COMPARISON OF SODIUM ALGINATE VERSUS HYDROXYPROPYL METHYLCELLULOSE AS ADHESIVE POLYMERS ON POLOXAMER BASED MELOXICAM GEL

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ABSTRACT
Objective: The main objective of this study is to investigate the texture and release properties of two different mucoadhesive polymers; sodium alginate and hydroxypropylmethylcellulose, on a poloxamer based meloxicam gel.

Materials and Methods: Poloxamer 407 (26% w/w) was dissolved in cold water with sodium alginate (0.5% w/w) or hydroxypropylmethylcellulose (0.5% w/w) and meloxicam was added (0.1% w/w). Gelling temperature, texture properties, in vitro gel erosion and in vitro drug release were studied on the formulations.

Results and Discussion: Even though both two formulations showed similar texture characteristics, the gel prepared with poloxamer-hydroxypropylmethylcellulose had better adhesive property than poloxamer-sodium alginate gel. Also, the in vitro release of meloxicam from poloxamer-hydroxypropylmethylcellulose gel was slightly slower than poloxamer-sodium alginate, while in vitro erosion of gels were not significantly different from each other.

As a conclusion; due to slower release, appropriate texture properties with a better adhesive characteristic, poloxamer-hydroxypropylmethylcellulose polymer combination was found to be promising for preparing gel formulations with meloxicam.

Key Words: HPMC; Meloxicam; Poloxamer 407; Sodium alginate; Texture analysis

INTRODUCTION
Meloxicam (MLX) is a non-steroidal anti-inflammatory drug, which is efficient for the treatment of joint diseases such as rheumatoid arthritis and osteoarthritis.

Although MLX is a COX-2 inhibitor, its oral administration still produces some gastrointestinal side effects, such as irritation or pain of the stomach, ulceration, gastric perforation and bleeding. Thus, it is not suitable for the treatment of rheumatological patients with gastric ulcers. Having appropriate physicochemical properties for potential transdermal delivery; such as low
oral dose (7.5–15 mg/day), low molecular weight (354.1) and good local tissue tolerability, topical or transdermal formulations of MLX should be a good alternative for oral administration \[^1,2\]. However, poor aqueous solubility of this drug give rise to difficulties in designing of topical or transdermal pharmaceutical formulations \[^3\].

Poloxamers (PEO–PPO block copolymers), especially Poloxamer 407 (P407) which has excellent thermo-sensitive gelling properties at concentrations above 20 % w/w, has been widely used in pharmaceutical field because of its relatively low toxicity and ability to form clear gels in aqueous media. P407 is a good alternative for topical use, because of its ease of preparation, reverse thermal gelation behavior and good drug release characteristics \[^4,5\]. Also, P407 can enhance the solubilization of poorly water-soluble drugs \[^6\]. However, poor bioadhesiveness can limit the use of this polymer as a topical or transdermal preparation \[^7\]. This property can be modified by using various polymers such as chitosan, carboxopol, polyvinylmethylmethacrylate, hydroxypropyl methylcellulose (HPMC) and sodium alginate (Na-Alg) \[^1,7,8,9\].

Na-Alg, copolymer of 1, 4-linked β-d-mannuronic acid and α-l-guluronic acid, is an anionic polysaccharide, which naturally occurs in seaweed. It has the ability to form gels between 0.5-1% w/w, is stable at pH 5-10 and can control the release of drugs from the prepared formulations \[^1\]. HPMC is also a naturally derived polymer, which has hydrophilic characteristic and swelling properties. HPMC shows thermogelation property which is caused by the hydrophobic interaction between the hydrophobic substitutions \[^10\].

In this study, two different adhesive polymers, Na-Alg and HPMC were added in the same concentration to a P407 based meloxicam gel for modifying the gel texture and in vitro drug release characteristics. The performance of gel bases were evaluated by means of gelation temperature, texture properties (gel strength, compressibility, adhesiveness, cohesiveness and elasticity), in vitro gel erosion and in vitro drug release studies.

**MATERIALS AND METHODS**

Poloxamer 407 (P407; Pluronic F-127®, Sigma, USA), Hydroxypropylmethyl cellulose (HPMC; Methocel K100 PRM LV, Dow Chemical Company, Germany; 100 cP), Sodium Alginate (Na-Alg; Sigma; 250 cP), Meloxicam (MLX; Fargem, Turkey).

**Preparation of transdermal gels**

Transdermal gel formulations were prepared on a weight percentage basis using the "cold method" first described by Schmolka \[^11\]. Briefly, a weighed amount of copolymer was slowly added to cold water and then stored in a refrigerator (4-5 °C) for 48 hours. This polymeric mixture was mixed with a gentle mixing (100 rpm) in cold environment for 10-15 min at every 12 h periods, to ensure complete dissolution. Eventually, a clear and viscous gel or solution formed \[^4\]. Na-Alg or HPMC polymers were gelled at cold water
before the addition of P407. After formation of a clear solution, meloxicam was added by weight percentage to the polymeric mixture. The contents of the prepared gels are given in Table 1.

