Formulation and *in vitro* Evaluation of In-situ Gelling Liquid Suppositories for Naproxen

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Abstract

In-situ gelation is a process of gel formation at the site of application, in which a drug product formulation that exists as a liquid has been transformed into a gel upon contact with body fluids. As a drug delivery agent, the in-situ gel has an advantage of providing sustained release of the drug agent. In-situ gelling liquid suppositories using poloxamer 188 (26-30% W/W) as a suppository base with 10% W/W naproxen were prepared, the gelation temperature of these preparations were measured and they were all above the physiological temperature. Additives such as polyvinylpyrrolidin "PVP" ,hydroxylpropylmethylcellulose "HPMC", sodium alginate and sodium chloride were used in concentration ranging from (0.25-1%W/W) to modulate the gelation temperature and gel strength .The best preparation was obtained through using a combination of poloxamer 188, sodium alginate, naproxen and distilled water (29,0.5,10and 60.5 % W/W respectively)with gelation temperature of 33.6ºC±0.2 and gel strength of 28±2 seconds. The release of drug from this preparation was sustained for about 12 hours and it was faster than conventional solid suppository (Proxen® 500) and oral tablets (Naproxen®500) using dialysis tubing method.

Key words: - naproxen, in-situ gelation, liquid suppository**,** poloxamer188

الخلاصة

إن عملية التحول الذاتي للمستحضر الدوائي الى هلام في موضع الإستعمال تتضمن إعطاء المستحضر بشكل سائل والذي يتحول الى هلام عند تماسه مع سوائل الجسم ومن فوائد هذه العملية إنها تساعد على تحرر الدواء بشكل طويل الأمد .لذلك تم تحضير التحاميل السائلة الموضعية التحول الى هلام للنابروكسين باستعمال البولوكسامر١٨٨) ٢٦ ٣٠ %وزن /وزن(كمادة أساسية لتحضير التحاميل مع ١٠ %وزن /وزن من النابروكسين وعند قياس درجة حرارة التحول الى هلام لهذه المستحضرات وجد انها فوق درجة حرارة الجسم الفزيولوجية .ولتغيير درجة حرارة وقوة التحول الى هلام لهذه التحاميل تم إستخدام مواد إضافية مثل بولي فنيل بايرولدون ، هيدروكسي بروبيل مثيل سليلوز، الجنيت الصوديوم وكلوريد الصوديوم بتراكيزتتراوح بين)٢٥, ٠ ,١ %وزن/وزن(.وإن أفضل مستحضر تم الحصول عليه من مزج البولوكسامر١٨٨، الجنيت الصوديوم ، كلوريد الصوديوم و ماء مقطر)٢٩ ، ٥, ٠ , ١٠ ، ٦٠,٥ % وزن /وزن بالتعاقب (بدرجة حرارة تحول الى هلام ٦, ٣٣± ٢,٥٠ م وبقوة ٢٨± ٢ ثانية .ولقد أظهرت الدراسة الخارجية للتحرر والتي اجريت بإستخدام قناة الميز الغشائي بأن تحرر الدواء من هذا المستحضر كان طويل الأمد بمدة ١٢ساعة تقريبا كما وإنه أسرع من التحاميل الصلبة التقليدية والحبوب الفموية .

Introduction

Naproxen is a non steroidal anti-inflammatory drug used for painful and inflammatory rheumatic arthritis, osteoarthritis, non articular rheumatism, in acute injury, migraine and tension headache, postoperative pain and pain associated with gynecological procedures.[1] Its main adverse effects are gastrointestinal, of which peptic ulcer, with or without bleeding is the most sever effect. In addition esophageal ulceration may rise due to incorrect consumption. Therefore rectal delivery has been explored as a potential method of avoiding gastric irritation that may occur when this drug is administered orally. [2] The ideal suppository would be easy to administer without any pain during insertion and would remain at the administered site avoiding the first-pass effect in the liver and the gastrointestinal tract. Several problems are associated with the solid suppositories such as giving the felling of alien, discomfort and refusal to the patient with the possibility of lowering patient compliance. Furthermore, solid suppositories might reach the end of the colon allowing the carried drug to undergo the first-pass effect. [3] To solve these problems, there have been several attempts to develop suppositories which exist as liquid at room temperature but gels at physiological one so they are easy to administer to the anus. [4, 5] Suitable gel strength with suitable bioadhesive force is required in liquid suppositories so as not to leak out from the anus after administration and not to reach the end of the colon [6, 7]

