Preparation of Dendritic Mesoporous Silica Nanomaterials Loaded with Toosendanin-Fumaracetin and its Anti-Peripheral Pain Study

Jingjing Tang, Xilong Qiu*

University of Tianjin Traditional Chinese Medicine, Tianjin 301600, China

1943927749@qq.com*

Abstract. Objective: A novel dendritic mesoporous silica nanomaterials (DMSN) was prepared and the traditional Chinese Medicine Component "Toosendanin-Tetrahydropalmatine" was loaded into DMSN in order to improve the solubility of Tetrahydropalmatine B, reduce the toxicity of Toosendanin, and enhance the anti-peripheral pain effect of the traditional. Chinese Medicine "Toosendanin-Tetrahydropalmatine" through preliminary pharmacodynamics study. Methods: DMSN were prepared using the sol-gel method and characterized by scanning electron microscope (SEM) and Fourier Transform Infrared Spectrometer (FT-IR). The preliminary study of the anti-peripheral pain pharmacodynamics of the drug-loaded system in mice was evaluated by the hot plate method. Results: The prepared DMSN has an excellent spherical shape in SEM, the size distribution of the DMSN is about 200nm, the size distribution is uniform, and the dispersion is good. The infrared results showed that the synthesized DMSN had organic functional groups and chemical structures. Compared with the control group, the pain threshold of DMSN loaded with the Toosendanin-tetrahydropalmatine group was prolonged by 45 seconds. Conclusion: The synthesized DMSN loaded with Toosendanin and Tetrahydropalmatine could release stably and continuously and had the effect of extending the pain threshold of mice. Therefore, DMSN drug delivery system has potential value in improving the bioabsorption of dangerous drugs and enhancing the bioavailability of poorly soluble drugs.

Key words: DMSN; Toosendanin; Tetrahydropalmatine; Analgesic effect.

1. Introduction

Historically,the former president of the American Pain Society,James Campbell,introduced the idea of “Pain as the 5th Vital Sign” (P5VS) in 1996. Pain can impact physical, emotional and social functioning for the individuals living with pain, often resulting in significant personal and societal burden [1,2]. Opioids have obvious analgesic effect and have central and peripheral analgesic effects. However,because their analgesic effect is related to opioid receptors, they are prone to dependence.Due to the efficacy in reducing the pain, non-steroidal anti-inflammatory drugs (NSAIDs) are aslo the most popularly used medicines,However, it also has certain side effects, which will cause certain damage to the liver, kidney and other important organs[3,4].

Traditional Chinese medicine has a good prospect in the treatment of pain.Jinlingzi Powder is made up of 1:1 compatibility of Fructus Toosendan and Rhizoma Corydalis, and is a representative formula suitable for various pain conditions[5]. The main pharmacologically active ingredient ofFructus Toosendan is Toosendanin[6,7]. According to modern pharmacological research, Toosendanin has insecticidal, antibacterial and anti-inflammatory effects and has significant analgesic effects[8]. However, Toosendanin has certain side effects, such as hepatotoxicity, pregnancy toxicity, muscle weakness and respiratory depression, which limit its clinical application[9]. Rhizoma Corydalis is the dry tuber of the Papaveraceae plant Rhizoma Corydalis[10]. Which has a perennial herb with a 300-year cultivation history and it is a typical medicinal raw material that goes through processing and compatibility to achieve a better therapeutic effect. Its main active ingredient is Tetrahydropalmatine, which has a good analgesic effect[11- 14]. And also commonly used to treat other various medical diseases, such as insomnia, cardiovascular disease, hypertension, gastric ulcer, cancer and inflammation The analgesic effect can reach 40% of morphine,

and the addiction rate is much lower than that of morphine drugs. Still, its clinical application is also limited due to its poor stability and almost insoluble in water and alkaline solutions[15]. Nanoparticles have been widely used for more specific and effective treatment of complex diseases.The conventional mesoporous silica nanoparticles (CMSN) has proved to be effective treatment for various diseases. However, the clinical application of CMSN is limited, partly due to its potential cytotoxicity. Dendritic mesoporous silica nanomaterials (DMSN)

is a novel porous material with three-dimensional open dendritic framework structure[16,17]. The central radiative pore structure possessed by DMSN is favorable for the delivery of drug components along the major radiative pore channels and has mild properties such as better biocompatibility and low toxicity,which have attracted considerable attention for its application in the field of drug delivery and biomedicine.Thus,this nanomaterial is a novel and promising carrier platform for clinical applications[18]. In this study, DMSN was prepared for loading traditional Chinese medicine component "Toosendanin- Tetrahydropalmatine" to investigate whether it could enhance the pharmacological effects of "Toosendanin-Tetrahydropalmatine" against peripheral pain in mice.

