**In Situ Gelling Formulation of Naproxen for Oral Sustained Delivery System**

Hala S. Yousif*1 and Yehia I. Khalil *

* Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq

**Abstract**

Naproxen is a non-steroidal anti-inflammatory drug, which has antipyretic and anti-inflammatory effect. It is extensively bound to plasma albumin, and exhibits gastric toxicity, so it may be more efficient to deliver the drug in its sustained release dosage form and adequate blood level is achieved. Three liquid formulations with in situ gelling properties have been assessed for their potential for the oral sustained delivery of naproxen. The formulations were dilute solutions of: (a) pectin; (b) gellan gum; and; (c) sodium alginate, all containing complexed calcium ion that form gels when these ions are released in the acidic environment of the stomach. The viscosity of the sols and drug release were measured, and was found to be dependent on the type and concentration of the gelling agent. Pectin sol shows the highest viscosity and drug release. The influence of variation of gastric pH and the effect of added 1.6 mM Ca**++** ions on the gelation property and the release profile of the liquid formulations were examined. The efficiency of gelation was significantly reduced with increase of pH. In addition the influence of different concentrations of sorbitol were determined. The results showed that 10% w/v sorbitol is the best concentration that maintained fluidity and ease of administration for the selected formula. The selected formula was examined for its stability and expiration date, and it was found that there was no evidence of physical changes under experimental conditions, with estimated expiration of about 4.1 years and pH of the formula stated at 5.1.

**Key word:** naproxen, in situ gelling, oral preparations, gel.

**Introduction**

Solutions that undergo sol-gel transformation when they meet physiological conditions may serve as an in situ gelling drug delivery system (1). In situ is a Latin phrase meaning in the place. The new concept of an in situ gelling formulation in the precorneal region will lead to an increased bioavailability, due to slower drainage (3). Gels are transparent or translucent, non-greasy, semisolid preparations. These are also termed jellies consisting of either suspensions made up of small inorganic particles, or large organic molecules interpenetrated by a liquid (4). Hydrogel is three-dimensional hydrophilic polymeric networks capable of imbibing large quantities of water have generated a lot of interest recently as delivery system for pharmaceutically active agents (5). One of the main characteristics of hydrogels is that they contain ingredients that are dispersible as colloids or are water-soluble (6). The swelling of environmentally sensitive hydrogel can be affected by many stimulus, these are: temperature, pH, ionic concentration, electrical field, inflammation, solvent concentration, light and radiation, magnetic field and glucose concentration (6). According to the mechanism by which sol - gel phase transition occur, the following three types of systems can be recognized (7):...
1- pH triggered systems.
2- Temperature sensitive system.
3- Ion activated system.

From the point of view of patient acceptability, a liquid dosage form that can sustain drug release and remains in contact for extended period of time, improving the bioavailability, reducing the dose concentration and frequency may be achieved by in situ gelling formulations (8). Gelation of the orally administered liquid formulations (Ion activated system) was ensured by the inclusion of calcium ions in the formulation as a soluble complex designed to break down to release free calcium ions on encountering the acidic environment of the stomach (9). The gelation was delayed until the orally administered solution reached the stomach by complexing the calcium with sodium citrate (8). Naproxen is a non-steroidal anti-inflammatory drug (NSAID) advocated for use in painful and inflammatory rheumatic arthritis, osteoarthritis, migraine, postoperative pain and postpartum pain (10). The goal of this study is to prepare liquid formulation of naproxen with in situ gelling properties and assessed for its potential sustained oral delivery system.

**Experimental Materials and Equipments**


**Method of Preparation**

**Preparation of the Sols:**

Sodium alginate and pectin solution of concentrations 1.0, 1.5 and 2.0 % (w/v) were prepared by adding the polymer to distilled water containing 0.25% (w/v) sodium citrate and 0.075% (w/v) calcium chloride and heating to 60°C for sodium alginate and 40–50°C for pectin while stirring. Naproxen equivalent to 2.5% (w/v) was then dispersed in the resulting solution after cooling to below 40°C (12). Gellan gum solutions of concentrations 0.25, 0.5 and 1.0% (w/v) were prepared by adding the gum to distilled water containing 0.17% w/v sodium citrate and heating to 90°C while stirring. After cooling to below 40°C appropriate amounts of calcium chloride 0.016% (w/v) and 2.5% (w/v) naproxen were then dispersed in the resulting solution (12).