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Poloxamer series is a group of non ionic surface active compounds of polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer .[8] It is the most common base of liquid suppositories in which their solutions were known to exhibit the phenomenon of reverse thermal gelation; remaining as a solution at low temperature and gelling when the temperature increases. By modulating the gelation temperature of different poloxamer solutions, liquid base can be formulated which form a gel in the rectum at body temperature with suitable gel strength [4, 9, 10] Furthermore, poloxamers were reported not to cause any damage on mucosal membrane. [11] This study was carried out to prepare an acceptable in-situ gelling liquid suppository for naproxen through studying different variables affecting the physicochemical properties and the in vitro release of the drug from this preparation.

Materials and Instruments

Materials

Naproxen, Hydroxypropylmethylcellulose (HPMC) supplied by Samara Drug Industry (SDI), Poloxamer 188(BASF, United Pharmaceuticals, Jordan), Polyvinylp-yrrolidone (PVP), Disodium Hydrogen Phosphate , Potassium Dihydrogen Phosphate (BDH Chemicals, LTD, Liverpool, England) , Sodium Alginate (Hopkins and Williams, LTD, England), Sodium Chloride (Evans Medical , LTD, Liverpool, England) Dialysis tubing 36/32 with clips (Medicell International LTD, Liverpool, England), Proxen®500 Suppositories (Grünenthal Pharma AG, Suisse), Naprox®500 Tablets (Medical Bahri, Syria)

Instruments

Hot Plate with Magnetic Stirrer (IKA®-WEKE, Copley,MBH and Co.KG, D-7921, Germany), Manually Modified Gardener Can-type Mobilometer , Sartorius balance (Werke-GMBH, type 2842, Germany),pH-meter (Hanna Instruments pH 211 Microprocessor, Italy), USP Dissolution apparatus, Type II (Copley Scientific LTD, England), UV.Visible Spectrophotometer (Carrywin UV.Varian,100i spectrum, Australia), Water bath (Mammert, Germany)

Method

Preparation of Liquid Suppository

Naproxen and various amounts of excipient, except the liquid suppository base "poloxamer 188", were completely dispersed in the specified amount of distilled water with continuous agitation at room temperature and cooled down to 4°C. Poloxamer 188 was then slowly added to the solution with continuous agitation. The liquid suppository was left at 4°C until a clear solution was obtained. [4] Several preparations were prepared according to the factors that affect the physicochemical properties of the resultant liquid suppositories in order to get an acceptable formula.

Evaluation of In-situ Gelling Liquid Suppositories:-

1. Gelation Temperature:-

A 20-ml transparent vial containing a magnetic bar and 10 g of the liquid suppository was placed in a low-temperature thermostat water bath.A digital themosensor connected to a thermositor was immersed in the liquid suppository. The liquid suppository was heated at a constant stirring "100 (rpm)".When the magnetic bar stopped moving due to gelation, the temperature displayed on the thermistor was determined as the gelation temperature. [4] Only those liquid suppository preparations that pass the gelation temperature test were subjected to the next tests.

