European Journal of Pharmaceutical Sciences 76 (2015) 1–9

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Formulation and evaluation of biodegradable nanoparticles for the oral delivery of fenretinide

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ARTICLE INFO

Article history:
Received 16 December 2014
Received in revised form 27 March 2015
Accepted 27 April 2015
Available online 28 April 2015

Chemical compounds studied in this article:
Fenretinide (Pubchem CID: 5288209)

Keywords:
Fenretinide
Formulation
Biodegradable
Nanoparticles

ABSTRACT

Fenretinide is an anticancer drug with low water solubility and poor bioavailability. The goal of this study was to develop biodegradable polymeric nanoparticles of fenretinide with the intent of increasing its apparent aqueous solubility and intestinal permeability. Three biodegradable polymers were investigated for this purpose: two different poly lactide-co-glycolide (PLGA) polymers, one acid terminated and one ester terminated, and one poly lactide-co-glycolide/polyethylene glycol (PLGA/PEG) diblock copolymer. Nanoparticles were obtained by using an emulsification solvent evaporation technique. The formulations were characterized by differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and particle size analysis. Dissolution studies and Caco-2 cell permeation studies were also carried out for all formulations. Ultra high performance liquid chromatography coupled with mass spectrometry (UPLC/MS) and ultraviolet detection was used for the quantitative determination of fenretinide. Drug loading and the type of polymer affected the nanoparticles' physical properties, drug release rate, and cell permeability. While the acid terminated PLGA nanoparticles performed the best in drug release, the ester terminated PLGA nanoparticles performed the best in the Caco-2 cell permeability assays. The PLGA/PEG copolymer nanoparticles performed better than the formulations with ester terminated PLGA in terms of drug release but had the poorest performance in terms of cell permeation. All three categories of formulations performed better than the drug alone in both drug release and cell permeation studies.

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1. Introduction

Cancer is a major health concern worldwide. In the United States alone, the National Cancer Institute estimates 1,665,540 new cases of cancer and an accompanying 585,720 deaths in 2014 (Howlader et al., 2014). Correspondingly, a large number of compounds, both natural and synthetic, are screened for their ability to treat cancer. The National Institute of Health has estimated that it has screened over 80,000 compounds since 1990 (National Cancer Institute, 2006). The screenings have focused on compounds intended to treat specific cancers, such as lung (Daoud et al., 2014), breast (Koval et al., 2014), and prostate cancer (Ding et al., 2013), and they have focused on general anti-tumor effects. While these tests reveal anti-tumor effects, in most cases they do not reveal whether the compound may be useful for treating cancer from a practical standpoint. Many of these potential therapeutic agents have low intrinsic aqueous solubility (over 40% of all new substances are considered insoluble in water) (Savjani et al., 2012), have low bioavailability, or a combination of both. Therefore, the solubility of these compounds must be altered through chemical modification or through formulation. While chemical modification has been used for many years as a viable method for increasing a compound's solubility (Patel et al., 2009), this method presents a serious regulatory problem because these compounds may not be considered equivalent to the parent compound. For compounds which have been shown to have some effectiveness in treating cancer, chemical modification will certainly require reexamination of the new compound. Drug formulation does not inherently change the chemical state of the drug and may be considered, if successful, a superior method of modifying a drug's bioavailability. While many specific formulation approaches exist, the main modification methods used to date include modifying the local environment of the drug, reducing the drug's particle size, and encapsulating the drug in a soluble form (Savjani et al., 2012). The encapsulation method can include emulsions, self-emulsifying systems, or encapsulation in a rigid system. The

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http://dx.doi.org/10.1016/j.ejps.2015.04.024
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approach in this study focuses on drug encapsulation in a rigid nanoparticle system.

Nanoparticle formulations can enhance the bioavailability of poorly water soluble drugs by addressing drug dissolution and/or permeability. Tuning the physicochemical properties of nanoparticle carriers can alter the drug absorption, distribution, and elimination during gut transit (Li and Huang, 2008). Nanoparticles and microparticles can enhance the transcellular and paracellular transport of drugs in the GI tract (Gamboa and Leong, 2013; Mathiowitz et al., 1997). Particularly, carrier chemical composition, size, and morphology have been shown to be important determining factors of nanoparticle transport across the intestine following oral administration (Bhardwaj et al., 2006). Particle size, specifically in the nanometer range, can also improve drug dissolution for poorly water soluble drugs (Möschwitzer and Müller, 2007).

Poly lactide-co-glycolide (PLGA) polymers are biodegradable polymers which have been used for several years as a means of encapsulating drugs for controlled release and targeted delivery. They have low intrinsic toxicity, readily form encapsulating matrices, and degrade at a reasonable rate into harmless byproducts. PLGA and modified PLGA polymers have been used to form nanoparticles as a means of increasing the dissolution and bioavailability of poorly water soluble compounds (Khalil et al., 2013; Teixeira et al., 2005). In these formulations, the PLGA not only serves as a means of reducing the particle size of the drug but also controls the release rate of the drug itself and reduces its intrinsic toxicity (Imbuluzqueta et al., 2013; Swami et al., 2012). In addition, these polymers can be modified to alter a formulation's pharmacokinetic and biodistribution properties; polyethylene glycol (PEG)/PLGA copolymers can enhance the bioavailability of nanoparticles by increasing drug residence time (Khalil et al., 2013). Overall, the combination of increased dissolution of the compound, increased residence time, and reduced toxicity make a nanoparticle formulation of PLGA with the cancer drug fenretinide an attractive pharmaceutical formulation.