2. Methods

First, the maximum absorption wavelengths of Toosendanin and Tetrahydropalmatine were measured using an ultraviolet photometer and a standard curve was drawn. Secondly, the DMSN carrier was prepared by the sol-gel method, and then the samples were loaded and determined. Thirdly, DMSN was characterized by a projection electron microscope, and the pain threshold of DMSN in mice was tested.

3. Results

3.1. TEM characterization of DMSN

To evaluate whether the prepared dmsn material was dendritic mesoporous silica nanospheres, we characterized the material using TEM. As shown in Figure 1 (A), the dendrimeric mesoporous silica nanospheres (DMSN) prepared in this paper have three-dimensional central radiation pore channels and multi-level pore structures. When its particle size was analyzed, it was found that Figure 1 (B), the prepared DMSN support had a better spherical shape,the size distribution was relatively uniform, and the size was distributed around 200 nm.

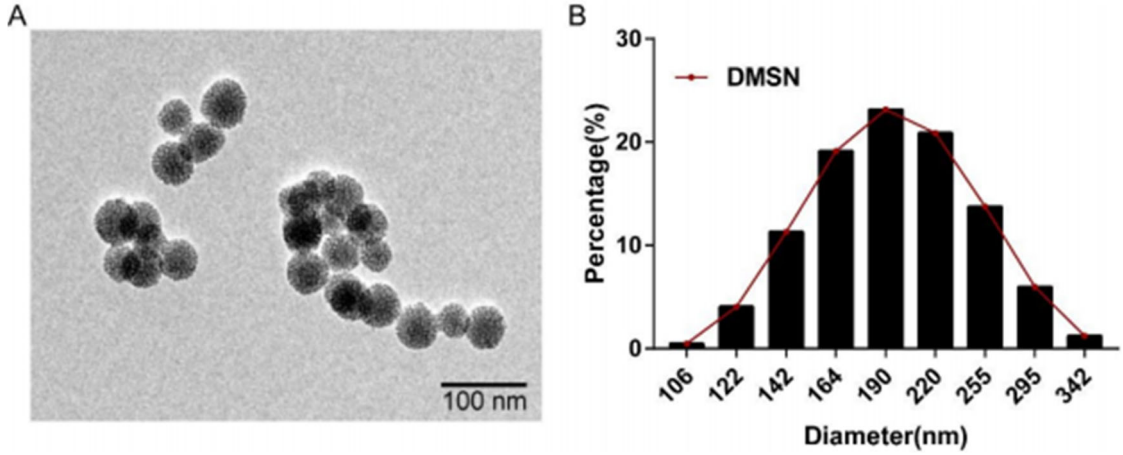

Figure 1. TEM image (A) and size distribution (B) of DMSN

3.2. Infrared absorption characteristic spectrum of DMSN

To further evaluate whether the DMSN was successfully synthesized, we utilized the Fourier Transform Infrared Spectrometer (FT-IR) to measure the DMSN materials. Result as shown in Figure 2, the bending vibration absorption peak of Si-O-Si bond

appeared at 465 cm- 1, the antisymmetric stretching vibration peak originated from Si-O bond appeared at 1080 cm- 1, while the typical -OH absorption characteristic peak at 3440-3460 cm- 1 was Si-OH and adsorbed water molecules from the surface of DMSN. The infrared result indicated that the dendritic mesoporous silica nanomaterials synthesized this time possessed the organic functional groups that should be available as well as the chemical structure.