2. Gel Strength:-

The gel strength of the liquid suppositories was measured using manually modified Gardener Can type mobilometer (figure 1).[12] A 50 g of the liquid suppository was transferred to a 100 ml graduated cylinder, and the cylinder was kept at 36.5°C for 30 minute in a water bath.A "35 g" weight of an appropriate size was then placed on the surface of the liquid suppository in the cylinder, and the time in second(s) required for this disc to move 5 cm down through the gelled suppository was measured and taken as an arbitrary index of gel strength. [13] Only those liquid suppository preparations that pass the gel strength test were subjected to the next test.

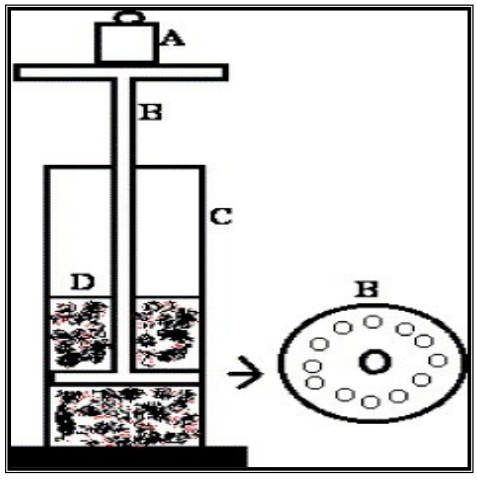


Figure 1.[11]: Gel-Strength Measuring Device
(A): weight, (B): device, (C): mess cylinder , (D): Liquid

3. Dissolution Test:-

To perform the in vitro release test for liquid suppositories a semipermeable membrane "Dialysis tubing 36/32"[14] of 7 cm in length with clips [15] was used. A 5 g weight of the liquid suppository containing 500 mg naproxen was inserted into the semipermeable membrane tubing and both sides of the tube were closed with the clips to prevent leakage. The semipermeable membrane tube was then placed in a dissolution tester. Drug release test was performed at 36.5°C using the USP dissolution apparatus type II at 100 rpm with 500 ml Sorensen's phosphate buffer pH 6.8 as a dissolution medium.At one hour intervals, 5 ml of the dissolution medium was sampled and filtered. The volume inside the jar was kept constant by addition of an equal volume"5 ml" of the same buffer solution. [6, 9] The filtrate was analyzed spectrophotometrically for naproxen content at 331 nm.

Factors Affecting the Physicochemical Properties of the In-situ Gelling Liquid Suppositories

1. Effect of Poloxamer 188 Concentration

Different concentration of poloxamer 188 ranging from 26-30%w/w [4] were used to prepare a plain liquid suppository, and the effect of poloxamer 188 concentration on the gelation temperature and gel strength was studied.

2. Effect of Addition of Naproxen

Naproxen in a dose of 500 mg (10% w/w), the usual rectal dose, was added to the different concentrations of poloxamer 188 solutions to study its effect on the physicochemical properties of the resultant medicated liquid suppository.

3. Effect of Addition of Additives

Different additives including "PVP", "HPMC", sodium alginate and sodium chloride were added in different concentrations ranging from (0.25-1.0% w/w)[4,9,10] to the different concentrations of poloxamer solutions and their effect on the gelation temperature, gel strength and dissolution behavior of the resultant liquid suppositories were then studied.

Factors Affecting the in vitro Release of Naproxen

1. Effect of Formulation Components

To study the effect of the liquid suppository components; "the base and the additives", on the naproxen release profile, an in vitro release of the drug powder was performed and compared with that from the liquid suppository. A 500 mg naproxen powder was inserted into the semipermeable membrane tubing and then the release test was performed as mentioned previously.

2. Effect of Dosage Forms

To study the effect of the dosage forms on the in vitro release of naproxen a comparison was done between the liquid suppository and other dosage forms. A commercial solid suppository (Proxen®500) or commercial oral tablet (Naprox®500) containing 500mg naproxen were inserted into the semipermeable membrane and then the dissolution test was performed as mentioned previously. The release profile of these dosage forms were then compared with that of the liquid suppository.

