Sustained Release of Naltrexone from Poly(*N*-Isopropylacrylamide) Microgels

ANNA-LENA KJØNIKSEN,[1,2] MARIA TERESA CALEJO,[1,3] KAIZHENG ZHU,[4] ANA MARIA S. CARDOSO,[5] MARIA C. PEDROSO DE LIMA,[5,6] AMÁLIA S. JURADO,[5,6] BO NYSTRÖM,[4] SVERRE ARNE SANDE[1]

[1]Department of Pharmacy, School of Pharmacy, University of Oslo, Blindern, N-0316 Oslo, Norway
[2]Faculty of Engineering, Østfold University College, N-1757 Halden, Norway
[3]Department of Electronics and Communications Engineering, Tampere University of Technology, FI-33101 Tampere, Finland
[4]Department of Chemistry, University of Oslo, Blindern, N-0315 Oslo, Norway
[5]CNC – Centre for Neuroscience and Cell Biology, University of Coimbra, Coimbra, Portugal
[6]Department of Life Sciences, University of Coimbra, Coimbra, Portugal

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ABSTRACT: The release of the opioid antagonist naltrexone from neutral poly(*N*-isopropylacrylamide) (PNIPAAM) microgels and negatively charged PNIPAAM microgels containing acrylic acid groups (PNIPAAM-*co*-PAA) has been studied at various microgel and drug concentrations. The release curves were found to be well represented by the Weibull equation. The release rates were observed to be dependent on the microgel concentration. At most conditions, the release from the charged microgels was slower than for the neutral microgels. In addition, the charged microgels exhibited a release lag time, which was dependent on the microgel concentration. No significant lag time could be observed for the neutral microgels. Increasing the naltrexone concentration did not significantly affect the release rates from the neutral microgels, but the release from the charged microgels became faster. The microgels did not exhibit any significant cytotoxic effect on HeLa cells at the tested concentrations. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:227–234, 2014

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INTRODUCTION

Naltrexone (Fig. 1) is an opioid antagonist, and has been used to treat heroin and alcohol addiction. However, oral naltrexone formulations have drawbacks such as patient noncompliance,[1] fluctuating plasma levels,[2] and the extensive first-pass metabolism of naltrexone.[3] Injectable depot formulations that can give a sustained release of naltrexone over an extended period of time could prevent the problems encountered with oral dosage forms. Several systems such as poly(L-lactide) microspheres,[4,5] poly lactide-*co*-glycolide (PLGA) microspheres,[6] poly(D,L-lactide-*co*-glycolide) microspheres,[7] polyethylene glycol-*graft*-methyl methacrylate crosslinked nanoparticles,[8] and nanoparticles produced from a blend of poly(*N*-isopropylacrylamide-acrylamide-vinylpyrrolidone) and PLGA[9] have been suggested for sustained release dosage forms for naltrexone. There is however still need for improving the release profile and drug loading capacity of the systems. Utilizing new kinds of thermosensitive *in situ* gelling microgels might therefore be of interest.

The release of a drug that is encapsulated into micro- or nanoparticles is dependent on a number of factors such as particle size,[10–13] drug size,[14,15] the degree of swelling of the particles,[16–18] erosion of the particles,[19] and associative interactions between the drug and the particles, for example, hydrophobic interactions,[15] hydrogen bonds,[20,21] or electrostatic interactions.[14]

Nano- and microparticles that are formed using thermosensitive polymers with a lower critical solution temperature (LCST) have a swollen structure at temperatures below the transition temperature and a more compact (collapsed) structure at higher temperatures. This effect can be utilized both to increase the loading capacity and modulate the release of a drug from the particles. Increased loading rate and capacity may be expected for drug loading in the swollen state, whereas the drug release is often found to be slower when the systems are heated to temperatures above the LCST of the particles due to reduced porosity. This phenomenon has been observed for several different systems such as: core–shell nanoparticles containing a poly(L-lactic acid) core and a poly(*N*-isopropylacrylamide) (PNIPAAM) thermosensitive shell,[22] alginate-hydroxypropylcellulose microbeads,[23] poly(*N*-vinyl caprolactam) nanoparticles,[24] poly(*N*-isopropylacrylamide-*co*-caprolactam) microspheres,[25] and PNIPAAM microspheres grafted with poly(itaconic acid) groups.[14] Interestingly, microspheres of elastin-like polypeptides (ELP) exhibited faster release rates above the LCST due to the opening of micropores in the microspheres by the contraction of the thermosensitive ELP molecules.[26] Faster release rates above the LCST was also observed for chitosan-*g*-poly(*N*-vinylcaprolactam) and chitosan-*g*-PNIPAAM nanoparticles.[20,21] This was explained by the ability of the drug to form hydrogen bonds with the nanoparticles at temperatures below the LCST. This capacity was lost above the LCST, and hence faster release rates are promoted.

