liquid and semi-solid pharmaceutical formulations is important in view of their complex nature and their possible influence on manufacturing processes. Poloxamer 407 is a triblock (PEO-PPO-PEO) copolymer with a central hydrophobic chain of polyoxypropylene (PPO) and two identical lateral hydrophilic chains of polyoxyethylene (PEO). It has a molecular weight of 12.5 KDa and a PEO/PPO ratio of 2:1 (Schmolka, 1972; Pandit & Wang, 1998; Bohorques et al., 1999). A 20 % (w/w) Poloxamer 407 solution has unusual rheological characteristics including thermoreversible gelling, gel-sol transition temperature and viscosity, which have to be studied, understood and controlled before they can be used. The presence of additives like inorganic salts (Jorgensen et al., 1997; Edsman et al., 1998), drugs (Veyries et al., 1999), penetration enhancers (Bentley et al., 1999) and polyethylene glycol (Edsman et al., 1998) can change some rheological characteristics of these gels. The polymer solution is a highly viscous gel at room temperature, but becomes a liquid at refrigerator temperature (5 °C). The gel undergoes thermoreversible gelling and can be cooled and warmed many times without changing its properties (Schmolka, 1972). Poloxamer 407 is biocompatible and due to its stability is used in pharmaceutical preparations; its low toxicity and weak immunogenic properties make it a suitable vehicle for drug delivery. A Poloxamer 407 aqueous solution is injectable when cold (5-10°C); at physiological temperatures it forms a gel in situ (Johnston & Miller, 1985; Veyries et al., 1999; Paavola et al., 2000). Poloxamer 407 gels have been tested as sustained drug release systems for transdermal (Miyazaki et al., 1995; Bentley et al., 1999; Shin et al., 2000), and injectable (Barichello et al., 1999; Veyries et al., 1999, 1998a, 1998b, 2000) application.

Nimesulide, a widely-used nonsteroidal anti-inflammatory drug (NSAID) with local anti-inflammatory and anesthetic effects, is five to sixteen times more selective than other drugs of the same class, for the inhibition of cyclooxygenase-2 (COX-2), and is also employed, by topical administration, for regional management of acute and chronic major pain (Tognella, 1993). Its usefulness is limited by a short duration of action and the fact that inhibitory COX-2 selectivity is lost when nimesulide is administered orally. Repeated injections have been used to achieve long and constant pain relief. However, complications may arise from long-term administration and these techniques have been contraindicated in certain patients. A long-acting single-dose injection formulation would be clinically important as a means of extending the action of nimesulide; Poloxamer 407 gels could prolong the release and action of nimesulide.

In the present study, a rheological characterization of Poloxamer 407 gel was performed in order to understand its thermal gelling. Three polymer concentrations were...
studied with the aim of obtaining gels with a range of rheological characteristics, including gel viscosity and sol-gel transition temperature, which could influence the nimesulide-releasing process.

MATERIALS AND METHODS

Poloxamer 407 (Pluronic F-127®) was purchased from Basf. Nimesulide was purchased from Galena, a chemical products distributor (Campinas, São Paulo, Brazil), and NaOH was purchased from Synth (São Paulo, Brazil). Magnetic stirrer by Corning, Vortexer AP 56 by Phoenix, Micropipettes by Finnpette 4027, 100µL - 1000 µL and Rheometer (model ARES) from Rheometric Scientific, inside diameter 25mm, outside diameter 27 mm and height 32 mm.

Gel preparation

Gels were prepared on a weight basis using the cold method (Schmolka, 1972). Concentrations of Poloxamer 407 and of nimesulide are expressed as percent by weight (% w/w). An appropriate amount of Poloxamer 407 to yield 22%, 25% and 28 % gels was slowly added to cold distilled water (5°C) under constant stirring. The dispersion was kept in the refrigerator (6-12 h) until a clear solution was formed. An appropriate amount of nimesulide to yield a 2% mixture and a molar equivalent amount of NaOH was then dissolved in the cold solution, to form a soluble salt of nimesulide.

Study of rheological properties

The rheological properties of the gels were studied in an ARES strain-control rheometer and the measuring system consisted of concentric cylinders of Couette geometry, with an inner diameter of 25 mm, an outer diameter of 27 mm and a height of 32 mm. An oven surrounded the cylinders so that the whole unit could be heated or cooled. A thermocouple connected to the inner cylinder determined the temperature. Ten mL of cold polymer solutions were transferred to the cylinders. To measure linear viscoelastic properties, the instrument was kept in the oscillatory mode, in which the outer cylinder performs dynamic oscillations at a given frequency, w. To measure steady-state shear properties, the same geometry was used; in this case, the outer cylinder rotated at a given angular velocity, producing a shear rate gradient through the gap between the two cylinders.