Statistical Analysis

Results are given as a mean ± S.D for triplicate samples. The results were statistically analyzed by using analysis of variance (ANOVA) table and t-test, P-values less than 0.05 was considered significant

Results and Discussion

Physicochemical Properties of the In-situ Gelling Liquid Suppositories

The temperature dependent gelation of poloxamer solutions could be explained to be due to desolvation of hydrophilic chains of the polymer as a result of the breakage of the hydrogen bonds that have been established between the solvent and these chains. This phenomenon favors hydrophobic interaction among the hydrophobic chains of the polymer[16] and the polymer self-assemble spontaneously, forming micelles. [17, 18] Raising the temperature of poloxamer solutions will be accompanied by an increase in the micellar aggregation number and a decrease of a critical micelle concentration allowing the formation of a more closely packed and more viscous gel. [19] An accepted liquid suppository must have a gelation temperature in the range of (30-36°C) and gel strength of (10-50 seconds), so as to be in a liquid form at room temperature and to form a gel phase instantly in the rectum without leakage. [4, 9, 10]

Factors Affecting the Physicochemical Properties of the In-situ Gelling Liquid Suppositories

1. Effect of Poloxamer 188 Concentration

Table (1) shows the effect of poloxamer 188 concentration on the gelation temperature of the prepared liquid suppositories. The results indicated that increasing the poloxamer 188 concentration from 26 % to 30 % w/w was accompanied with a decrease in the gelation temperature. These results were in agreement with those reported by Choi.H.G. et al. [4] The increment in poloxamer 188 concentration led to an apparent dramatic

increase of micellar size and polydispersibility which could be the reason for such reduction in the gelation temperature . It was suggested that such changes were a consequence of interactions between polyoxyethylene chains of adjacent micelles which, as a result of their dehydration, experience increased friction with a resulting tendency to form multimolecular units leading eventually to gel formation [20]

Table (1): Gelation temperature of different naproxen suppositories

Concentration of Poloxamer 188 % w/w	Mean Gelation Temperature °C± S.D of poloxamer solutions	
	Plain	Medicated
26%	>50	45. 6 ± 0.1
27%	>50	43.1 ± 0.2
28%	>50	40.9 ± 0.2
29%	>50	37.7 ± 0.2
30%	48.0±0.1	35.2 ± 0

2. Effect of Addition of Naproxen

The incorporation of 10 % w/w (500 mg) of naproxen into the poloxamer 188 solutions of different concentrations decreased the gelation temperature of the resultant liquid suppositories as compared with the plain one, as shown in table (1). As a possible mechanism by which naproxen affected the gelation temperature of these preparations, it may be speculated that placing naproxen in the gel matrix would make its carboxyl group bonded strongly with the cross-linked reticular poloxamer gel through hydrogen bonding. This suggestion was based on the results obtained by El-Kamel AH. who found that if hydrogen bonding is supplemented to the poloxamer solutions by adding compounds containing a hydrogen-bonding forming group, the gelation temperature will decrease.[21]

3. Effect of Addition of Additives

Tables (2a-2e) show that the addition of any of the used additives PVP, HPMC, sodium alginate and sodium chloride, would lower the gelation temperature and reinforce the gel strength of the resultant liquid suppositories. The impact of additives on the gelation temperature and gel strength was found to be depending on their nature and concentration. Increasing the concentration of any of the used additives from 0.25 to 1.0 % w/w produced a gradual decrease in the gelation temperature and increase in the gel strength of the corresponding liquid suppositories. The gelation temperature lowering and gel strength increasing effect of PVP, HPMC and sodium alginate could be explained by their ability to bind to the polyoxyethylene chains present in the poloxamer molecules through hydrogen bonds. This will promote dehydration causing an increase in entanglement of adjacent molecules which will lead to gelation at lower temperature and reinforce the gel strength. [5, 9, 22] On the other hand, the reduction in the gelation temperature with the increase in gel strength by addition of sodium chloride could be attributed to its salting-out effect which results in dehydration of the polyoxyethylene chains, causing an increase in the entanglement of adjacent molecules.[17]

Table (2): Effect of addition of additives on the physicochemical propertie of liquid suppositories containing 10% w/w naproxen and different concentrations of poloxamer 188.