Correspondence to: Anna-Lena Kjøniksen (Telephone: +47-69104095; Fax: +47-69215002; E-mail: anna.l.kjoniksen@hiof.no)

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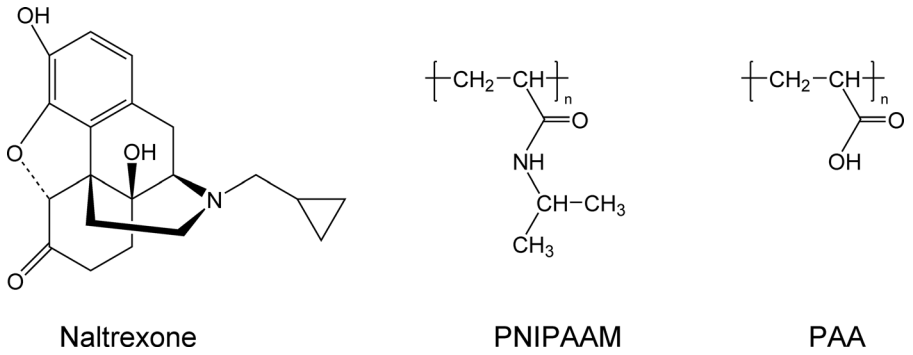

Figure 1. Chemical structure of naltrexone, PNIPAAM, and PAA.

For poly(*N*-isopropylacrylamide-*co*-acrylamide) and poly(*N*-isopropylacrylamide-*co*-*N*-hydroxymethyl acrylamide) microspheres, it was found that even though the drug release is slower above the LCST, there is an enhanced release of drug for a short period when the temperature is increased from below to above the LCST.[15,27] This effect was thought to be due to drug molecules that are dissolved in the solvent inside the swollen microspheres. When the samples are heated up, these drug molecules are squeezed out together with the solvent during the collapse of the network. Similar effects have also been observed for other thermoresponsive systems.[28]

In this study, we have investigated PNIPAAM microgels as a sustained drug delivery vehicle for naltrexone. The microgel concentrations utilized in this study are quite high, and it is not possible to measure their sizes using light scattering methods due to multiple scattering. However, previous studies of the same microgels at lower concentrations show that the microgels are swollen and have an open structure at low temperatures.[29] As the temperature is increased the microgels shrink, and at temperatures above the LCST of PNIPAAM (ca. 32°C) large aggregates with a compact structure are formed.

The drug is loaded into the microgels at a low temperature. At these conditions, the microgels are swollen in the solvent, and this open structure should make it easier for the drug to diffuse into the microgels. The microgel suspensions have a low viscosity and can be easily administrated to the patient through injection. When the samples are heated up to body temperature, the microgels collapse and they also aggregate into larger structures.[29] A schematic illustration of a possible mechanism for loading of naltrexone into the PNIPAAM microgels is depicted in Figure 2. The conjecture is that both the more compact structure and the formation of larger aggregates at 37°C should slow down the diffusion of naltrexone out of the microgels. As naltrexone contains hydrophobic domains, associative interactions between the drug and the PNIPAAM microgels could also result in slower drug release rates.

Naltrexone is positively charged at physiological pH.[30] We have therefore also studied PNIPAAM microgels containing 1 mol % acrylic acid groups to see if the electrostatic interactions between the drug and the oppositely charged microgels can slow down the release rates. At low microgel concentrations, this low charge density was observed to have little effect on the contraction and aggregation behavior of the microgels in water.[29] Any changes in the observed release profiles are therefore mainly expected to be due to electrostatic interactions between the drug and the microgels.

As for any proposed drug delivery system, the toxicity of the formulation is of vital importance. We have therefore also conducted *in vitro* cytotoxicity studies on the microgels at the considered concentrations.

MATERIALS AND METHODS

The naltrexone (USPH1453504) was purchased from VWR International (West Chester, Pennsylvania, USA), and the chemicals used for making the buffer solution were purchased from Sigma–Aldrich (St. Louis, Missouri, USA).

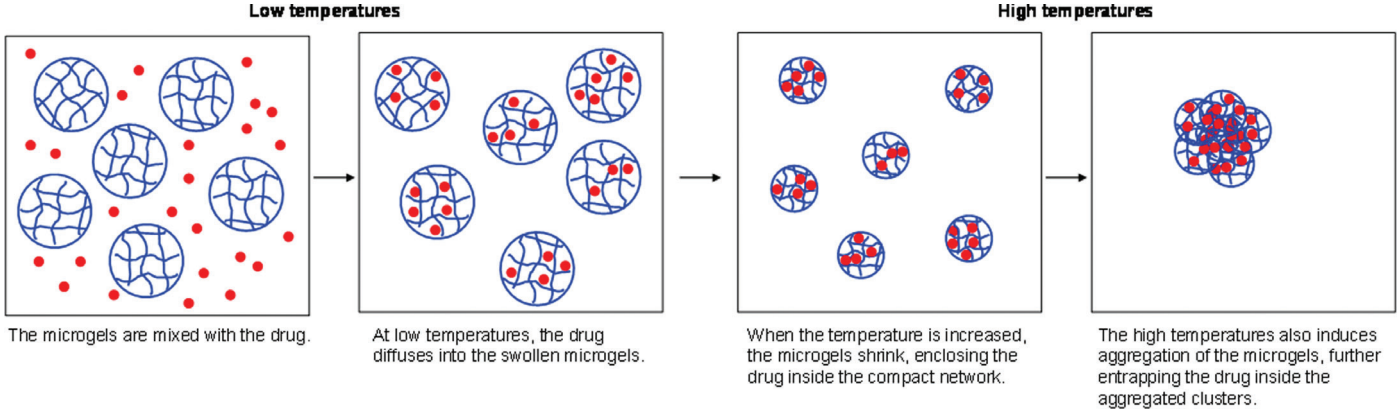

Figure 2. Schematic illustration of the proposed loading of naltrexone into the microgels.

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