Biomedicine & Pharmacotherapy 78 (2016) 14–22

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Original article

Preparation and pharmaceutical evaluation of acetaminophen nano-fiber tablets: Application of a solvent-based electrospinning method for tableting

Mami Hamori[a], Kana Nagano[a], Sayaka Kakimoto[a], Kazumasa Naruhashi[a], Akiko Kiriyama[b], Asako Nishimura[a], Nobuhito Shibata[a,*]

[a] Department of Biopharmaceutics, Faculty of Pharmaceutical Science, Doshisha Women's College of Liberal Arts, Kyotanabe, Kyoto 610-0395, Japan
[b] Department of Pharmacokinetics, Faculty of Pharmaceutical Science, Doshisha Women's College of Liberal Arts, Kyotanabe, Kyoto 610-0395, Japan

ARTICLE INFO

Article history:
Received 27 October 2015
Accepted 21 December 2015

Keywords:
Electrospinning
Nano-fibers
Methacrylic acid copolymer S
Acetaminophen
Pharmacokinetics
Controlled release

ABSTRACT

In this study, we developed nano-fiber-based tablets with acetaminophen (AAP; Log P_{ow} = 0.51) for controlled-release delivery systems and evaluated *in vitro* drug dissolution and *in vivo* pharmacokinetics in rats. Nano-fibers made from methacrylic acid copolymer S (MAC; EUDRAGIT® S100) and containing AAP were prepared using a solvent-based electrospinning (ES) method. *In vitro* dissolution rate profiles of AAP showed tableting pressure-dependent decreases and pH-dependent increases. The results of tablet tracking by X-ray irradiation showed tablets based on MAC nano-fibers did not disintegrate in the upper intestinal lumen and had the properties of a long-term-acting tablet. In addition, the *in vitro* release profiles of AAP from nano-fiber tablets prepared by dissolving MAC with AAP (NFT), nano-fiber tablets prepared by adsorbing AAP to drug-free MAC nano-fibers (NFT_{adso}), and tablets prepared by adsorbing half the amount of AAP to MAC nano-fibers containing the remaining amount of AAP (NFT_{half}) showed independent controlled-release aspects of AAP compared with physical mixture tablets (PMT). *In vivo* pharmacokinetic studies in rats after intraduodenal administration of 14 mg/rat AAP in NFT, NFT_{adso}, and NFT_{half} demonstrated that all these tablets based on MAC nano-fibers showed sustained-release profiles compared with PMT, and showed ultra-sustained release properties for AAP. These new tablets based on MAC nano-fibers did not disintegrate in the intestine in the lower pH region, and the tablets could regulate the release of AAP in a pH-dependent manner. The ES method is a useful technique to prepare nano-fibers and showed promising results as an oral delivery system for sustained-release regulation.
© 2015 Elsevier Masson SAS. All rights reserved.

1. Introduction

The electrospinning (ES) method has being actively developed and studied in the textile industry, where the ES apparatus consists of a power supply, nano-fiber collection plate, and syringe pump to push out the polymer solution [1,2]. A high voltage (kV) is applied between the capillary tip of the syringe and the nano-fiber collection plate. On the nano-fiber collection plate, nano-fibers form by vaporizing the solvent to make the polymer solution form a superfine thread. Moreover, the ES method is capable of producing of nano-fibers at room temperature; therefore, it allows nano-fibers to be made from natural or artificial polymers, proteins and materials that are vulnerable to heat degradation. In this way, because of the simplicity of the ES method, significant progress has been made in biomedical applications in the last few years, such as tissue engineering [3,4], wound dressings and healing [5,6], drug-delivery systems (DDSs) [7,8], nutraceutical delivery [9,10], and nano-fiber-supported enzyme catalysis [11,12]. In the field of pharmaceutics, it is predicted that controlled-release DDSs or tissue-targeting could be available if drug-loaded nano-fibers can be obtained. In particular, several biodegradable polymers, such as poly-(ε-caprolactone) [13], whey protein [14], polycaprolactone [8], gelatin [15], poly(lactic acid) [7], chitosan/alginate [16], polylactic acid or polylactic-*co*-glycolic acid [17] have been used for preparing nano-fibers including bioactive drugs for DDS formulations.

On the other hand, there are several problems to overcome with the ES apparatus to prepare nano-fibers, such as the risk of electrical shock, difficulty in peeling away of nano-fibers, inadequate mass for manufacturing, and difficulty in the condition settings for the purpose of biomedical applications. Essentially, the basic principle of ES is to apply an optimal high voltage to the

* Corresponding author. Fax: +81 774 65 8498.
E-mail address: nshibata@dwc.doshisha.ac.jp (N. Shibata).

http://dx.doi.org/10.1016/j.biopha.2015.12.023
0753-3322/© 2015 Elsevier Masson SAS. All rights reserved.

polymer solution that overcomes the surface tension of the polymer solution, and to induce the polymer jet formation [18]. Beside the voltage, the viscosity, polymer molecular weight [19], surface tension [4], conductivity, and dipole moment as a solution factors [20–23], flow rate, distance between electrodes, needle shape or size, and collector composition as processing parameters [4,24–26], and ambient parameters including temperature, humidity, and air flow [4] all affect the diameter or shape of nano-fibers. It is, therefore, necessary to design an optimal equipment for ES and to determine the exact ES parameters to obtain uniform nano-fibers.