Linear viscoelastic properties measured were the complex modulus \( G'(w) \) and \( G''(w) \), and the complex viscosity, \( \eta^*(w) \). \( G'(w) = G' + i G'' \), where \( G' \) is the elastic modulus and \( G'' \) is the viscous modulus. \( G' \) is related to the storage of energy during the cycle, or elastic energy, while \( G'' \) is related to the dissipation loss of energy during the cycle, or viscous energy. \( \eta^*(w) = \eta^s - i \eta^i \), where \( \eta^s \) is the dynamic viscosity and \( \eta^i \) is the imaginary viscosity (Ricci et al., 2002).

G' and G" were determined between 0.1 and 100 rad.s\(^{-1}\). The advantage of using linear viscoelastic properties to physically characterize materials is that the deformation being very small, the internal structure of the material is preserved during the measurements.

The sol-gel transition temperature of Poloxamer 407 gels was determined by making oscillation measurements at 1 rad.s\(^{-1}\) while the temperature was increased at 2°C.min\(^{-1}\). The sol-gel transition temperature was determined by plotting temperature as a function of the elastic modulus \( G' \). It was defined as the point where the elastic modulus was halfway between \( G' \) for the solution and \( G' \) for the gel (Edsman et al., 1998). The sol-gel transition temperature was measured for all gels.

RESULTS

Effect of additives on the sol-gel transition temperature

Effect of nimesulide salt addition

The sol-gel transition temperature may be changed by the addition of the drug. Plots of \( G' \) over a range of temperatures across the sol-gel transition, for a 25% w/w solution of Poloxamer 407 in the presence and in the absence of 2% w/w nimesulide, are shown in Figure 1. The elastic modulus, \( G' \), is low for the liquids and rises with the temperature as a result of gel formation. At the end of the sol-gel transition, the elastic modulus becomes independent of temperature.

Figure 1. Sol-gel transition of 25% Poloxamer 407 gels in the absence(A) and presence (B) of 2% nimesulide, the elastic modulus, \( G' \), is plotted against temperature, at a frequency of 1 rad s\(^{-1}\).
Figure 2. Effect of polymer concentration on the sol-gel transition temperature for Poloxamer 407 gels containing 2% nimesulide in solution: elastic modulus, (G') is plotted as a function of temperature, at a frequency of 1 rad s\(^{-1}\). Concentrations of the gels: 22%, 25% and 28%, as indicated.

The presence of nimesulide in the gel resulted in a small increase in the transition temperature (Table 1) and did not affect the gelling process; under these experimental conditions, both gels have similar viscosity.

Table 1 - Sol-gel transition temperature for the 25% Poloxamer 407 gels

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sol-gel transition temperature, (ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25% gel without nimesulide</td>
<td>13.14</td>
</tr>
<tr>
<td>25% gel containing 2% nimesulide</td>
<td>15.81</td>
</tr>
</tbody>
</table>

The transition temperature decreased with increasing polymer concentration (Table 2) and the curve was displaced to the left (Figure 2). All gels had a sol-gel transition below 20ºC. The relationship between transition temperature and concentration is presented in Table 2.

Effect of polymer concentration

The sol-gel transition temperatures for the 22%, 25% and 28% Poloxamer 407 solutions containing 2% nimesulide are shown in Figure 2. It can be observed that G' is low at low temperatures but increases dramatically with increasing temperature, as a result of the gel-forming process. At the end of the sol-gel transition, G' becomes independent of the temperature.

Figure 3. Viscous modulus (G'') as a function of temperature at a frequency of 1 rad s\(^{-1}\). Concentration of the gels: 22%, 25% and 28%, as indicated.
warming, equilibrium is established between monomers and temperatures, it exists as monomers in solution. Upon with increasing temperature, it aggregates in micelles to exhibit thermoreversible gelling and in aqueous solution, that it formed a stable and homogeneous gel. Poloxamer 407 exhibits good compatibility with Poloxamer 407, with the advantage of NaOH. As a result, nimesulide sodium salt showed that was hard to resuspend. This problem solved by turning directly in the gels, but an unstable suspension was obtained at this temperature.

Measurements of the viscous modulus (G') for the 22%, 25% and 28% gels containing 2% nimesulide, shown in Figure 3, were made at a frequency of 1rad.s⁻¹, at 37 °C. It can be observed that Poloxamer 407 gels are viscoelastic fluids, having a large G'.

**DISCUSSION**

The rheological properties of Poloxamer 407 gels were characterized in this study to get a better understanding of the process of thermal gelling in situ. Poloxamer 407 gels could prolong the presence of a drug at the injection site, thus extending its therapeutic effect, and the rheological characteristics of the gels should be known because they can affect the rates of dissolution and release of the drug from the gel.

Numerous attempts have been made to sustain local drug levels and thereby prolong their therapeutic effect and many authors have recognized the potential of Poloxamer 407 gels for sustained topical drug delivery in various therapeutic situations. Gels have been tested as a drug delivery system for the external application of antinecancer drugs (Miyazaki et al., 1995), anti-inflammatory drugs (Chin & Jun, 1991; Mengi & Deshpande, 1992; Miyazaki et al., 1995), antibiotics (Esposito et al., 1996) and in the treatment of burns (Henry & Schmolka, 1989). They have also been investigated as injectable formulations (the type of administration proposed here) for peptides (Pec et al., 1999), interleukin-2 (Johnston et al., 1992), and antibiotics (Veyries et al., 1999).