**Gelation Property**

Instantaneous gelation was checked by addition of the sols dropwise to simulated gastric fluid pH 1.2 (14).

**The Effect of Different Concentrations of Calcium Chloride and Sodium Citrate on the Gelling Properties:**

The optimum quantities of calcium chloride and sodium citrate that maintained fluidity of the formulation before administration and resulted in gelation when the formulation was added to simulated gastric fluid, were determined by preliminary tests in which pectin sols 1%, (w/v) containing sodium citrate concentrations of 0.125, 0.25 and 0.50% (w/v) and calcium chloride concentrations of 0.05, 0.075 and 0.1% (w/v) were added dropwise to 50 ml simulated gastric fluid (pH 1.2).

**Measurement of the Rheological Properties of Sols:**

The viscosity of sols prepared in water was determined at room temperature (25°C) with Brookfield Digital Viscometer (14).

**Measurement of In Vitro Drug Release:**

The release rates of naproxen were measured using plastic dialysis cells similar to that described previously by Miyazaki et al (15, 16). The capacity of each half-cell was 4 ml and the surface area of the membranes was 2.67 cm². Solvs of pectin, gellan gum or alginate were placed in the donor compartment individually. An equal volume of simulated gastric (pH 1.2) or intestinal (pH 6.8) fluid was placed in the receptor compartment. The donor phase and the aqueous receptor phase were separated by a cellulose membrane. The assembled cell was shaken horizontally at rate of 60 strokes per min. in an incubator maintained at 37°C temperature. The total volume of the receptor solution was removed at intervals and replaced by fresh release medium. The drug concentration of the samples was determined using UV spectrophotometer

**Effect of pH and Added Ca²⁺ Ion on:**

**The gelation:**

The influence of pH on the gelation characteristics of 1% (w/v) pectin sols was determined by immersion of 30 ml sol enclosed in cellulose membrane tubing into simulated gastric fluid (150 ml) with pH values range 1.0–5.0. After equilibration for 24
hr at room temperature, the contents of the tube were passed through a sieve (No. 6.5, 2.80 mm) over a period of 30 seconds and the weight of the gel remaining in the sieve was determined by balance. The experiments were repeated in the presence of added 1.6 mM Ca\(^{++}\).  

**In vitro release:**

- **The effect of pH:**

  The in vitro release of naproxen from 1.0% (w/v) pectin was measured using an equal volume of simulated gastric (pH 1.2 and 3.0) for 1 hour and intestinal (pH 6.8) fluid for 5 hours placed in the receptor compartment\(^{(17)}\).

- **The effect of Ca\(^{++}\):**

  The release measurement was done at pH 3 using 1.0% (w/v) pectin sol alone and with added 1.6 mM Ca\(^{++}\).  

**Effect of Different Concentrations of Sorbitol:**

- **Rheological properties:**

  Different concentrations of sorbitol (0, 5, 10, 20, 30, and 40% w/v) were added to 2.0% (w/v) pectin sols loaded with 2.5% (w/v) naproxen, and the viscosities were measured\(^{(18)}\).

- **In vitro release:**

  The in vitro release was measured for 2.0% (w/v) pectin sols loaded with 2.5% (w/v) naproxen, in presence of different concentrations of sorbitol (0, 5, 10 and 20% w/v)\(^{(18)}\).

**Stability Study:**

Several glass containers (each containing 4 ml) of the selected formula were incubated at 35, 50 and 60°C for 90 days. Samples were taken at specified time intervals and assayed for their drug content. The physical appearance and the pH of the formula were also evaluated.

