

Controlled Release of Naproxen Sodium from Supermacroporous Cryogels

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Abstract: Cryogels are gel matrices that have interconnected macropores and are formed in freezing-thawing systems. These interconnected macropores give elasticity to cryogels. Transdermal controlled-release systems can be used to deliver drugs with short biological half-life and can maintain plasma levels of very potent drugs within a narrow therapeutic range for prolonged periods. In this study, cryogels have been used in a different area—transdermal controlled-release system, to obtain controlled drug release medium. For this purpose, naproxen sodium has been selected as a model drug. Naproxen, a propionic acid derivative, is a NSAID (nonsteroidal anti-inflammatory drug). For controlled releasing of naproxen sodium, cryogels that have naproxen sodium in macropores have been prepared in sheet form for local application. Acrylamide based cryogel bands have been synthesized by free radical cryogelation process. These cryogel bands have different pore size and includes naproxen sodium in their pores. This cryogel material has been characterized by swelling tests and SEM. Then, releasing of naproxen sodium from cryogels has been investigated at two different pH values, 7.4 and 5.5. According to experimental data, it has seen that these cryogel matrices that including naproxen sodium in macropores could be used in controlled drug releasing systems as bandages or other transdermal controlled releasing agents at room temperature.

Key words: Cryogel, macropores controlled release, naproxen sodium, transdermal releasing agent.

1. Introduction

In general, the goal of a sustained-release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero-order release from the dosage form. Zero-order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (i.e., a constant release rate). Sustained-release systems generally do not attain this type of release and usually try to mimic zero-order release by providing а slow first-order fashion drug in (i.e., concentration-dependent). Systems that are designated as prolonged release can also be considered as attempts

at achieving sustained-release delivery. Repeat-action tablets are an alternative method of sustained releasing in which multiple doses of a drug are contained within a dosage form, and each dose is released at a periodic interval. Commonly, the release rate of drug is not altered and does not result in sustained delivery once drug release has begun. Enteric-coated tablets are an example of this type of dosage form [1, 2]. Transdermal controlled-release systems can be applied for delivering many drugs which have short biological half-life to maintain plasma levels. If problems occur with the system, or a change in the status of the patient requires modification of therapy, the system is easily accessible and removed. Current controlled transdermal-release systems can be classified into four types which are membrane permeation-controlled system, adhesive dispersion-type system, matrix

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diffusion-controlled system and microreservoir dissolution-controlled system [3, 4].

Polymers are used as carriers for the delivery of drugs, proteins, targeting moieties, and imaging agents. Recently, interest in polymer conjugation with biologically active components has increased remarkably. In this study, acrylamide based cryogels have been used as a polymeric material for designing polymer drug bioconjugated material and naproxen sodium is selected as a model drug that has a binding capacity to the interconnected macropores of acrylamide cryogel. Naproxen is a propionic acid derivative which is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis. It is also used in dysmenorrhoea, headache including migraine, postoperative pain, soft-tissue disorders, acute gout, and fever. Naproxen is usually given orally as the free acid or sodium salt.

Cryogels are gel matrices that are formed in frozen solutions of monomeric or polymeric precursors. interconnected macropores Cryogels have or supermacropores with a pore size range from 10 µm to 100 µm. The common continuous supermacroporous monolithic matrix of cryogels is always produced by radical cryo-copolimerization of monomers such as AAm (acrylamide), DMAA (dimethylacrylamide), 2-hydroxyl ethylmethacrylate with cross-linker MBAAm (N,N'-methylene bis acrylamide) induced by redox initiator APS (ammonium per sulfate) and TEMED (N, N, N', N'-tetramethylethylenediamine) in a frozen aqueous under the freezing condition when most of the solvent is frozen while dissolved monomers are concentrated in small nonfrozen regions. When the aqueous mixture of monomers is kept frozen below its freezing point, solvent crystallization takes place and ice crystals or ice blocks occur in the mixture bulk. At the thawing step, frozen mixture bulk is melted at the room temperature and cryogel structure with interconnected supermacropores is formed [5, 6]. Cryogels are highly elastic and about 70 % of the total liquid inside of the cryogel can be removed by mechanical compression. The compressed cryogels swell again when contacted with liquid and restore the original shape within less than a minute [7]. So, swelling tests of cryogels are the other ways of characterization beside SEM images.

In this study, we have investigated cryogels as a different area—drug release. For this purpose: firstly, different sized macroporous structured acrylamide based cryogels that naproxen sodium loaded in its pores have been synthesized then, releasing of naproxen sodium from macroporous cryogels has been investigated at pH 7.4 and 5.5.

2. Materials and Methods

AAm (99%), MBAAm, TEMED, NaCl, Naproxen Sodium were supplied by Sigma-Aldrich, Fluka, BioChemica, Carlo Erba, Abdi İbrahim Drug Company, respectively. APS was obtained from local sources. K_2HPO_4 and Na_2HPO_4 were bought from Merck. All water used in the experiments was purified using a Barnstead (Dubuque, IA) ROpure LP[®] reverse osmosis unit with a high flow cellulose acetate membrane (Barnstead D2731) followed by a Barnstead D3804 NANOpure[®] organic/colloid removal and ion exchange packed-bed system.

