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Nanoparticle-loaded gels for topical delivery of nitrofurazone: Effect of particle size on skin permeation and retention

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ABSTRACT

In this study, the effect of particle size on skin permeation and retention of nitrofurazone (NTZ) from nanoparticle-loaded gels (NP-gels) was investigated to identify the suitable particle size of NTZ nanoparticle for topical delivery in order to achieve high deposition and low permeation of NTZ in the skin. NTZ nanosuspensions (NTZ-NSs) with three different particle size (299, 611, 906 nm) were prepared using wet media milling technique by adjusting milling speed and milling time, and then incorporated in carbopol gels for topical application. SEM and XRPD results showed that NTZ nanoparticles were well encapsulated in the gels network. The dissolution and the skin permeation of NTZ from NP-gels were particle size dependent and in an order of 299 nm > 611 nm > 906 nm, however, the skin deposition was in the order of 611 nm > 299 nm > 906 nm. The results demonstrated that the skin permeation and retention of NTZ from NP-gels were particle size dependent and the optimal size range was around 611 nm for topical application.

1. Introduction

Nitrofurazone (NTZ) is a topical antibiotic, active against both of Gram-positive and Gram-negative bacteria. It exhibits bactericidal activity by inhibiting bacterial enzymes involved in carbohydrate metabolism [1,2]. As an antimicrobial agent, NTZ is mainly used to treat wounds, burns and skin infection [3]. However, the poor water solubility of NTZ limits its therapeutic effect. Even though NTZ possesses high permeation rate through the skin due to its high lipophilicity, the release rate of NTZ restricted by its low aqueous solubility, leading poor permeation of an effective drug concentration into the skin [4].

In our previous study, formulation of NTZ as nanoparticle-loaded gel (NP-gel) has been performed with the aim of increasing its water solubility and maintaining its therapeutically relevant concentrations in the skin [5]. NTZ NP-gel exhibited a significant enhancement in dissolution rate and higher deposition of NTZ in rats' skin compared to the NTZ marketed gel. It was demonstrated that NP-gel offered a suitable way for topical delivery of NTZ. However, the permeation of NTZ across the skin from NP-gel was also enhanced, which is not expected and may cause obvious side effect. Therefore, further study is needed to improve NTZ retention in the skin layers and minimize drug permeation through skin.

Nanoparticle-loaded gel (NP-gel) is developed by incorporating nanosuspensions in a gel matrix with other excipients [5,6]. Nanosuspensions (NSs), as a particle size reduction's technology, have been reported to favor tretinoin accumulation into the skin with low drug permeation [7], but it is also able to improve the permeation of glabridin across the skin [8]. This might be because each drug NSs has different physicochemical properties and thereby different behaviors in biological environment [9,10]. Drug physicochemical properties, particle size and stabilizers were reported to be the factors influencing drug permeation rate through the skin [11,12]. In addition, polymer nanoparticles with size approximately 700 nm can accumulate in the hair follicles, and act as a depot to prolong drug diffusion into the surrounding cells [13]. However, no study has been performed to investigate the influence of these factors on skin retention of drug from NP-gels. The present study was performed to investigate the influence of particle size on skin permeation and retention of NTZ from NP-gels and identify the suitable particle size of NTZ nanoparticle from NP-gels for topical delivery to achieve high deposition and low permeation of NTZ in the skin. In addition, NTZ NP-gels loaded NTZ NSs with different particle size were characterized for particle size distribution, drug content, spreadability, pH, morphology, crystalline state and in vitro dissolution.

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2. Materials and methods

2.1. Materials

Nitrofurazone (NTZ, 98% purity) was supplied by Suzhou No.5 Pharm. FTY. Co., LTD. (Suzhou, China); NTZ marketed gel (0.1%, w/w) was purchased from Jiangsu Zhongdan Pharmaceutical Co., Ltd (Taixing, China). Sodium dodecyl sulfate (SDS) and Kollidon® 30 (PVP K-30) were obtained from the BASF Corp. (Ludwigshafen, Germany); Carbopol 940 was provided by Guangzhou Bo Feng Chemical Co., Ltd. (Guangzhou, China); Methanol of HPLC grade was obtained from Fisher Scientific (MA, USA); All other reagents were of analytical grade.

2.2. Preparation of NTZ-NSs with three different particle sizes

Wet media milling method was introduced to prepare NTZ-NSs in accordance to our previous study [5]. Briefly, 40 mg NTZ was dispersed in 4 mL of distilled water containing 0.23% (w/v) SDS and 0.32% (w/v) PVP K30. The obtained suspension was milled in a glass vial containing 4.1 mL of yttrium stabilized zirconium oxide beads (0.4–0.6 mm) under magnetic stirring (DF-101S, Beijing Hengfeng Chang Wei Technology Co., Ltd., Beijing, China) with different milling speed and time (Table 1) at room temperature to obtain NTZ-NS1, NTZ-NS2 and NTZ-NS3, respectively.

2.3. Formulation of NTZ NP-gels

The detailed procedure for preparation of NTZ NP-gels is described in our previous work [5]. Briefly, 1 g carbopol 940 was soaked in an appropriate amount of distilled water for sufficient swelling and then mixed with the glycerin (10 g) and NTZ-NSs (10 mL) under stirring at 800 rpm using a mechanical agitator (85-2, Changzhou Guohua Electric Appliance Co., Ltd., Jiangsu Province, China). The mixture was then adjusted to 100 g with distilled water to get a final NTZ concentration of 0.1% (w/w). The dispersion was neutralized using triethanolamine in pH range of 6.0–8.0. The gel stood approximately 12 h to remove the entrapped air bubbles. NTZ-NS1, NTZ-NS2 and NTZ-NS3 were used to prepare NP-gel-1, NP-gel-2 and NP-gel-3.

