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Crosslinked poly(vinyl alcohol) hydrogel microspheres containing dispersed fenofibrate nanocrystals as an oral sustained delivery system

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ABSTRACT

Poorly water soluble drugs often show low oral bioavailability due to their low dissolution rate. In the present study, cross-linked poly(vinyl alcohol) hydrogel microspheres were prepared. Nanocrystals of fenofibrate as a model of poorly water soluble drugs were dispersed within the poly(vinyl alcohol) hydrogel microspheres by swelling the microspheres with fenofibrate/methanol solution, followed by evaporation of the solvent methanol. The fenofibrate dissolution rate from the fenofibrate-loaded hydrogel microspheres in a medium simulating gastrointestinal tract conditions was much higher than the dissolution rate of free fenofibrate. And the dissolution assay also showed that fenofibrate released from the hydrogel in a sustained manner. *In vivo* pharmacokinetic study showed that the fenofibrate-loaded hydrogel microspheres showed much higher bioavailability compared with free fenofibrate, and similar bioavailability but longer half-lives and mean residence time and lower maximum plasma concentration compared with a marked fenofibrate formulation Lipanthyl® after oral administration in rats, indicating that the fenofibrate-loaded PVA hydrogel exhibited lower fluctuation in plasma drug concentration and more sustained release behavior.

1. Introduction

Oral route is the most common and preferable way of drug administration due to its non-invasion, convenience, good patient compliance and low medicine production costs. The oral products account for nearly 70% of the value in the USA pharmaceutical market [1]. The administration of lipophilic drugs via oral route, however, is limited owing to the low water solubility and slow dissolution rate in the gastrointestinal tract, resulting in low bioavailability. Up to 40% of the marketed drugs and approximately 70% of drugs coming from synthesis or high throughput screening are lipophilic drugs or poorly water soluble drugs, and most of them are defined as the biopharmaceutical classification system (BCS) class II drugs, which possess low water solubility but high permeability [2,3]. The oral bioavailability of poorly water soluble drugs especially BCS class II drugs can be enhanced by increasing the dissolution rate of the drugs in the gastrointestinal tract, as their bioavailability is limited by their dissolution rate.

Various formulation strategies have been investigated to improve the dissolution rate of poorly water soluble drugs, such as salt formation [4,5], nanoemulsions [6,7], micelles [8,9], liposomes [10,11], mesoporous microparticles or microspheres [12,13], nanocrystals [2,14] and amorphous solid dispersions [14,15]. Each of these formulation strategies has its own advantages and shortcomings, and is applicable for a special category of drugs with particular physicochemical properties. Among these approaches, nanocrystals and amorphous solid dispersions are the most successful strategies, and many products based on these two strategies are on the market [1,15,16]. The major advantages of nanocrystal formulations are high drug loading capacity, high bioavailability due to small particle sizes and easy scale-up for manufacture. The shortcomings of nanocrystal formulations include: (1) complex manufacturing; (2) agglomeration and crystal growth during storage; (3) high energy input; (4) selection of the type and amount of the stabilizer remaining empirical; and (5) lack of controlled release [17,18]. The drugs in amorphous solid dispersions show increased solubility over the crystalline form due to its high energy state (higher Gibbs' free energy) [19]. The limitations of amorphous solid dispersions include [15]: (1) The amorphous drug tends to undergoing crystallization during storage; (2) The selection of the carrier polymers and the optimization of the drug loading in the amorphous solid dispersions remain largely empirical and rely mainly on experimental screening.

Cross-linked polymeric microspheres or microparticles such as ion exchange resins have been clinically used as drug carriers for oral drug

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delivery and as sequestrants for disease-causing substances presented in the gastrointestinal fluids [20–23]. When given orally, these insoluble cross-linked polymeric microspheres or microparticles are confined to and non-absorbed in the gastrointestinal tract, resulting in no or minimal toxicity [20–23]. In our previous work [13], an oral sustained release formulation of methotrexate was prepared by adsorption of the drug into porous poly(styrene-divinylbenzene) microspheres. The oral formulations show the advantages of high loading capacity, high bioavailability, sustained release, low toxicity, low cost, and easy scale-up. In an our unpublished work, more hydrophobic drugs fenofibrate and megestrol acetate were loaded into porous poly(styrene-divinylbenzene) microspheres and porous poly(methyl acrylate-divinylbenzene) microspheres by adsorption of the drugs on the porous microspheres via a similar procedure as described previously [13]. In this unpublished work, we found that the release rate of the loaded drugs in media simulating gastrointestinal tract fluids was very low, and this observation can be attributed to the very strong hydrophobic effects and $\pi-\pi$ stacking between the drug molecules and the surface of the porous microspheres [13]. In the present work, an alternative strategy for enhancing bioavailability of poorly water soluble drugs, using fenofibrate as a model drug, was presented. Fenofibrate, a blood-lipid lowering agent, has a strong ability on decreasing plasma cholesterol, glycerin trimyristate concentration, and it can also increase the plasma high density lipoprotein (HDL) concentration. Fenofibrate is a typical lipophilic BCS class II drug with very low solubility in water (5.5 μg/mL [24]), which results in a low oral bioavailability [25–27]. In our this strategy, in situ formed fenofibrate nanocrystals were dispersed in cross-linked poly(vinyl alcohol) (PVA) hydrogel microspheres. The network confinement in the PVA hydrogel prevented aggregation or crystal growth of drug nanocrystals. Small size of the nanocrystals resulted in high dissolution rate. This strategy is applicable for drugs soluble in methanol, in which the hydrogel is swellable. The advantages of the strategy include easy for preparation, low cost, same or similar preparation process for different drugs and sustained release.

