Preparation and Characterization of Polymeric Prodrugs of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) by Cold Plasma Technique

Yukinori Yamauchi*1, Naoki Doi2, Yasushi Sasai2, Shin-ichi Kondo2, and Masayuki Kuzuya3

1Department of Pharmaceutical Physical Chemistry, College of Pharmaceutical Sciences, Matsuyama University, 4-2 Bunkyo-cho, Matsuyama, Ehime 790-8578, Japan
2Laboratory of Pharmaceutical Physical Chemistry, Gifu Pharmaceutical University, 1-25-4 Daigaku-Nishi, Gifu 501-1196, Japan
3Department of Health & Welfare, Chubu Gakuin University, 2-1, Kirigaoka, Seki-shi, Gifu, 501-3993, Japan
*yyamauch@cc.matsuyama-u.ac.jp

A methacrylic-type polymerizable derivative of naproxen (NP), planned as a prodrug, was directly synthesized from the reaction between 2-hydroxyethyl methacrylate (HEMA) and NP by the esterification method. Then, the polymeric prodrugs containing NP pendent groups were synthesized by the free radical polymerization on plasma irradiated pharmaceutical excipient powders. Hydrolysis of the polymeric prodrugs was carried out in conditions similar to physiological conditions and the results showed that the studied polymeric prodrugs in the present investigation can be used as carriers in controlled drug release, to meet the need for prolonged and better control of drug administration.

Keywords: Plasma irradiation, Drug delivery system, Cellulose derivatives, Polymeric prodrugs

1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen (NP), aspirin and indomethacin are among the most widely used drugs in the treatment of inflammation, pain and arthritis. The beneficial effect is associated with inhibition of cyclooxygenases (COX) that convert arachidonic acid into prostaglandins in inflammatory processes. Side effects associated with long-term use of NSAIDs (COX inhibitors) such as gastrointestinal damage and elevated risk of stroke, however, can limit their use and exploration in new indications. It is widely believed that eliminating the gastrointestinal side effects and reducing the toxicity associated with the NSAIDs use can be achieved via chemical modifications of the main functional groups contained in the NSAIDs structure [1].

Prodrugs can be utilized for a variety of purposes, including improvement of the bioavailability or pharmacokinetics of a drug, decreasing drug toxicity, facilitating administration of the drug, or delivering the drug effectively to specific cells or tissues [2].

Over the years, we have been working on the development of plasma-assisted preparation of polymeric prodrugs applicable to oral, topical and injectable drug delivery system [3-10].

Herein we report a novel NP, one of the most commonly used NSAIDs, delivery system based on a polymeric prodrug by using plasma technique. It was proposed to synthesize a polymeric prodrug of NP for oral administration by coupling the drug to 2-hydroxyethyl methacrylate (HEMA) by ester linkages and polymerizing the resultant product to get polymeric prodrug. The prodrug should undergo hydrolysis of its ester linkages to cleave the parent drug in a sustained manner which may result in maintaining the plasma drug level within the therapeutic range. Therefore, the NP release from the system via chemical hydrolysis was also evaluated in buffer solutions mimicking the
conditions of upper and lower gastrointestinal tract.

2. Experimental

2.1. Materials

A NP standard and HEMA were purchased from the Tokyo Chemical Industry Co. (Tokyo, Japan). Powdered micro crystalline cellulose (MCC, Ceolus KG-802) and low-substituted hydroxypropyl cellulose (L-HPC, LH-21), kindly supplied by Asahi Kasei Co. (Tokyo, Japan) and Shin-Etsu Chemical Co. (Tokyo, Japan), respectively, were dried at 70°C for over 24 h in vacuo. All other materials used were of analytical grade, and procured from commercial sources.

2.2. Synthetic route for preparation of NP-HEMA

We designed a methacrylate derivative of NP (NP-HEMA) where NP was linked to HEMA via hydrolysable ester linkage. NP-HEMA was synthesized by direct esterification of NP with HEMA in the presence of N,N-dicyclohexyl carbodiimide (DCC) in CH2Cl2 solution (Scheme 1). The hydroxyl group of HEMA reacted with the carboxyl group of NP and the resulting water was absorbed by DCC to produce N,N-dicyclohexylurea as a white precipitate. The white precipitate was isolated and the solvent was evaporated in vacuum. The residue was recrystallized from ethyl acetate to give NP-HEMA as a stable monomer. The structure and physicochemical properties of the newly synthesized compound were confirmed by elemental analysis, IR, 1H NMR, mass spectral data, and chemical methods. (yield; 62%, mp 73.0–74.7°C).

![Scheme 1. The synthesis route of vinyl ester type derivative of naproxen (NP-HEMA).](image)

2.3. Plasma-induced graft-polymerization and ESR spectral measurement

Graft polymerization of NP-HEMA was carried out by a two-step method. Powdered pharmaceutical excipients, MCC and L-HPC, were treated with argon RF plasma reactor operating at a frequency of 13.56 MHz, a gas pressure of 40 Pa, and a power of 50 W. The plasma treatment time was 120 s. Immediately after the treatment, the plasma-irradiated powders were applied to mechanical vibration with NP-HEMA powder (10% by weight) in a Teflon twin-shell blender for the prescribed period of time at room temperature under strictly anaerobic conditions, and submitted to ESR measurement (Fig. 1). ESR spectra were recorded with a JES-FA200 spectrometer (JEOL) with X-band and 100 kHz field modulation. The procedure is essentially the same as that reported earlier [11-13]. After the grafting reaction, the powders were extracted with acetonitrile overnight to remove residual monomers.

