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Methotrexate-loaded porous polymeric adsorbents as oral sustained release formulations

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ABSTRACT

Methotrexate as a model drug with poor aqueous solubility was adsorbed into porous polymeric adsorbents, which was used as oral sustained release formulations. In vitro release assay in simulated gastrointestinal fluids showed that the methotrexate-loaded adsorbents showed distinct sustained release performance. The release rate increased with increase in pore size of the adsorbents. *In vivo* pharmacokinetic study showed that the maximal plasma methotrexate concentrations after oral administration of free methotrexate and methotrexate-loaded DA201-H (a commercial porous polymeric adsorbent) to rats occurred at 40 min and 5 h post-dose, respectively; and the plasma concentrations decreased to 22% after 5 h for free methotrexate and 44% after 24 h for methotrexate-loaded DA201-H, respectively. The load of methotrexate into the porous polymeric adsorbents not only resulted in obvious sustained release, but also enhanced the oral bioavailability of methotrexate. The areas under the curve, AUC_{0-24} and $AUC_{0\text{-inf}}$, for methotrexate-loaded DA201-H increased 3.3 and 7.7 times, respectively, compared to those for free methotrexate.

1. Introduction

It has been studied extensively in the development of drug delivery systems to optimize the drug therapeutics and to improve patient compliance. An ideal drug delivery system should deliver a drug to the target site for absorption or action at a controlled rate over a period of time. The controlled release is usually achieved by adding other ingredients (excipients) or loading the drug to a carrier in a formulation. Ion exchange resins have been used as functional excipients (e.g., taste masking agent, drug stabilizing agent, and sustained release agent) and also as active drug ingredients (e.g., cholestyramine for cholesterol lowering) in oral formulations and some of these formulations have been clinically used [1–8]. The limitation of using exchange resins as drug carriers is that the drugs must contain ionizable groups. In addition, polymer (e.g., Eudragit polmers) coating films on the surface of the ion exchange resins are often needed to achieve sustained release [4–7].

Porous polymeric adsorbents are comprised of crosslinked polymer beads with porous structure. They usually have the same polymeric matrix as the ion-exchange resins but without ionizable groups. Various porous polymeric adsorbents are commercially available and they are widely used in a variety of applications such as in the adsorption of organic compounds from aqueous solutions [9–12]. Porous polymeric adsorbents have advantages such as high specific surface areas and tunable pore sizes, variable surface hydrophobicity/hydrophilicity, which can be controlled by selection of monomers in the polymerization or by post-chemical modification, and availability in low cost and in large quantity. A variety of functional groups can also be introduced onto the surfaces of porous polymeric adsorbents [13]. The driving forces for the adsorption of organic compounds from aqueous media include hydrophobic effect, π-π stacking, and hydrogen bonding [9,14–17].

Methotrexate (MTX) is an antimetabolite and antifolate drug that interferes in the formation of DNA, RNA and proteins. It is widely used for the treatment of malignancies (e.g., childhood acute lymphocytic leukemia, osteosarcoma, lung cancer, and breast cancer) and in the therapy of auto-immune diseases (e.g., rheumatoid arthritis, psoriasis, and lupus) [18,19]. MTX can be administered clinically via different routes, such as oral, intravenous, subcutaneous and/or intra-muscullar administration routes [20]. And MTX is one of a few chemotherapy agents that have been clinically applied via oral administration route [21]. The clinical efficacy of MTX is often compromised by toxic dose-related side effects, short half-life in the bloodstream, and low bioavailability due to its poor water solubility and permeability [20,22,23]. Many MTX delivery systems suitable for oral administration have been reported, including MTX-loaded mesoporous silica nanoparticles

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[24,25], solid lipid nanoparticles [26], self microemulsifying delivery system [27], proteinoid microspheres [28], gelatin microspheres [29], beta-casein nanovehicles [30], chitosan microspheres [31], and crosslinked guar gum microspheres [32]. The problems existed in these oral sustained release systems include: (1) the release is often non-ideal sustained release, i.e., either very slow release (e.g., the time needed for release of 50% of the loaded MTX in media simulating gastrointestinal fluids are several days [29], which are much longer than the residence time of the formulations in the gastrointestinal tract), or too rapid release [24–28,31], and (2) toxic crosslinking agent glutarladehyde, which can be released in gastrointestinal tract, was used [29,32].

In this paper, MTX was loaded into porous polymeric adsorbents and the MTX-loaded adsorbents were tested as oral sustained release formulations. The loading was performed by the adsorption of MTX from an aqueous medium into porous polymeric adsorbents. The process is green, reproducible and easy up-scalable. This MTX oral sustained release formulation overcomes the disadvantages of the MTX oral formulations mentioned above. To our best knowledge, there is no study on using porous polymeric adsorbents as carriers for oral drug release.

2. Materials and methods

2.1. Materials

MTX (90%) was purchased from Shengbaolai Biotechnology Co., Ltd. (Hubei, China). Porous polymeric adsorbents ADS-5 and H-103 were purchased from Tianjin Nankai Hecheng Science & Technology Co., Ltd. (Tianjin, China). Porous polymeric adsorbent DA201-H was purchased from Jiangsu Suqing Water Treatment Engineering Group (Jiangyin, China). Polymeric adsorbents were sieved to a particle diameter range of 0.25–0.43 mm (40–60 mesh), soaked in ethanol for 24 h and then washed by de-ionized water before use.