Table 1: Contents of gels (% w/w)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>P407</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>HPMC</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>Na-Alg</td>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>MLX</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Water</td>
<td>Q.s. to 100</td>
<td>Q.s. to 100</td>
</tr>
</tbody>
</table>

Gelation temperature

Gelation temperatures were measured on a thermostatic magnetic stirrer by using a digital thermometer (n=3). The formulations were gently stirred at 100 rpm until the in situ gel occurs by micellization.

Texture profile analyses (TPA)

TPA were carried out with TA.XT Plus Texture Analyzer (Stable Micro Systems, UK) in TPA mode, as explained in our previous studies [12,13]. Briefly, formulations were analysed in the bottles of identical dimensions with a fixed height. Perspex (P/0.5) probe was used in the studies. This probe was compressed twice into each sample to a depth of 10 mm at a rate of 2 mm/sec (for all test speeds) allowing a delay period of 10 sec between the two compressions (n=3). Gel strength, compressibility, adhesiveness, cohesiveness and elasticity characteristics of the prepared gels were defined from the resultant force-time plot of TPA graph.

In vitro gel erosion studies

In vitro gel erosions of the formulations were studied during in vitro drug release studies with a membraneless method [12,14]. Briefly, 1 gram polymeric solution was weighed into a 1.5 cm diameter glass vial. Both the solution and vials were cooled at +4°C before weighing and gelled at 37°C in an oven in order to ensure a gel with a smooth surface without any bubbles. Then 1 ml of PBS buffer (pH 7.4, 37°C) was layered on the gel in an incubator (MaxQ 4450, ThermoScientific) adjusted to 37°C. Samples were incubated (50 rpm, 37°C) for 6 h. At every hour, vials were weighed after the removal of the entire release medium (the vials were completely dried and kept at 37°C before the weighing) and the differences in weights of vials give the amount of gel formulation dissolved during that time period.

The erosion profiles of formulations were then obtained from the cumulative weight of each gel formulation dissolved versus time.

In vitro drug release studies

In vitro drug release studies were performed with the same method during gel erosion analysis [12,14]. At every hour, the entire release medium was taken out and renewed with fresh buffer (n=3). The samples were measured spectrophotometrically at 365 nm (Shimadzu 1604, Japan).
Data analysis of in vitro drug release

The data of in vitro drug release studies were subjected to theoretical analysis to determine the order of kinetic release according to zero order, first order, Higuchi models and Korsmayer-Peppas release kinetics.

RESULTS AND DISCUSSION

In this study, a P407 based meloxicam gel was modified for its mechanical and release properties with two different adhesive polymers; HPMC and Na-Alg (Table 1). Both of the modifying polymers were used in the same concentration (0.5 % w/w) and also their viscosity characteristics were nearly the same (100cP and 250 cP viscosity grade, respectively for HPMC and Na-Alg).

Effect of MLX on gelation temperature and texture properties of P407 (26 % w/w) was investigated in our previous study and no significant difference was found between the gels prepared with or without MLX (19.0 ±1.7 °C and 18.8±0.4 °C, respectively) [12]. Contrarily, addition of the adhesive polymers used in this study slightly decreased the gelling temperature of P407 gel (16.97±0.25°C and 14.33±0.15°C for P407:HPMC and P407:Na-Alg, respectively).

The mechanical parameters (gel strength, compressibility, adhesiveness, cohesiveness and elasticity) were derived from force-time curve of TPA graphs studied by TA.XT Plus Texture Analyser (Table 2). TPA permits to evaluate textural properties of formulations in order to gather information about the physical gel structure. Here, hardness (gel strength) is defined as the maximum peak force during the first compression cycle of TPA while compressibility defines the work required to deform the product during the first compression of probe. Adhesiveness is defined as the negative force area for the first compression cycle and represents the work required to overcome the attractive forces between the surface of the gel and the surface of the probe in physiological conditions [8]. Higher values of adhesiveness is advantageous as it means an increased adhesion on the application surface. Besides, lower values of cohesiveness, indicating spreading of the formulation, is preferred [15].