(a): with 30% w/w poloxamer 188

Types of additives	Conc.of additives	Mean Gelation Temperature (°C) ± S.D	Mean Gel Strength (seconds) ±S.D
No	——	35.2 ± 0	102 ± 2.3
	0.25	29.8 ± 0.1	/**
	0.5	/	/
	0.75	/	/
	1.0	/	/
	0.25	34.7 ± 0.1	200 ± 1.8
	0.5	33.1 ± 0.4	/
	0.75	31.8 ± 0.4	/
	1.0	30 ± 0.1	/
	0.25	33.7 ± 0	146 ± 2.04
	0.5	31.4 ± 0.1	/
	0.75	29 ± 0.4	/
	1.0	/	/
	0.25	34.2 ± 0.5	Not fall*
	0.5	32.4 ± 0.1	/
	0.75	31.1 ± 0.1	/
	1.0	30.2 ±0.3	/

***not full up to 300seconds**
****not done**

(b) : with 29% w/w poloxamer 188

Types of additives	Conc.of additives	Mean Gelation Temperature (°C) ± S.D	Mean Gel Strength (seconds) ±S.D
No	——	37.7 ± 0.2	/**
	0.25	33.8 ± 0	Not fall*
	0.5	30.2 ± 0.1	/
	0.75	27.1 ± 0.5	/
	1.0	/	/
	0.25	37 ± 0.1	/
	0.5	36.6 ± 0	/
	0.75	36.3 ± 0	/
	1.0	34.2 ± 0.1	253 ± 2.3
	0.25	36.8 ± 0	/
	0.5	33.6 ±0.2	28 ± 2
	0.75	30.5 ± 0	83 ± 3.72
	1.0	27.7 ± 0.1	/
	0.25	35.4 ± 0	150 ± 1.5
	0.5	34 ± 0	/
	0.75	32.7 ± 0.1	/
	1.0	31 ± 0.1	/

***not full up to 300seconds**
****not done**

(d): 27% w/w poloxamer 188

Type of additives	Conc. of additives	Mean Gelation Temperature (°C) ± S.D	Mean Gel Strength (seconds) ± S.D
No	——	43.1 ± 0.2	/**
	0.25	36.1 ±0.1	/
	0.5	32.4 ± 0	348 ± 3.77
	0.75	28.3 ± 0	/
	1.0	/	/
	0.25	/	/
	0.5	/	/
	0.75	/	/
	1.0	/	/
	0.25	/	/
	0.5	37.2 ± 0	/
	0.75	34.3 ±0	2 ± 4.25
	1.0	34.6 ± 0	3 ± 2.86
	0.25	39.5 ±0	/
	0.5	36.1 ± 0	/
	0.75	35.2 ± 0.1	98 ± 1.79
	1.0	33.5 ± 0.2	/

****not done**

(c): 28% w/w poloxamer 188

Type of additives	Conc. of additives	Mean Gelation Temperature (°C) ± S.D	Mean Gel Strength (seconds) ± S.D
No	——	40.9 ± 0	/**
	0.25	34.1 ± 0.1	Not fall*
	0.5	30.6 ± 0.58	/
	0.75	27.6 ± 0.3	/
	1.0	/	/
	0.25	37.4 ± 0	/
	0.5	/	/
	0.75	/	/
	1.0	/	253 ± 2.3
	0.25	37.7 ± 0.4	/
	0.5	34.8 ±0.2	3 ± 1.96
	0.75	33.9 ± 0	14 ± 2.03
	1.0	33.6 ± 0.1	99 ± 1.43
	0.25	35.9 ± 0	95 ± 0.9
	0.5	34.9 ± 0.3	/
	0.75	33.7 ± 0.58	/
	1.0	32 ± 0.2	/