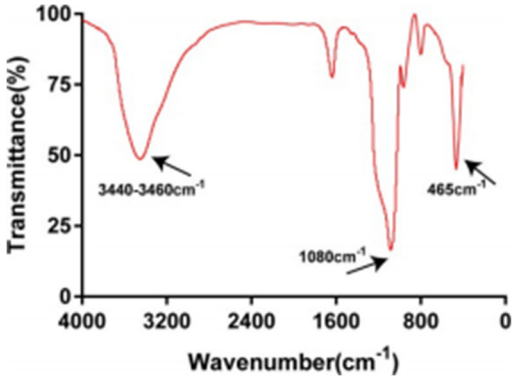

Figure 2. Fourier infrared spectrogram of DMSN

3.3. Effects of DMSN loaded Toosendanin-Tetrahydropalmatine on pain thresholds in hot plate induced mice

We performed a mouse hot plate pain threshold experiment to evaluate the anti-peripheral pain efficacy after DMSN loading Toosendanin-Tetrahydropalmatine. The results are shown in Figure 3, after administration for 0.5 h, 1 h, 2 h, and 3 h, DMSN@Drugs Group (DMSN loaded with Toosendanin- Tetrahydropalmatine) the pain threshold value increased gradually and exceeded 60 s at 3 h. Compared with Drugs group (only Toosendanin-Tetrahydropalmatine), vehicle group (normal saline) or DMSN group (only DMSN), the slope of the pain threshold curve of DMSN@Drugs group was the largest, and all had statistical differences (P values less than 0.05). This result indicates that after Toosendanin- Tetrahydropalmatine is entrapped in DMSN, it can prolong the pain threshold and improve the anti-peripheral pain efficacy of Toosendanin-Tetrahydropalmatine in mice induced by the hot plate.

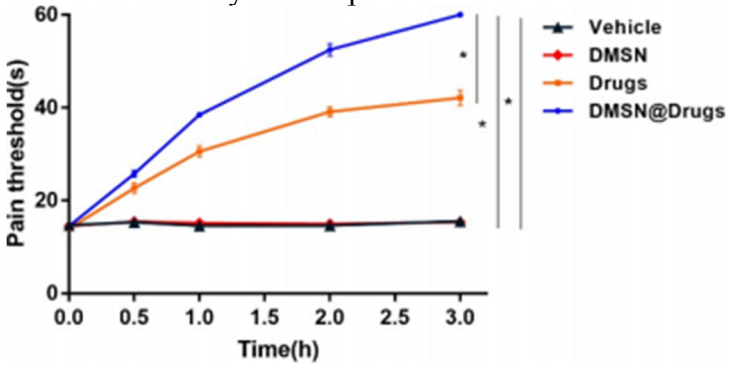

Figure 3. The Effects of Vehicle, DMSN, Drugs and DMSN@Drugs on hot plate induced pain threshold in mice. * $p < 0.05$ and p values were obtained by student's t-test.

4. Conclusion

Pain is the fifth vital sign, eeriously disturbing people's physical and mental health.Opioids or non steroidal anti- inflammatory drugs can treat pain and relieve temporary pain, but there are side effects, which patients can not tolerate or damage organs. Traditional Chinese medicine (TCM) has good therapeutic prospects, but it may have limitations such as toxicity or instability of active ingredients.The development of DMSN provides a new way for the treatment of pain.

In this study, a dendritic mesoporous silica nanomaterials loading system, DMSN, was successfully prepared. Related characterizations were carried out, resulting in a nanomaterial with uniform size distribution approximately spherical a surface full of mesoporous pore channels. After the synthesized DMSN is loaded with Toosendanin-Tetrahydropalmatine, a stable and sustained release can be achieved, which not only reduces the toxicity ofTCM components but also avoids the instability and difficult solubility of the active components of TCM. In the analgesic experiment, this nano drug loaded system could improve the pain threshold value of mice from about 15 s to after 60 s, showing excellent drug release and persistence of analgesia. Thus, the DMSN drug loading system is potentially valuable in enhancing the bioabsorption of unstable drugs and improving the bioavailability of insoluble drugs, which provides some scientific basis for further exploration of the pharmaceutical potential of the dendritic mesoporous silica carrier naurene and also offers the possibility of future finished pharmaceutical materials.

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