It is known that sol-gel transition temperatures can be changed by additives (Miller & Drabik, 1984; Valdnere et al., 1984; Gilbert et al., 1987; Edsman et al., 1998) and that inorganic salts (NaCl, NaH₂PO₄ and Na₂CO₃) decrease this temperature.

In preliminary tests, we tried to suspend nimesulide directly in the gels, but an unstable suspension was obtained that was hard to resuspend. This problem solved by turning nimesulide into its soluble salt by adding the molar equivalent amount of NaOH. As a result, nimesulide sodium salt showed good compatibility with Poloxamer 407, with the advantage that it formed a stable and homogeneous gel. Poloxamer 407 exhibits thermoreversible gelling and in aqueous solution, with increasing temperature, it aggregates in micelles to minimize the free energy of the solution, whereas at low temperatures, it exists as monomers in solution. Upon warming, equilibrium is established between monomers and micelles and eventually aggregates are formed at higher temperatures. It is generally accepted that these micelles are spherical and consist of a PPO core with a PEO water-swollen shell. This conformation is attributed to the fact that PPO is poorly water-soluble (hydrophobic) and PEO is highly soluble in aqueous solvents (Cabana et al., 1997; Moore et al., 2000).

The sol-gel transition temperature of Poloxamer 407 gels is defined here as the point where the elastic modulus, G', is halfway between the values for the solution and the gel. Rheological characteristics are changed by raising the temperature and the process can be divided into three phases. During the first phase, prior to the gelling point, the elastic properties have low values and the samples are characterized as a viscous liquid. The second phase corresponds to gelling. From this point onward, G' values increase, and the samples became gels with elastic behavior. The last phase consists of the stabilization of the G' values, above the transition temperature.

Increasing the polymer concentration in the solution also modified the rheological properties. In particular it decreased the sol-gel transition temperature (Table 2). At high concentrations, the preparations would already be gels at room temperature and this lowering of the transition temperature would render gel manipulation difficult, because the increase in the polymer concentration increases the viscosity of the gel.

Poloxamer 407 gels are viscoelastic materials. They have an elastic modulus (G'), characteristic of solid materials, and a viscous modulus (G''), characteristic of liquid materials.

Gel properties at the sol-gel transition temperature were changed by addition of the drug being studied. The nimesulide salt is more hydrophilic than lipophylic and thus is primarily located on the outside of the Poloxamer 407 micelles in the gels. It can interfere with the gelling process and with the physical-chemical characteristics of the polymer solution. For instance, the sol-gel transition temperature of the 25% Poloxamer 407 solution containing 2% nimesulide (15.81°C) was higher than that of the solution prepared in the absence of the drug (13.14°C), but such an increase cannot affect the gelling performance of the formulation, because the body temperature is near 37°C, well above the sol-gel transition temperature.

Beyond the results described above, Poloxamer 407 gels offer the advantage of thixotropic behavior, so that when they are deformed by shear, as in like a piston press, their viscosity falls, resulting in more fluid solutions. This would facilitate the flow of formulations and consequently their injectable administration at low temperatures (below the sol-gel temperature transition).

**ACKNOWLEDGEMENTS**

This research was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Brazil.
**RESUMO**

*Poloxamer 407 nimesulide gels*

As propriedades de geleificação termo-reversível de géis de Poloxamer 407 com nimesulida foram caracterizadas por reologia. A nimesulida é um fármaco anestésico e antiinflamatório local utilizado no tratamento de dor crónica e aguda e por apresentar um período de ação curto seria de grande importância clínica produzir-se uma forma farmacêutica com uma simples e única aplicação e de ação prolongada. Assim o desenvolvimento de um gel de poloxamer 407 de aplicação intramuscular, podria prolongar a liberação e consequentemente a ação farmacológica da nimesulida. No presente estudo foram preparados géis aquosos pelo método a frio, com três diferentes concentrações de poloxamer contendo nimesulida e medidas de viscosidade e determinação da temperatura ótima de transição sol-gel foram obtidas e empregadas para estudos reológicos. Os géis de poloxamer 407 são pseudoplásticos e viscoelásticos que possuem um modo elástico ($G'$), característica de material sólido e um módulo viscoso ($G''$), característica de materiais líquidos. Como géis pseudoplásticos, a deformação através do cisalhamento causou a diminuição da viscosidade. Além disso, o aumento da concentração de poloxamer causou o aumento da viscosidade dos géis o que poderá alterar a velocidade de liberação da nimesulida. Além disso, a incorporação da nimesulida ao gel, provocou o decaimento da temperatura de transição sol-gel.

*Palavras-chave*: géis de Poloxamer 407; nimesulida; caracterização reológica; viscosidade; temperatura de transição sol-gel.

**BIBLIOGRAPHICAL REFERENCES**


Pandit NK, Wang D. Salts effects on the diffusion and release...