***not full up to 300seconds**
****not done**

(e): 26% w/w poloxamer 188

Type of additives	Conc. of additives	Mean Gelation Temperature (°C) ± S.D	Mean Gel Strength (seconds) ± S.D
No	——	45.6 ± .1	/**
	0.25	/	/
	0.5	33.4 ± 0.1	212 ± 1.53
	0.75	29.8 ± 0	/
	1.0	/	/
	0.25	/	/
	0.5	/	/
	0.75	/	/
	1.0	/	/
	0.25	/	/
	0.5	/	/
	0.75	35.9 ± 0.2	1 ± 1.63
	1.0	35 ±0	2 ± 1.46
	0.25	/	/
	0.5	/	/
	0.75	36 ± 0	46 ± 1.32
	1.0	34.2 ± 0.1	63 ± 2.61

****not done**

Dissolution Test

Three naproxen liquid suppositories passed the gelation temperature and gel strength tests (nomenclated as A, B and C) were subjected to the dissolution test. Table (3) summarizes the constituents of each liquid suppository. In addition, these liquid suppositories (A, B and C) may have a mucoadhesive force that prevent the gelled suppositories from reaching the end of the colon, the pathway for the first-pass effect, which may be related to their ability to bind strongly to the oligosaccharide chains of the rectal mucous membrane through the hydrophilic groups of poloxamer and the additives.[4,6,9] The percentage of naproxen released from these preparations to the dissolution medium for 12 hours [23 , 24], was selected for the comparison study. In addition, the time required for 100 % release for the drug from these three preparations were also measured, table (4). It was found that there is no significant difference in the percentage of drug released among these three preparations, ($P > 0.05$), and all of them gave sustained drug release, since they released about 70 % of the drug within 12 hours as shown in figure (2) and table (4). The in-situ gelling liquid suppository (A), which had suitable gelation temperature and an intermediate gel strength was selected for further study, since it may has a lower chance to be leaked from the rectum and easier to be administered than the others.

Table (3): The constituents of the in-situ gelling liquid suppositories with their physicochemical properties

	Constituents of the liquid suppository		Physicochemical properties	
	Component	Conc. % w/w	Mean Gelation temperat-ure (°C)± S.D	Mean Gel Strength Sec. ± S.D
-	Poloxamer 188	29	33.6 ± 0.2	28 ± 2
	Sodium alginate	0.5		
	Naproxen	10		
	Distilled water	60.5		
	Poloxamer 188	28	33.9 ± 0	14 ± 2.03
	Sodium alginate	0.75		
	Naproxen	10		
	Distilled water	61.25		
-	Poloxamer 188	26	36 ± 0	46 ± 1.32
	Sodium chloride	0.75		
	Naproxen	10		
	Distilled water	63.25		

Table (4): Percentage released of naproxen from in-situ gelling liquid suppositories and the time required for 100% release

Liquid Suppository	%Released for 12 hours	Time for 100 % release (hours)
A	66.64	20
B	72.86	17
C	69.73	21

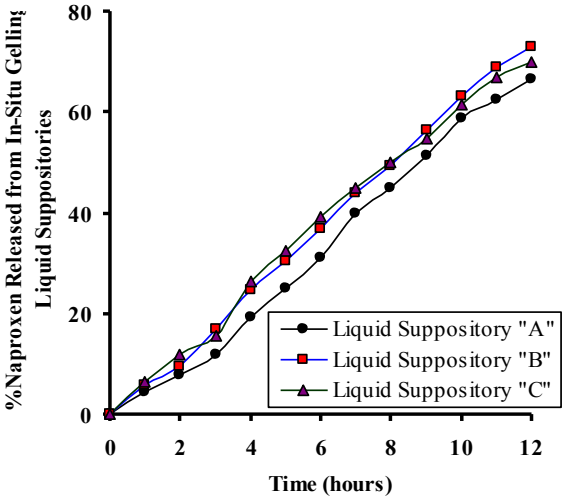


Figure 2. Percentage of naproxen released from three different in- situ gelling liquid suppositories in Sorenson's phosphate buffer pH 6.8 at 36.5ºC using dialysis tubing method