Fenretinide (N-4-hydroxyphenyl retinamide, 4-HPR) is a synthetic retinoid investigated for the treatment of breast cancer as early as 1979 due to is ability to accumulate in breast tissue (Moon et al., 1979). Its investigative use has expanded beyond its initial application in breast cancer to include cancer chemoprevention (Decensi et al., 2009), the treatment of macular degeneration (Mata et al., 2013), and the treatment of obesity-related type 2 diabetes (Graham et al., 2006). However, oral administration of fenretinide has shown poor therapeutic efficacy in clinical trials. This poor performance is most often attributed to its low bioavailability (Reynolds et al., 2000; Vaishampayan et al., 2005; Villablanca et al., 2011). The reformulation of fenretinide into a more readily soluble, and hence more bioavailable dosage form, is necessary to further its clinical utility. In this study, biodegradable fenretinide polymeric nanoparticles have been prepared and characterized. The release of fenretinide from the formulations and the *in vitro* intestinal cellular transport of fenretinide have been evaluated.

2. Materials and methods

2.1. Materials

The two PLGA polymers, Resomer RG502 (ester terminated) and Resomer RG502H (acid terminated), and the PLGA/PEG copolymer (RGP d50105) were obtained from Boehringer Ingelheim (Ingelheim am Rhein, Germany). Dichloromethane, ethanol, methanol, 30,000–70,000 MW polyvinyl alcohol (PVA), bovine serum albumin (BSA), HEPES, glucose, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium phosphate monobasic, potassium phosphate dibasic, sodium hydroxide, hydrochloric acid, formic acid, Hanks' Balanced Salt Solution (HBSS), and Lucifer yellow were obtained from Sigma Aldrich (St. Louis, MO). Fenretinide was purchased from R&D Systems, Inc. (Minneapolis, MN). All cell culture media were purchased from Thermo Fisher Scientific (Waltham, MA).

2.2. Preparation of nanoparticles

Two 7000–17,000 MW PLGA polymers, one ester terminated (Resomer RG502, R1) and one acid terminated (Resomer RG502H, R2), and one PLGA/PEG di-block copolymer (R3) were used as the polymers in the formulation of nanoparticles by an emulsification solvent evaporation technique. Nanoparticles of each of the three biodegradable polymers were prepared containing 0%, 5%, 10%, and 20% fenretinide (*w*/*w*) in the formulation (Table 1).

For each of the 12 formulations, 150 mg of polymer was dissolved in 1.5 mL of dichloromethane. After complete dissolution of the polymers, 95.6 μL of ethanol was added to the batch prior to the addition of the drug. This sequence of addition was used because the solubility of the drug in the dichloromethane/ethanol combination was much greater than in either of the solvents individually (Wischke et al., 2010). No drug was added to the blank formulations. Once the polymer and drug were dissolved, 1 mL of a 1% aqueous solution of PVA (30,000–70,000 MW) was added to the organic solution, and the mixture was sonicated for 20 s at 40 W with a Vibra-Cell™ ultrasonic probe (Sonic & Materials Inc., Newton, CT). This pre-emulsion was placed in an Emulsiflex C3 homogenizer (Avestin, Inc., Ottawa, Ontario, Canada) along with 20 mL of the 1% aqueous solution of PVA. The mixture was homogenized for 15 min at 15,000 psi. During the homogenization process, the mixture was circulated through a heat exchange coil immersed in an ice bath to prevent heating of the sample. The homogenized mixture was then transferred to a beaker containing 59 mL of the 1% PVA solution, the homogenizer was rinsed with 20 mL of the PVA solution which was transferred to the beaker, and the resulting mixture (100 mL) was magnetically stirred overnight to facilitate complete evaporation of the organic solvents. The product was centrifuged in an ultracentrifuge (Beckman Coulter Indianapolis, IN) at 35,000 rpm. The supernatant was removed, and the pellet was rinsed with deionized water and was centrifuged again. This process was repeated four times for complete removal of the PVA. The pellet was dispersed in 5 mL of deionized water and freeze-dried at −30 °C for 48 h. This process was repeated for each of the three polymers with the three drug

Table 1
Nanoparticle formulations.

Formulation designation[a]	Drug content (%)	Fenretinide (mg)	Polymer R1 (mg)[b]	Polymer R2 (mg)[c]	Polymer R3 (mg)[d]
R1-B	0	–	150	–	–
R1-5	5	7.89	150	–	–
R1-10	10	16.67	150	–	–
R1-20	20	37.50	150	–	–
R2-B	0	–	–	150	–
R2-5	5	7.89	–	150	–
R2-10	10	16.67	–	150	–
R2-20	20	37.50	–	150	–
R3-B	0	–	–	–	150
R3-5	5	7.89	–	–	150
R3-10	10	16.67	–	–	150
R3-20	20	37.50	–	–	150

[a] B = blank formulation; 5 = 5% drug loading; 10 = 10% drug loading; 20 = 20% drug loading.
[b] 7000–17,000 MW PLGA polymer ester terminated.
[c] 7000–17,000 MW PLGA polymer acid terminated.
[d] Di-block copolymer containing an ester terminated PLGA (10,000 MW) and 10% PEG (5000 MW).

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