In our previous report [27], we constructed an ES apparatus and examined various operating conditions for the ES apparatus using methacrylic acid copolymer S (MAC, trade name Eudragit® S100), which is an enteric polymer commonly used as a pharmaceutical additive, to achieve the controlled drug-delivery. In the case of MAC, besides the viscosity of polymer solution and the diluting organic solvent, there were no factors to alter the mean diameter of MAC nano-fibers within the studied range. Moreover, as a new formulation based on MAC nano-fibers, we prepared MAC nano-fiber matrix-supported oral capsules for uranine and nifedipine, and evaluated *in vitro* dissolution and *in vivo* pharmacokinetics in rats [28].

In this study, utilizing the solvent-based ES method, we prepared tablets based on MAC nano-fibers including acetaminophen (AAP) as a controlled-release delivery system, and then evaluated the *in vitro* drug dissolution profiles and *in vivo* pharmacokinetics in rats.

2. Materials and methods

2.1. Materials and preparation of solutions

Methacrylic acid copolymer S (Eudragit S100®) was kindly supplied by Evonik Degussa Japan Co., Ltd. (Tokyo, Japan). 4′-hydroxyacetanilide (acetaminophen: AAP, $\mathrm{Log}\,P_{ow} = 0.51$) was purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). All other chemicals and reagents were of analytical grade and were used without further purification. A standard stock solution of AAP was prepared by dissolving in acetone at a final concentration of 500 μg/mL, and calibration standards were prepared by diluting this standard stock solution to various concentrations. The calibration curve samples were prepared by adding known amounts of working standards to plasma at a volume ratio of 1:10.

2.2. Preparation of nano-fibers including acetaminophen by solvent-based electrospinning

Nano-fibers including AAP were prepared by the solvent-based ES method using the apparatus described previously [27]. In brief, Fig. 1a shows schematic representation of the ES apparatus equipped with a high-voltage supplier, syringe with a syringe pump and nano-fiber collection plate.

The polymer solutions including AAP was prepared by mixing MAC and the drug in acetone to final concentrations of AAP and MAC of 2.0% (w/v) and 12.5% (w/v), respectively. The polymer solution including AAP was extracted into a syringe with a stainless-steel needle (14 gauge), and the syringe was fixed at a designated position in the ES apparatus. A nano-fiber collection plate made from copper with a conductor-rod of stainless steel was negatively charged and a grounding wire was connected to the collection plate. The voltage applied between the needle and the

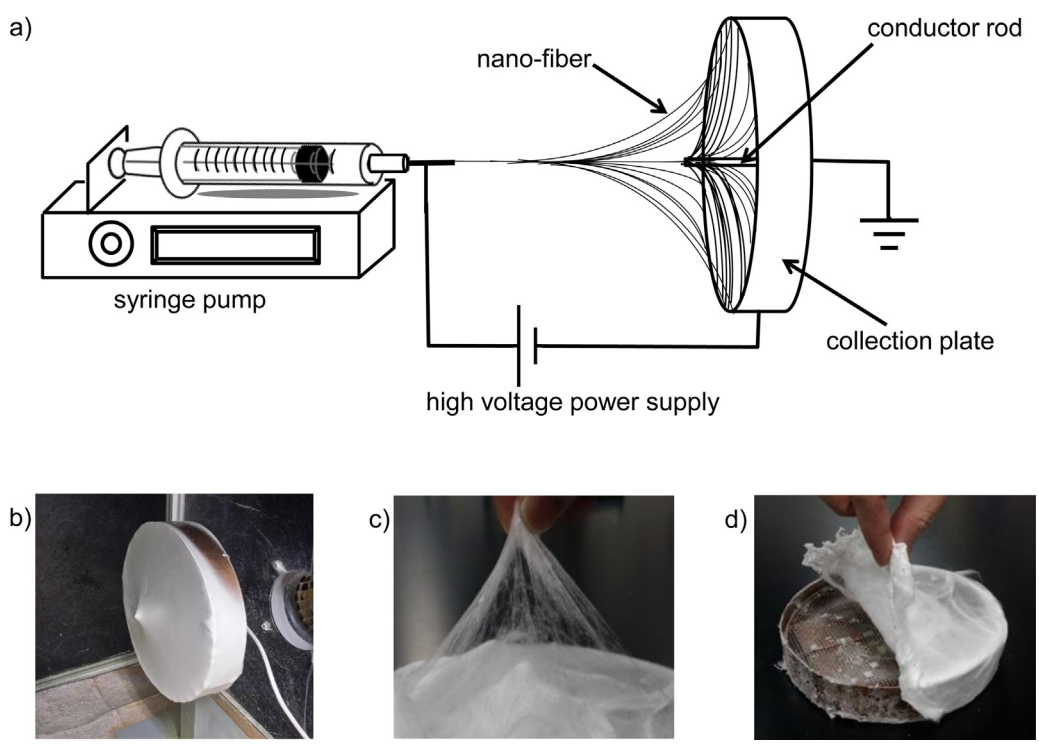

Fig. 1. Construction of ES apparatus and nano-fiber formed at collection plate: The ES method applies high voltage to a capillary tip and allows a polymer solution to extrude and form nano-fibers. (a) Overall construction of the device, (b) state at the just end of polymer extrusion, (c) MAC nano-fiber formed at collection plate, (d) pealing out nano-fiber sheet after extrusion. The MAC concentration in acetone, the voltage between cathode and anode, the distance between them and the flow rate of MAC solution were set at 12.5%(w/v), 25 kV, 10 cm and 10 mL/h, respectively.

Download English Version:

https://daneshyari.com/en/article/2523900

Download Persian Version:

https://daneshyari.com/article/2523900

Daneshyari.com