2.1 Preparation of Different Pore Sized Cryogel Bands

For the preparation of acrylamide cryogel, as a general procedure of preparing cryogels, 0.765 g of acrylamide was dissolved in 20 mL of deionized water. Then, MBAAm was added into acrylamide solution as crosslinking agent. Naproxen Sodium was added into that mixture and treated ultrasonically for 5 min. The solution was cooled for 3-4 min in an ice bath. Lastly, APS and TEMED were added and stirred quickly. Solution was poured into petri dish and frozen at -18 °C during 16 h. At the end of freezing time, frozen solution was thawed at room temperature. Pore sizes were changed by using different amounts of cross-linking agent (MBAAm), and initiator agent

(TEMED) during polymerization process. At the end of freezing-thawing, different pore sized (F1, F2, F3, F4) cryogel bands were synthesized. The amounts of reagents for the preparation of each cryogel bands were given in Table 1. The synthesized cryogel material was used as controlled drug releasing bandage.

2.2 Characterization of Cryogel Bands

Because cryogels are highly hydrophilic materials, characterization of cryogels bands were made by swelling tests. According to macropore size, each cryogel has different water capture capacity. Cryogels that have large macropores can swell much more than the cryogels that have smaller macropores. For determination of the swelling ratios of cryogel bands, initially cryogel sample was washed until washing was clear. Then, it was dried to constant mass and the mass of dried sample was weighed (± 0.0001 g). These dried samples were being placed into deionized water as a swelling medium at room temperature for 4 h and the wet sample was weighed. The swelling ratio was calculated by using Eq. (1):

Swelling ratio $\% = [W_s - W_0/W_0] \times 100$ Eq.(1) Where, W_0 and W_s are the weights of cryogels before and after swelling, respectively. Swelling ratios of each pore sized cryogels were determined by the same method.

The size of macropores was determined by scanning electron microscopy (SEM, LEO S440) images. So, SEM is another way to characterize cryogels [8].

2.3 Determination of Releasing of the Amount of Naproxen Sodium

Spectrophotometric method was used for drug assay.

 Table 1
 Contents of naproxen loaded cryogel formulations.

Naproxen sodium releasing studies were investigated at two different pH values. pH 5.5 was chosen to investigate naproxen sodium releasing behaviour from cryogel in transdermal applications and pH 7.4 was chosen to investigate the naproxen sodium releasing behaviour from cryogel in vivo systems at body temperature. Firstly, series of naproxen sodium solutions (from 100 μ g·mL⁻¹ to 500 μ g·mL⁻¹) in pH 7.4 buffer were prepared and calibration curve was created UV for naproxen sodium response of spectrophotometer versus concentration (UV-2401 PC, UV-Visible Spectrophotometer (Shimadzu)) at 330 nm. Then, cryogel band including naproxen sodium in its macropores sample was placed into 1,000 mL of pH 7.4 buffer solution. Releasing of naproxen sodium from cryogel macropores was investigated by spectrophotometrically at 330 nm by taking 3 mL of solution from releasing media every 15 min at 37 °C and the response of UV spectrophotometer was recorded. All these procedures were repeated for pH 5.5 buffer releasing media.

2.4 In vitro Dissolution Test

Dissolution test was performed according to the paddle over disk method described in USP XXXI, apparatus 5. The rotating speed was 50 rpm and the temperature was 37 ± 0.5 °C. Dissolution studies were carried out in 900 mL of medium pH 5.5 and 7.4 buffer solutions in USP XXXI [9]. 3 mL of each sample was taken from the dissolution medium at certain time intervals by the aid of an injector fitted with a Schleicher-Schuell filter paper, and an equal volume of the same medium was returned to the system after each withdrawal. The absorbances of the samples were

Formulations	Contents of formulations					
	Acrylamide	Deionized water	MBAAm	Naproxen sodium	APS	TEMED
F1	0.765 g	20 mL	0.112 g	0.0897 g	0.02 g	20 µL
F2	0.765 g	20 mL	0.120 g	0.0897 g	0.02 g	45 µL
F3	0.765 g	20 mL	0.130 g	0.0897 g	0.02 g	75 μL
F4	0.765 g	20 mL	0.135 g	0.0897 g	0.02 g	100 µL

MBAAm: N, N' Methylene bis acrylamide; APS: Ammonium per sulfate; TEMED: N, N, N', N'-tetramethylethylenediamine.

measured by using UV spectrophotometer at 330 nm against blank. The blank is dissolution samples of placebo formulation (without naproxen sodium) corresponding to each formulation. The amounts of Naproxen released were found by using the standard curve equation. Dissolution profiles of cryogel formulations were plotted for pH 5.5 (Fig. 1) and pH 7.4 (Fig. 2).