Table 2: Texture properties of gels

<table>
<thead>
<tr>
<th></th>
<th>P407:Na-Alg</th>
<th>P407:HPMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardness (N)</td>
<td>0.7965 ±</td>
<td>0.8381 ±</td>
</tr>
<tr>
<td>Adhesiveness (N.sec)</td>
<td>0.6104 ±</td>
<td>2.4377 ±</td>
</tr>
<tr>
<td>Compressibility (N.sec)</td>
<td>0.2621</td>
<td>0.1216</td>
</tr>
<tr>
<td>Cohesiveness (N.sec)</td>
<td>2.7790 ±</td>
<td>2.7340 ±</td>
</tr>
<tr>
<td>Elasticity</td>
<td>0.9206 ±</td>
<td>0.9517± 0.0192</td>
</tr>
<tr>
<td></td>
<td>0.9913 ±</td>
<td>0.9923 ±</td>
</tr>
<tr>
<td></td>
<td>0.0012</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

As seen from the Table 2, gel hardness of P407:Na-Alg gel was slightly lower than P407:HPMC gel. However, both two gels have low values of cohesiveness and in general, their hardness were appropriate for application. On the contrary to other texture
properties, adhesiveness of P407:HPMC gel was significantly higher than P407:Na-Alg gel.

Despite the in vitro gel erosion data, in vitro drug release from gels were significantly different from each other (Figure 2). In vitro MLX release from P407:HPMC was slower than P407:Na-Alg gel (55.1 % and 78.23 %, respectively for P407:Na-Alg and P407:HPMC).

When the in vitro gel erosion data evaluated; significant difference was not observed in erosion profiles until 300 minutes (Figure 1). However, while the gel formulation prepared with Na-Alg was undergoing a fast after 300 minutes, the gel prepared with HPMC was still slowly eroding (90.2±7.0% and 73.08± 8.1%, respectively for P407:Na-Alg and P407:HPMC after 6 hours). This could be attributed to the lower gel hardness of P407:Na-Alg.

In our previous study, we evaluated that 68.5 % w/w porsion of P407 (26 %w/w) gel undergone to erosion in release medium after 6 hours, without any modifying polymers \cite{12}. The use of an adhesive HPMC or Na-Alg polymer in a low concentration (0.5 % w/w) caused to a slight increase in gel erosion because of swelling properties of these polymers.

Association of bioadhesive polymer to poloxamer generally slows down the in vitro release because of their release retarding effects due to overall microgel viscosity or gel strength. This release retarding effect can also be possible of adhesive polymer’s squeezing effect on the aqueous channels of poloxamer micelles, through which the drug diffuses \cite{9}. Besides, both HPMC and Na-Alg polymers show swelling effect, but the thermogelling characteristic of HPMC causes to form an elastic gel with increasing temperature \cite{7}. Thus, despite the slight inceasing in erosion, with the existence of HPMC polymer P407:HPMC gel showed slower MLX release than P407:Na-Alg gel (Figure 2). This was
probably due to the high ratio of hydroxypropoxyl groups of HPMC which causes slower release of drug by forming a barrier layer on the surface of gel formulation \[16\] and also due to the higher gel hardness of this gel.

Data analysis for in vitro release kinetics showed that (Table 3), formulations generally fitted to both Zero-order and Korsmeyer-Peppas kinetics, according to their high \( r^2 \) values. High \( r^2 \) values were obtained for Higuchi model as well. Moore et al. (2000) indicated that, drug release and gel dissolution from poloxamer gels generally fitted to Zero-order, at least for the first 90% of release process \[17\]. Yuan et al (2012), also indicated that, the in situ gels which had non-Fickian release shows a erosion-diffusion controlled release\[9\]. According to Korsmeyer-Peppas kinetics, diffusional exponent values of formulations obtained in our study showed a non-Fickian (0.45 < \( n = 0.89 \)) diffusion mechanism of drug release, which indicated a erosion-diffusion profile, for both of the formulations \[18\].

**CONCLUSION**

This study indicated that a release of MLX at least for 6 hours, could be achieved with both P407:Na-Alg and P407:HPMC based gel formulations. However, because of better texture properties (especially adhesive properties and gel hardness) with swelling characteristic which causes slower release of drug by forming a barrier layer on the surface of gel, P407:HPMC combination was found to be more promising for further studies.

**Table 3: Release kinetics of meloxicam from gels**

<table>
<thead>
<tr>
<th></th>
<th>First order</th>
<th>Zero order</th>
<th>Higuchi</th>
<th>Korsmeyer- Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( r^2 )</td>
<td>( k )</td>
<td>( r^2 )</td>
<td>( k )</td>
</tr>
<tr>
<td>P407:HPMC</td>
<td>0.9856</td>
<td>0.002</td>
<td>0.9977</td>
<td>0.151</td>
</tr>
<tr>
<td>P407:Na-Alg</td>
<td>0.9863</td>
<td>0.004</td>
<td>0.9847</td>
<td>0.210</td>
</tr>
</tbody>
</table>

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