2.4. Characterization of NTZ-NSs and NTZ NP-gels

2.4.1. Particle size analysis

The average diameter and polydispersity index (PDI) of NTZ-NSs (NTZ-NS1, NTZ-NS2 and NTZ-NS3) were measured using a laser particle size analyzer (Winner 801, Jinan Winner Particle Instrument Stock Co., Ltd. China). NTZ-NSs were diluted with distilled water and analyzed at 25 °C.

2.4.2. Determination of drug content, spreadability and pH

The drug content of NTZ NP-gels (NTZ NP-gel-1, NTZ NP-gel-2 and NTZ NP-gel-3) was determined as follows [5]: 0.1 g NTZ NP-gels was dissolved in 10 mL methanol and then stirred for 12 h to disrupt the gel structure and make NTZ completely dissolve in methanol. The solution was filtered by 0.45 μm polyamide filter and then analyzed by HPLC method as described in Section 2.7. NTZ content was calculated as follows:

$$Drug\ content = \frac{amount\ of\ NTZ\ detected\ by\ HPLC}{total\ amount\ of\ NTZ\ employed} \times 100\%$$

The spreadability of NTZ NP-gels is expressed in terms of time taken in seconds by two slides to slip off from the gel placed in between under application of specific load [14]. It was calculated by the below formula:

$$S = \frac{ML}{T}$$

where S is spreadability of NTZ NP-gels, M is weight tied to upper slide, L is length travel by upper slide, and T is time.

The pH of NTZ NP-gels was determined at 25 °C using pH meter (pHS-25; Nanjing Everich Medicare Import and Export Co., Ltd. Nanjing, China).

2.4.3. Morphology

The morphology of NTZ-NSs (NTZ-NS1, NTZ-NS2 and NTZ-NS3) and NTZ NP-gels (NTZ NP-gel-1, NTZ NP-gel-2 and NTZ NP-gel-3) were investigated by scanning electron microscopy (SEM, S-4800, Hitachi, Japan). The samples of NTZ-NSs and NTZ NP-gels were made according to our previous report [5] and then observed at an acceleration voltage of 5 kV.

2.4.4. X-ray powder diffractometry (XRPD)

XRPD patterns of NTZ-NSs and NTZ NP-gels were obtained in step scan mode using Cu line as the source of radiation, and runs at a current of 25 mA, a voltage of 40 kV and a scanning rate of 2°/min over a 2θ range of 3–60° using an X-ray diffractometer (D/Max-2500PC, Rigaku, Japan).

2.5. In vitro dissolution study

In vitro dissolution of NTZ-NSs and NTZ NP-gels were performed using dialysis bag diffusion method with phosphate-buffered saline (PBS, pH7.4) as dissolution media [5,15]. NTZ-NSs (NTZ-NS1, NTZ-NS2 and NTZ-NS3) and NTZ NP-gels (NTZ NP-gel-1, NTZ NP-gel-2 and NTZ NP-gel-3) with equivalent of 10 mg NTZ were placed into dialysis bags (MWCO 8–14 kDa, Beijing Biotopped Technology Co., Ltd., Beijing, China) and then immersed in a beaker filled with 300 mL dissolution media. The dissolution media was stirred at 100 rpm using magnetic stirrer (SH-2, Beijing Jinbeide Industrial And Trading Co., Ltd., Beijing, China) and the temperature maintained at 32 °C using a recirculating water bath. At predetermined time points, 1 mL dissolution medium was collected and immediately replaced with the same volume of fresh dissolution medium. Each sample was passed through a 0.45 μm polyamide filter and then measured by HPLC method as describe in Section 2.7.

2.6. In vitro skin permeation and retention study

Franz diffusion cells with an effective diffusion area of 1.77 cm^2, and a receptor volume of 22.5 mL were used to assess in vitro skin permeation and retention of NTZ NP-gels (NTZ NP-gel-1, NTZ NP-gel-2 and NTZ NP-gel-3) [5,16]. Abdominal skin excised from Sprague Dawley rats was washed with isotonic NaCl after removing hair, adhering fat and other visceral tissue. It was sandwiched securely between donor and receptor compartments of the Franz cells, with the stratum corneum (SC) side facing the donor compartment. The acceptor compartment was filled with phosphate buffer saline (PBS, pH 7.4), maintained at 37 °C and stirred at 500 rpm at 37 °C. NTZ NP-gels with 1 mg of NTZ were placed on the skin surface in the donor compartment. At time intervals of 0.5, 1, 2, 3, 5, 7, 9, 12, and 24 h, 1 mL aliquots was collected from the receiver compartment and immediately replaced with equal volume of fresh receptor medium. All the collected samples

Table 1
Optimal process parameters and particle size of NTZ-NSs (mean ± SD; n = 3).

NTZ-NSs	milling speed (rpm)	milling time (h)	particle size (nm)	PDI
NTZ-NS1	1200	4.5	299 ± 15	0.198 ± 0.014
NTZ-NS2	1200	2.0	611 ± 29*	0.233 ± 0.018*
NTZ-NS3	1000	1.5	906 ± 37*#	0.352 ± 0.026*#

Note: *$P < 0.05$ versus the NTZ-NS1, #$P < 0.05$ versus the NTZ-NS2.

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