2. Materials and methods

2.1. Materials

Fenofibrate (98%) was purchased from TCI (Shanghai) Development Co., Ltd. Vinyl acetate was obtained from Beijing HWRK Chemical Co., Ltd. Lipanthyl® was a product of Abbott Laboratories. Sodium taurocholate (> 99.9%) was provided by Tianjin Mai Abram Biological Technology Co. Ltd. 2,2′-Azobis(isobutyronitrile) (AIBN, > 99%) from Tianjin Chemical Company, China) was recrystallized from ethanol before use. Triallyl isocyanurate (TAIC, > 98.5%) was supplied by Tianjin Nankai Hecheng Science & Technology Co., Ltd. Sodium oleate (> 99.5%) was from Tianjin Yuanli Chemical Co. Ltd. Fenofibric acid (> 98%) was from Ark Pharm. Naproxen (> 99.9%) was purchased from Shanghai Dibai Chemical Technology Co., Ltd. Deionized water was used in all experiments.

2.2. Preparation of cross-linked poly(vinyl alcohol)

Cross-linked poly(vinyl acetate) microspheres were prepared first by a suspension free radical polymerization procedure. As an example, the preparation of microspheric copolymer of vinyl acetate and TAIC with 3% cross-lining degree was described as following. In a 500 mL round-bottomed three-neck glass flask equipped with a mechanical stirrer and a condenser, an organic phase consisted of vinyl acetate (38.8 g), TAIC (1.2 g) and AIBN (0.3 g) was suspended in an aqueous phase consisted of distilled water (200 mL), NaCl (50 g) and gelatin (1 g). While the flask was purged with nitrogen, the mixture was stirred to give a suspension of oil droplets with a suitable size in the aqueous phase. The polymerization was then carried out at 65 °C for 12 h. The resulting microspheres were washed with hot water thoroughly, extracted with acetone in a Soxhlet apparatus for 10 h and finally dried under vacuum. The prepared cross-linked poly(vinyl acetate) microspheres diameter range of 38–75 μm (200–400 mesh) were collected by sieving and denoted PVAc-3-1. Similarly, cross-linked poly(vinyl acetate) microspheres with 3% cross-linking degree and diameter range of 180–250 μm (60–80 mesh) were prepared and denoted PVAc-3-2. Cross-linked poly(vinyl acetate) microspheres with 6% cross-linking degree were prepared in the same way and denoted similarly PVAc-6-1 and PVAc-6-2 with diameter ranges of 38–75 μm (200–400 mesh) and 180–250 μm (60–80 mesh), respectively.

Cross-linked poly(vinyl alcohol) microspheres were prepared by saponification of the as-prepared cross-linked poly(vinyl acetate) microspheres. In a typical process, cross-linked poly(vinyl acetate) microspheres (20 g) were suspended in a turbid liquid of 5% sodium hydroxide in methanol (400 mL) and the mixture was stirred at 40 °C for 12 h. The microspheres were then rinsed thoroughly with water and ethanol, followed by drying under vacuum. Cross-linked poly(vinyl alcohol) microspheres prepared from PVAc-3-1, PVAc-3-2, PVAc-6-1 and PVAc-6-2 were denoted PVA-3-1, PVA-3-2, PVA-6-1 and PVA-6-2, respectively.

2.3. Swelling studies

A PVA microsphere sample was loaded in a cylinder and the microsphere bed volume was recorded. Deionized water was added to the cylinder to completely immerse the microspheres. The swollen microsphere bed volume was then recorded at various time points. After the bed volume reached a plateau, the swollen microspheres were filtered using a sintered glass funnel and dried under vacuum. The water content was calculated from the difference between the swollen microsphere weight before and after drying.

The water-swollen microspheres were suspended in excess methanol and the mixture was stirred for 6 h or longer. After filtration, the hydrogel was re-suspended in methanol as shown above and the procedure was repeated for 4 times. The methanol content of the methanol-swollen microspheres was measured in the same way as in measuring water content shown above.

2.4. Loading of fenofibrate into PVA microspheres

The as prepared PVA microspheres (0.5 g) were swollen in water for 2 h. The water in the swollen PVA microspheres was replaced with methanol. After filtration using a sintered glass funnel, the methanol-swollen PVA microspheres were suspended in a solution of fenofibrate (400 mg) in methanol (1 mL) at 60 °C and the mixture was shaken for 12 h at the same temperature. The resulting microspheres were filtered and dried under vacuum.

2.5. Determination of fenofibrate loading capacity

The fenofibrate loading capacity was analyzed by the following procedure. A sample of fenofibrate-loaded PVA microspheres was suspended in a certain volume of methanol and the mixture was stirred until the absorption of the supernatant at 286 nm unchanged. The fenofibrate concentration in the supernatant was determined by spectrophotometry at 286 nm using a standard calibration curve experimentally obtained with the same solvent. The fenofibrate loading capacity was expressed as the amount of loaded fenofibrate divided by the amount of dry drug-free PVA microspheres.

2.6. In vitro release assay

In vitro release was carried out in FeSSIF (fed-state simulated intestinal fluid, pH 6.7), which was composed of sodium taurocholate (7.5 mM), sodium oleate (30 mM), sodium dihydrogen phosphate (7.3 mM) and disodium hydrogen phosphate (2.6 mM) based on a