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Nanosuspensions based gel as delivery system of nitrofurazone for enhanced dermal bioavailability

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ABSTRACT

The purpose of this study was to develop stable nitrofurazone nanosuspensions based gel (NTZ nanogel) suitable for topical delivery with a view to increase skin bioavailability. NTZ nanosuspension (NTZ-NS) was fabricated by wet media milling technique, optimized by Box–Behnken design and then suitably gelled for systematically characterization. In order to confirm the advantages of NTZ nanogel for dermal application, skin permeation and retention studies in vitro were performed in comparison with NTZ marketed gel by using Franz diffusion cells. SEM showed that NTZ-NS were rectangular in shape and still stably kept their particle size after suitably gelled by carbopol preparation. In vitro dissolution studies exhibited a significant enhancement in dissolution rate of the drug from nanogel (85.73%) in comparison to the NTZ marketed gel (70.55%) after 24 h. In vitro permeation studies indicated that the amount of NTZ permeated through skin of NTZ nanogel (220.89 μg/cm^2) after 24 h was higher than NTZ marketed gel (61.30 μg/cm^2), and NTZ nanogel increased the accumulative amount of NTZ in rats' skin 5.5 times than NTZ marketed gel. These results suggested that nanogel is eligible for the use as suitable nanomedicine for topical delivery of poorly soluble drugs such as NTZ.

1. Introduction

Nitrofurazone (NTZ), a nitroheterocyclic topic antiseptic, has been reported to show bactericidal activity against a great variety of Gram-positive and Gram-negative bacteria, acting by inhibiting bacterial enzymes involved in carbohydrate metabolism [1,2]. It exhibits bactericidal activity toward most pathogens that commonly cause surface skin infections, including *Staphylococcus aureus* (including Methicillin-Resistant *Staphylococcus aureus* (MRSA) strains), Streptococcus, *Escherichia coli*, *Clostridium perfringens*, Enterobacter aerogenes, and Proteus organisms [3]. NTZ is used as an antimicrobial agent in the treatment of infected wounds from traumatisms, burns or surgical interventions [4]. However, in spite of its clinical significance as an antimicrobial agent, NTZ therapy has limitation on its low aqueous solubility. Poor solubility causes a slow release rate from the formulation which in turn limits the penetration of an effective drug concentration into the skin. Moreover, due to its high permeability through the skin, NTZ remains for a limited time in the location applied [5]. Therefore, it needs to be incorporated into a proper vehicle to increase the solubility of NTZ and maintain therapeutically relevant concentrations of NTZ in the epidermis/dermis.

In order to overcome the poor water solubility of NTZ, various approaches have been studied such as the use of surfactants [6], co-solvents [4], nanoemulsion [7], solid dispersion [8], microencapsulation [9], etc. In particular, cosolvents have been widely used as vehicles as well as penetration enhancers in the topical formulations of NTZ such as gel, cream and ointment [4]. However, these approaches have their own shortcomings, such as drug leakage, poor stability, low drug loading, complex manufacturing approaches or high toxicity [10,11]. Cosolvent systems were often thermodynamically unstable due to the crystallization of drug molecules immediately after formulation or even during storage [12], and may alter the structure of the skin to induce skin irritation and modify the penetration rate [13].

Recently, nanosuspensions based gel (also called nanogel) have received considerable attention in topical application due to their

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ability to enhance delivery to the skin and overcome bioavailability issues caused by poor water drug solubility [12,14–17]. Nanogel is molecular gel based on nanosuspension system. It is developed by incorporating nanosuspension with gel matrix and other excipients [18]. It has dual advantages of nanosuspension and gel. Nanosuspensions (NS), as a particle size reduction's technology, have been reported to increase dermal drug bioavailability by enhancing its dissolution velocity and saturation solubility, thus, leading to an increased concentration gradient with a consequent improved skin penetration of drugs [17,19]. Moreover, NS are able to especially favour drug accumulation into the skin and at the same time to reduce drug delivery to the systemic circulation [20]. Meantime, topical gels have been proved to be a beneficial vehicle for topical drug delivery or for the localized drug action on skin with the advantages of good biocompatibility and adhesion, easy absorption after local administration, no irritation to the skin and mucous membranes [21–23]. Therefore, the purpose of this study was to develop stable nitrofurazone nanosuspensions based gel (NTZ nanogel) suitable for topical delivery with a view to increase skin bioavailability.