**Results and Discussion**

**Gelling Property**

In this study Ca\(^{++}\) ions were included in all formulations for induction of gelation. However, for ease of administration the prepared formula must be introduced in a fluid (sol) state. This was achieved by addition of sufficient sodium citrate to the formulation to form a complex with all of the Ca\(^{++}\) ions present in the formulation and hence to effectively remove them from solution. Then, in the acidic environment of the stomach the complex is broken down and the Ca\(^{++}\) ions released cause gelation to occur\(^{(19)}\). Instantaneous gelation was observed by addition of the sols of pectin, sodium alginate and gellan gum dropwise to simulated gastric fluid maintained at pH 1.2.

**The Effect of Different Concentrations of Calcium Chloride and Sodium Citrate on the Gelling Properties:**

The results indicated that the minimum concentration that maintained fluidity of the sol before administration and caused gelation of sols in the gastric fluids was 0.25% (w/v) sodium citrate and 0.075% (w/v) calcium chloride. Moreover, gelation occurred without exposure to simulated gastric fluid pH 1.2 in formulations containing 0.050, 0.075 or 0.1% (w/v) CaCl\(_2\) and sodium citrate concentration of 0.125% (w/v) as shown in table(1). The increase in calcium chloride content to 0.10% (w/v) with the same sodium citrate concentration caused gelation of the formulation before contact with simulated gastric fluid\(^{(13)}\).

<table>
<thead>
<tr>
<th>Sodium Citrate</th>
<th>0.125% (w/v)</th>
<th>0.25% (w/v)</th>
<th>0.5% (w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Chloride</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.05% (w/v)</td>
<td>Gel before administration</td>
<td>Sol before administration Friable and soft gel after administration</td>
<td>Sol before administration Friable and soft gel after administration</td>
</tr>
<tr>
<td>0.075% (w/v)</td>
<td>Gel before administration</td>
<td>Sol before administration Optimal gel strength after administration</td>
<td>Sol before administration Low gel strength after administration</td>
</tr>
<tr>
<td>0.1% (w/v)</td>
<td>Gel before administration</td>
<td>Gel before administration</td>
<td>Gel before administration</td>
</tr>
</tbody>
</table>

Table (1): The effect of different concentrations of sodium citrate and calcium chloride on the gelation of 1% (w/v) pectin sols before and after administration to simulated gastric fluid.
**Rheological Properties of the Sols:**
All the prepared sols revealed that the viscosity is increased as a function of increasing polymer concentration with shear thinning behavior. The rheograms profiles of different polymers used in this study, suggested that pectin sols used is more accepted one than other two polymers (gellan gum and sodium alginate), since pectin sols exhibited more or less fit profile with that obtained from commercial one Amrixen® suspension as a reference product. Moreover, the results indicated that best concentration required for incorporating pectin as a gelling agent is 1.5% (w/v) and to a lesser extent for 1.0% (w/v) concentration.

**Dissolution behavior (In Vitro Release):**
Large increment in the amount released of naproxen observed when the receptor solution was changed from simulated gastric fluid pH (1.2) to simulated intestinal fluid pH (6.8). This was expected since there will be change in the state of ionization of the acidic drug (pKa of naproxen is 4.2) accompanying the pH range. It is completely unionized at pH 1.2 and this lead to negligible drug release at this pH. Rigid gels are formed when the donor solutions of all systems are placed in contact with a receptor solution at pH 1.2 and, as a consequence, the amount of the drug released is lower than that at pH 6.8, which is referred to the high H+ ion concentration at pH 1.2 that is sufficient to cause the formation of rigid gels. There was a significant decrease in the release rate with increasing polymer concentration. This behavior may be attributed to the effect of mechanical barrier that set up by the random network of the polymer gel molecules which binds and entraps surrounding water. This aqueous phase in the polymer network acts as the region responsible for diffusion of the drug in the gel. The change of the polymer concentration of these gels could affect the diffusion pathway and thus the drug release. In addition, as the viscosity of the polymer sols increased with concentration, the solvent penetration into the core of the matrix will be decreased, and the drug release will be decreased. In an attempt to verify the effect of polymer types on the release of naproxen, the cumulative release profiles of 2.5% (w/v) naproxen from 1% (w/v) different gelling polymers were constructed as shown in figure (1).