![Fig. 1. Schematic diagram of experimental setup.](image)

2.4. Surface analysis

To confirm the chemical composition of the surface of MCC and L-HPC powders grafted NP-HEMA, X-ray photoelectron spectrum (XPS) measurement was carried out using the conventional photoelectron spectroscopy apparatus, Shimadzu ESCA-3400. The Mg Kα line (1253.6 eV), used as X-ray source, was incident at 45° with respect to the surface normal. The total energy resolution was approximately 0.5 eV. The base pressure in the photoelectron analysis chamber was maintained at least 5 × 10⁻⁶ Pa.

2.5. In vitro release studies

The in vitro hydrolysis behavior of polymeric prodrugs was studied in physiological conditions (aqueous phosphate or hydrochloric acid buffers (900 mL), at 37°C ± 0.5°C), using a dissolution test apparatus with an auto sampling apparatus.
(Toyama Sangyo Co., Osaka, Japan) at 100 rpm. The drug release at different time intervals was measured by a Shimadzu UV-1800 spectrometer (Shimadzu Inc., Kyoto, Japan) at 230 nm using UV system ver. 3.2 software (Toyama Sangyo Co., Osaka, Japan). It was made clear that none of the ingredients used in the formulations interfered with the assay. The release studies were conducted in triplicate, and the mean values were plotted versus time.

3. Results and discussion

3.1. ESR spectra plasma treatment of L-HPC powder

The radical-containing L-HPC plasma-irradiated for 120 s has been submitted to a weak vibratory mixing using a Teflon vessel, under which no mechanoradical is formed, with virgin NP-HEMA monomer under anaerobic conditions. Figure 2 shows the progressive changes of the ESR spectra of plasma-irradiated L-HPC powders on the duration of vibratory-mixing with NP-HEMA.

As a result, propagating radicals (L-HPC - (NP-HEMA)n • ) to suggest graft-polymerization of the NP-HEMA onto L-HPC were not observed, but the spectral intensity gradually decreased in the course of vibratory mixing, indicating the occurrence of radical recombination reactions to result in the formation of nonradical species.

The result also indicated that, even if radicals are formed at grafted chains on L-HPC, they can generally be considered to be unstable and should be dissipated during the course of vibratory mixing due to the radical recombination reactions, since they have a high degree of freedom in amorphous solid.

3.2. Surface analysis of the grafted polymeric powders

XPS has been used to assess the chemical changes that occur at the surface of MCC and L-HPC powders before and after vibratory mixing with NP-HEMA monomer for 1 h. Figure 3 shows the XPS C1s core-level spectra of virgin MCC, virgin L-HPC, NP-HEMA grafted MCC and NP-HEMA grafted L-HPC powders.

Spectra from the virgin MCC and L-HPC powders show two components at 285 and 286.4 eV which may be assigned to the presence of aliphatic –C–H and C–C, and –C–O bond, respectively. After NP-HEMA grafting polymerization, two additional peaks at 288 and 289.2 eV were observed in the powders. These peaks were attributed to the generation of keto (–C=O) and O=C–O bonds in the resulted polymeric prodrugs.

In conclusion, XPS analysis confirms the success of NP-HEMA graft polymerization onto the surface of plasma irradiated MCC and L-HPC powders.

3.3. Naproxen Release from Grafted Polymeric Prodrug Powders

Since the carboxyl group of NP is essential for the therapeutic action, the NP release in its original state from NP-HEMA homopolymer was
studied in three different buffer solutions (pH 1.2, 6.8 and 8.5) in order to evaluate the possible time of a prolonged action. As is clear in Fig. 4, the release rate of NP at alkaline medium was higher than that in acidic condition. It seems that polymeric prodrugs have a low degree of swelling in the acidic medium and the drug is protected against hydrolysis.

Fig. 4. NP release properties from polymeric prodrugs in phosphate buffer (pH 1.2–8.5) solutions at 37˚C. Each value is mean of three readings. ○, pH 1.2; ●, pH 6.8; □, pH 8.5.

Figure 5 illustrates the release property of NP in a buffer solution at pH 8.5 from the NP-HEMA grafted polymeric prodrugs by comparing with that of NP-HEMA homopolymer. As shown in Fig. 5, the degree of hydrolysis of both grafted polymeric prodrugs, MCC and L-HPC, increases more than NP-HEMA homopolymer. These results suggest that several factors such as hydrophilicity, swelling ability and neighboring effect of polymers can affect the overall rate of hydrolysis.

4. Conclusion

We have synthesized and evaluated a novel polymeric naproxen prodrug. The prodrug was obtained by linking naproxen molecule to HEMA and then polymerizing the obtained monomeric drug onto plasma-irradiated pharmaceutical excipient powders, namely MCC and L-HPC. The release profiles indicated that the hydrolytic behavior of polymeric prodrugs is strongly based on the pH value of the hydrolysis solution and the physicochemical properties, such as hydrophilicity and swelling ability, of polymer main chain. The obtained results suggested that these polymeric prodrugs could be useful for release of naproxen in controlled release systems after oral administration.

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