Factors Affecting the in vitro Release of Naproxen

1. Effect of the Formulation Components

To study the effect of the formulation components on the in vitro release of naproxen from the liquid suppositories, the percentage of drug release from the powder (500 mg) was compared with that from in-situ gelling liquid suppository (A), using the dialysis tubing method. The release profile for in-situ gelling liquid suppository (A) was similar to that for naproxen powder at the first five hours and it was significantly faster ($P<0.05$) after hour five as shown in figure (3). This could be attributed to the solubilizing effect of poloxamer 188, especially for the poorly water soluble drug. [8, 25]

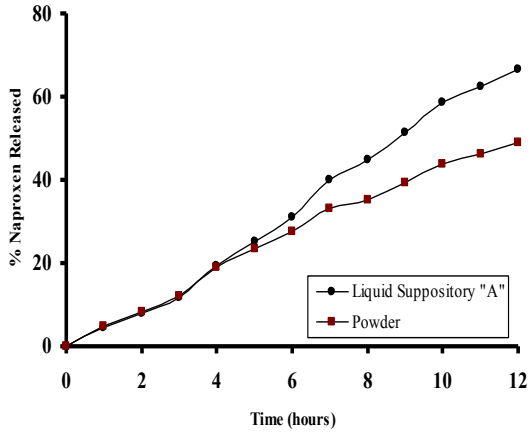


Figure 3. Effect of formulation components on the in vitro release of naproxen in Sorenson's phosphate buffer pH 6.8 at 36.5ºC using dialysis tubing method

2. Effect of the Dosage Form

To study the effect of the dosage form on the in vitro release of naproxen, the percentage released of the drug from the liquid suppository (A), commercial solid suppository and commercial oral tablet were compared by using dialysis tubing method. As shown in figure (4), the in-situ gelling liquid suppository had the faster release, followed by the commercial oral tablet and finally the commercial solid suppository. These results indicated that the dosage form design would affect the in vitro release of naproxen. A statistical analysis were done and showed a significant differences ($P<0.05$) for the percentage released of naproxen among these three dosage forms.The faster release from the in-situ gelling liquid suppository (A) could be due to the fluidity of the liquid suppository [7,9], and the solubilizing effect of poloxamer 188 for the poorly water soluble drug.[8, 25]

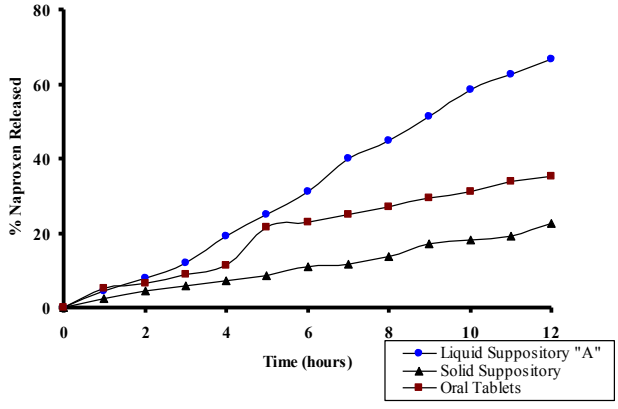


Figure 4. Effect of dosage Form on the in vitro release of naproxen in Sorenson's phosphate buffer pH 6.8 at 36.5ºC using dialysis tubing method

Future work

Further study on the stability, mucoadhesive property, clinical and pharmacokinetic study on human subjects for naproxen –loaded poloxamer in-situ gelling liquid suppositories is to be done.

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