2.2. Porosity measurement

Nitrogen adsorption/desorption isotherms of porous polymeric adsorbents were measured at 77 K on an ASAP 2020 Physisorption Analyzer (Micromeritics). Samples were degassed for 10 h at 90 °C before the measurements. Porosities of the porous polymeric adsorbents were computed using the Micromeritics software package associated with the instrument.

2.3. Preparation of MTX-loaded polymeric adsorbents.

MTX-loaded polymeric adsorbents were prepared via adsorption of MTX into polymeric adsorbents from aqueous media. Typically, MTX (60 mg) and H103 (wet, 300 mg) were dispersed in water (40 mL) and the mixture was stirred at 40 °C for 72 h. The aqueous phase was poured out and the polymeric adsorbent was washed several times with water.

2.4. Determination of MTX loading capacities.

A certain amount of dry MTX-loaded adsorbent was dispersed in a given volume of ethanol/100 mM aqueous NaOH solution (1/2, *v*/*v*) and the mixture was shaken for 8 h. MTX concentration in the supernatant was determined by spectrophotometry at 302 nm using a standard calibration curve experimentally obtained with the same solvent. MTX loading capacity was obtained by dividing the total quantity of MTX in the supernatant by the quantity of the adsorbent used.

2.5. In vitro release assay

The in vitro release process was performed as described below. A MTX-loaded adsorbent sample (30 mg) was dispersed in a medium simulating the pH value of gastric fluid (0.025 M HCl, pH 1.6, 30 mL) and the mixture was shaken at 37 °C for 2 h. The release medium was then replaced by a medium simulating the pH value of intestinal fluid (30 mM phosphate buffer, pH 6.8, 30 mL) and the mixture was shaken at 37 °C for 34 h. At the predetermined time points during the release process, 3 mL of the release medium was taken for MTX concentration analysis and 3 mL of the same fresh release medium was added. MTX concentration was analyzed by spectrophotometry at 302 nm.

2.6. In vivo plasma pharmacokinetic study

Sixteen Wistar rats (male, 250 ± 50 g) were divided into four groups (4 per group). All the animals were fasted but allowed free access to water for 12 h before the experiment. The test samples (free MTX, MTX-loaded H103, MTX-loaded ADS-5, and MTX-loaded DA201-H) were intragastrically administrated to the rats at a MTX dose of 60 mg/kg by gavage. At predetermined time points, 400 μL of blood samples were collected from each animal via the saphenous vein. The blood samples were centrifuged at 10,000 rpm for 2 min and the plasma samples were collected. All samples were stocked at −20 °C. To each of plasma samples (200 μL), 40 μL of trichloroacetic acid (2 M in ethanol) was added and the mixture was vortexed for 2 min, and then centrifuged at 10,000 rpm for 15 min. Finally, 20 μL of the supernatant was analyzed by HPLC to determine MTX concentration. HPLC was performed using a Shimadzu LC- 10AT HPLC system (Shimadzu, Japan) with a reverse phase column (Phenomenex Luna 5u C18(2) 100A, 250 × 4.6 mm, 5 μm). The mobile phase was comprised of acetonitrile-buffer (0.01 M KH_2PO_4–0.02 M tetramethylammonium chloride, pH 2.5) (10/90, v/v) and an isocratic flow rate of 1 mL/min was used. The detection wavelength was 313 nm.

3. Results and discussion

3.1. MTX loading into porous polymeric adsorbents

Poly(styrene-divinylbenzene)-based porous polymeric adsorbents were mostly applied polymeric adsorbents. They are often used to adsorb hydrophobic molecules especially those with delocalized π-electrons from aqueous solutions by hydrophobic effect/π-π stacking. MTX, having a similar chemical structure to folic acid, is a hydrophobic compound with delocalized π electrons in the pteridine and benzene rings. It is predicted that MTX can be adsorbed into poly(styrene-divinylbenzene)-based porous polymeric adsorbents from aqueous media via hydrophobic effect and π-π stacking. Thus we selected poly(styrene-divinylbenzene)-based porous polymeric adsorbents as carriers of MTX in this work. Three commercially available porous polymeric adsorbents, H103, ADS-5 and DA201-H, which have the same poly(styrene-divinylbenzene) matrix but different pore structures, were used as carriers of MTX. The different pore structures especially pore sizes are expected to have effects on the drug release rate. Table 1 presented the porosities of these adsorbents provided by the suppliers. Due to these adsorbents were from

Table 1
Parameters of porous polymeric adsorbents.[a]

Adsorbent	Parameters provided by the suppliers		Parameters measured	
	S (m^2/g)	D (nm)	S[b] (m^2/g)	D[c] (nm)
H103	900–1000	8.4–9.4	1371	5.4
ADS-5	520–600	25–30	558	8.6
DA201-H	>800	6–8	897	7.1

[a] S, specific surface area, D, average pore diameter.
[b] Brunauer-Emmett-Teller (BET) specific surface area obtained from nitrogen adsorption isotherms.
[c] Barrett-Joyner-Halenda (BJH) average pore diameter obtained from nitrogen adsorption isotherms.