![Figure 1: Cumulative in vitro release of naproxen (2.5% w/v) from 1% (w/v) concentrations of pectin, sodium alginate and gellan gum gels.](image)

The results obtained indicated that the release of naproxen from different types of polymers was in the following order: pectin > sodium alginate > gellan gum. This suggests that the choice of the polymer base is of obvious importance for achieving a desired drug release. The explanation for this related to the diffusivity of the drug through any base depends on the nature and composition of individual base and the drug-vehicle interaction. Also, the solubility of the drug in the vehicle affects the drug release and diffusion. The release data over the whole time period were analyzed according to the treatment proposed by Higuchi for drug release from semisolid vehicles. For the initial cumulative drug released 50-60%, the amount "Q" of drug released per unit surface area from gel is proportional to the square root of time:

\[ Q = 2C_0 (D t / \pi)^{1/2} \]

In which Q is the amount of drug released per unit area; \( C_0 \) the initial drug concentration in the vehicle; D is the diffusion coefficient of the drug in the matrix and t is the time. Plots of Q versus \( t^{1/2} \), for the release of naproxen from all gels were linear after a short lag period indicative of diffusion controlled release as shown in figure (2). There is usually a lag period until water permeates the polymer mass to create pores for diffusion of the drug. Later, the drug released.
In Vitro Release:
- The effect of pH:

The release of drug was appreciably faster when pectin was exposed to receptor solutions at pH 3.0 over the initial 1 h release period as shown in figure (4). Observation of the donor cells showed that the formulations were in sol form throughout the duration of the release period. Diffusion of H⁺ ions from the receptor solution at this pH was insufficient to cause the release of complexed calcium ions and consequently gelation of the pectin was incomplete \(^{17}\).

Effect of Different Concentrations of Sorbitol:

High concentration of pectin sol was used to study the effect of different concentrations of sorbitol, since it could withstand the effect of high concentrations of sorbitol.

Rheological properties:

Figure (6) shows the influence of sorbitol concentration on the flow properties of 2% (w/v) pectin sol. The viscosity of the pectin sols increased appreciably as the sorbitol concentration was increased from 5 to 40% (w/v). Addition of 5% and 10% (w/v) sorbitol to the sols caused a reduction of viscosity at all

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**Figure (2):** Cumulative % released of naproxen as a function of square root of time from 1% (w/v) concentrations of pectin, sodium alginate and gellan gum gels.

**Effect of pH and Added Ca²⁺ Ion on:**

- The gelation:

The results show that the hydrogen ion concentration at pH 1.0–2.5 was sufficiently high to cause gelation in the absence of an additional source of calcium. Visual observation showed well-defined compact gels over this pH range. Although complete gelation was observed at pH 2.5–3.5, the resultant gels were not sufficiently strong to maintain their cylindrical form. However, at higher pH (pH >3.5) and when H⁺ ions are insufficient, the effective breakdown of the calcium complex in the sols and gelation was poor. Figure (3) showed that the addition of 1.6 mM Ca²⁺ ions was sufficient to cause almost complete gelation of formulations over the entire pH range examined. The gels formed at pH > 2 had a loose, less structured appearance.

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**Figure (3):** The effect of pH and added 1.6 mM Ca²⁺ ions on the weight of gel formed from 30 ml solutions (1.0% (w/v) pectin as a function of pH. Each value is the mean ± S.E of 3 determinations.

**Figure (4):** The effect of starting pH in the receptor solution on the release of naproxen from 1.0% (w/v) pectin gels.

- The effect of added Ca²⁺:

The influence of added 1.6 mM Ca²⁺ in the formula on drug release from pectin formulations exposed to receptor solutions at pH 3.0 is shown in Figure (5). Observations of the donor cells showed the presence of a thin gel layer on the surface of the cellulose membranes when calcium was included in the formulation but no gelation of the bulk of the sol \(^{16}\).