3. Results and Discussion

The releasing amount of Naproxen sodium was calculated using regression equation and regression coefficients. Regression equation is $C = 0.0106 \times \text{Abs} + 0.0524$, and regression coefficient r = 0.998 for pH 5.5. Regression equation and regression coefficient r

for pH 7.4 are $C = 0.0106 \times \text{Abs} + 0.1193$, r = 0.990 ($C = \text{concentration} (\mu \text{g/mL})$, Abs = absorbance), respectively.

3.1 Swelling Test Results

The cryogels were characterized by swelling tests [10-14]. Swelling ratios of F1-F4 cryogel band were calculated 1.799 %, 1.552 %, 1.139 % and 1.093 %, respectively. Swelling behaviour of cryogels formulations which have different pore size distribution, showed different swelling ratios. Pore sizes of cryogel bands are smaller through from F1 to F4. Cryogel band which has the largest pore size (F1) shows the higher amount of swelling ratio and the smallest pore sized cryogel band (F4) shows the little



Fig. 1 Naproxen sodium releasing from cryogels at pH 5.5.



Fig. 2 Naproxen sodium releasing from cryogels at pH 7.4.

amount of swelling ratio. The amount of MBAAm and TEMED changed the pore size of the synthesized cryogels.

It is known that the swelling degree is a significant factor that determines the releasing rates of drug from cryogel.

3.2 In Vitro Dissolution Results

Drug release profiles are given in Figs 1 and 2 (n = 6). The drug is released from cryogels depended upon pore size of cryogel bands. Approximately 100 % naproxen sodium was released in the first 20 min from control (powder naproxen). The release of active ingredient from cryogels was slower than that of control. On the other hand, as observed in F1-F4 cryogel formulations, pore size distribution has an important effect on the drug release rate. The main factor controlling drug release was the polymer structure (Table 1). Mechanisms for drug release from cryogel imply water

penetration in the system (with drug dissolution on the surface, causing its immediate release), hydration and swelling of cryogel, diffusion of the dissolved drug. The polymer swells to form a gel layer, naproxen sodium releases through the gel macropores and this process continues until the drug is completely released from the cryogel. The releasing naproxen sodium from synthesized cryogels at pH 5.5 were found to be 96.32%, 98.65%, 95.75% and 92.78% for powder naproxen, F1, F2, F3 and F4, respectively, in 4 h. The releasing naproxen sodium from synthesized cryogels at pH 7.4 were found to be 95.87%, 96.95%, 90.68% and 93.98% for powder naproxen, F1, F2, F3 and F4, respectively, in 4 h also. The results of releasing tests showed that, the pore size of cryogel band affects in vitro releasing of drug. When the pore size decreased, the in vitro releasing of drug was also decreased (from F1 to F4). According to these results, it appears that polymer structure is the main factor for improving the



Fig. 3 SEM images of (a) F1 cryogel; (b) F2 cryogel; (c) F3 cryogel and (d) F4 cryogel.

formulation and also effecting time-dependent characteristic changes such as the drug release rate from dosage forms.

3.3 SEM Images of Cryogel Bands

The cryogels were characterized by SEM. The synthesized cryogel polymers are capable of providing continuous drug release in an aqueous environment. Polymer structure affects the releasing behaviour of drug, Naproxen sodium in this study [15-18]. To discuss the effect of polymer structure in drug releasing, polymer structure is changed by synthesising cryogels in different pore sized. Pore size of cryogels modified using with various amount of cross-linking agent (MBAAm) and initiator pairs (APS and TEMED) in the synthesis stage. These ratios are given in Table 1. As it is seen from the SEM images of cryogels (Fig. 3), the pore size of cryogels is smaller and smaller from F1 to F4 formulation. From the releasing graphs, the smallest pore sized cryogel makes the drug releasing more controlled.

4. Conclusions

Cryogels are smart polymers that have interconnected macroporous and elastic structure. They are used in many areas for their capable of immobilization in its macropores, their stability, being undegradable and reusable polymers.

Herein, cryogels were investigated in drug releasing medium as a different area. Different pore sized cryogels were synthesized and each of them was investigated for the naproxen sodium releasing. The carried out experiments allow the conclusion that the main factors determining the controlled drug releasing rate are the degree of swelling, the degree of crosslinking, polymer structure and the pore size of cryogel band in the cryogel and the amount of comprised drug.

When the cryogel polymer is in contact with synthetic dissolution medium, this polymer swells because of the liquid transfer into the polymer. On the other hand, a releasing of the drug is observed, which does not follow a classical kinetic equation, as the kinetics is partially controlled by diffusion. This study shows that the diffusion release mechanism in a gel system comprising an insoluble hydrophilic gel-forming part depends greatly on the wettability of the added drug.

The experimental data showed that controlled drug releasing was succeeded by cryogel samples. Because cryogels are stable, undegradable and long-life materials, these cryogel samples are suitable for the preparation of transdermal releasing medium as bandages for the treatment of therapeutic systems with retarded drug release for the local application.

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