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shear rates. These changes in viscosity resulting from sorbitol addition, since it is hygroscopic and may withdrawn water to the gel structure that decreases viscosity and hence improving the ease of swallowing of the sols. A considerable increase of viscosity was noted with sorbitol concentrations between 20% and 40% (w/v), all formulations exhibiting a change of flow properties from shear thinning to Newtonian behavior. Sorbitol at higher concentrations binds with water molecules causing desolvation around the pectin chains and minimizing the hydrogen bonding of water molecules to pectin chains. As a consequence, pectin chains cross-linked together and result in increased viscosity.

In vitro release:

The release profiles of naproxen from gels of 2% (w/v) pectin containing sorbitol concentrations over the range 0–20% (w/v) was shown in figure (7). For gels containing 20% (w/v) sorbitol there was a pronounced increase of release after about 3 hours. No such inflection was observed for gels formed in the presence of 0, 5 and 10% (w/v) sorbitol. Observation of the contents of the donor cell during release measurements showed that the inflection in the plots for release from the formulation containing 20% (w/v) sorbitol coincided with a gel to sol transition, i.e. low gel strength to withstand a large decrease of hydrogen ion concentration; gels formed in formulations containing lower sorbitol contents retained their integrity throughout the measurement period.

Stability Study of Selected Formula (Prediction of expiration):

The final formula of this study was introduced into an exaggerated temperatures study maintained at (35, 50 and 60 ºC) to predict expiration date.

```
R /Naproxen                           2.5 gm
Pectin                                1.5 gm
Sodium Citrate                       0.25 gm
CaCl2                                 0.075 gm
Sorbitol                              10 gm
Methyl paraben                       0.2 gm
Propyl paraben                       0.02 gm
Dis. Water  up to                    100 gm
```

The degradation of naproxen in this formula followed first order kinetics since...
straight lines were obtained by plotting the logarithm of the percent remaining of naproxen versus time as shown in figure (8). The first-order reaction equation:

\[
\log C = \log C_o - K_1 t / 2.303
\]

Where \( C_o \) is the initial concentration of naproxen, \( C \) is the remaining concentration at time \( t \) and \( K_1 \) is the first order rate constant. The slope of the line is \(-K_1/2.303\) from which the rate constants obtained. Table (2) shows the degradation rate constants of naproxen at different temperatures. To determine the expiration date (\( t_{10\%} \)), Arrhenius plot was constructed to predict the degradation rate constant of naproxen at 25°C as shown in figure (9). The expiration date of naproxen in the suggested formula was calculated according to the first order reaction equation:

\[
t_{10\%} = \frac{0.105}{K_{25^\circ C}}
\]

The expiration date was found to be equal to 4.1 years with pH of 5.1 for whole the period.

![Figure (8): Accelerated stability study of naproxen in the selected formula at elevated temperatures (35, 50 and 60°C).](image)

**Table (2): Degradation rate constants (K) of naproxen sol at different temperatures.**

<table>
<thead>
<tr>
<th>Temperature</th>
<th>35°C</th>
<th>50°C</th>
<th>60°C</th>
<th>25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K ) (day(^{-1})) \times 10^4</td>
<td>1.545</td>
<td>3.97</td>
<td>6.91</td>
<td>0.695</td>
</tr>
</tbody>
</table>

![Figure (9): Arrhenius plot for expiration date estimation of naproxen in the selected formula.](image)

**Conclusions**

Based on the results obtained, the optimum concentration of calcium chloride was 0.075% (w/v) and sodium citrate was 0.25% (w/v) for in situ gelling formulations of naproxen. The gellation, viscosities of the sols and the in vitro release of naproxen from the gels were affected by the type and concentration of the gelling agent, initial loading of naproxen, and concentration of sorbitol in the formula, gastric pH and added Ca\(^{++}\) ions. The most promised selected formula was pectin-gel type, with stable physical properties maintained at pH 5.1 and 4.1 years shelf life.

**References**

5. Mukherjee D. and Banthia A.K., Preparation of Adrenochrome Hydrogel