2. Materials and methods

2.1. Materials

Nitrofurazone (NTZ, the purity is up to 98%) was purchased from Suzhou No.5 Pharm. FTY. Co., LTD. (Suzhou, China); NTZ marketed gel (0.1%, w/w) was supplied by Jiangsu Zhongdan Pharmaceutical Co., Ltd (Taixing, China). Hydroxypropylmethylcellulose E3 (HPMC E3) and Hydroxypropylmethylcellulose E5 (HPMC E5) were purchased from Anhui sunhere Pharmaceutical Excipients Co., Ltd. (Anhui, China); D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) was purchased from Xi'an Healthful Biotechnology Co., Ltd. (Xi'an, China); Sodium dodecyl sulfate (SDS), Kollidon® 30 (PVP K-30), Poloxamers 188 were obtained from the BASF Corp. (Ludwigshafen, Germany); Tween 80 was purchased from Sigma Aldrich Chemicals Pvt. Ltd. (St Louis, MO, USA); Carbopol 940 was purchased from Guangzhou Bo Feng Chemical Co., Ltd. (Guangzhou, China); All other reagents were of analytical grade.

2.2. Preparation of NTZ-NS

The NTZ-NS was generated by wet media milling method [24]. Briefly, 40 mg (1%, w/v) of NTZ was dispersed in 4 mL of aqueous solution containing stabilizers. The resulting suspension was poured into a glass vial containing yttrium stabilized zirconium oxide beads (0.4–0.6 mm) and stirred on a magnetic stirrer (SH-2, Beijing Jinbeide Industrial And Trading Co., Ltd., Beijing, China) at a speed of 1200 rpm and temperature of 25 °C.

2.3. Screening of stabilizers

Stabilizers were selected by determining the particle size distribution of the NTZ-NS. In this study, PVP K30, HPMC E3 and HPMC E5 as the polymer stabilizers alone or in combination with SDS, Tween 80, Poloxamers 188 and TPGS as the surfactants were evaluated. The most suitable stabilizers were identified by optimum particle size (PS) and polydispersity index (PDI). In these experiments, the drug concentration (1%, w/v), polymer concentration (0.2%, w/v), surfactant concentration (0.1%, w/v), distilled water (4 mL), stirring speed (1200 rpm), bead volume (4 mL) and milling time (1 h) were kept constant. Each experiment was performed in triplicate.

2.4. Experimental design

Initial screening studies were carried out for evaluating the effect of process parameters and formulation parameters on NTZ-NS and its stability. The bead volume and milling time were identified as critical process parameters and polymer and surfactant concentrations as critical formulation parameters. The Box-Behnken design was employed systematically to optimize the selected process and formulation parameters with PS, PDI and SI as dependent variables. Independent factors and their levels used in this study are shown in Table 1. The design contains 29 experimental runs as shown in Table 2 and analyzed by the statistical software package Design-Expert 8.0.6 (Stat-Ease Inc., USA).

2.5. Preparation of NTZ/SDS/PVP K30 physical mixture (PM)

PM of NTZ, SDS and PVP K30 was prepared in same proportion as used for the preparation of optimized NTZ-NS. NTZ, SDS and PVP K30 were poured in a mortar and mixed for 10 min until a homogenous mixture was obtained.

2.6. Formulation of NTZ nanogel

A topical nanogel containing 0.1% NTZ was formulated using carbopol 940 as gelling agent. Firstly, Carbopol 940 (1 g) was dispersed in distilled water and kept aside for 1 h for swelling. Glycerin (10 g) and NTZ-NS (10 mL) were added into the swelled carbopol 940 continuous stirring at a speed of 800 rpm using a mechanical agitator (85-2, Changzhou Guohua Electric Appliance Co., Ltd., Jiangsu Province, China). Appropriate amount of water was added to 100 g and mixed so as to get NTZ concentration in nanogel as 1% (w/w). The dispersion was neutralized using triethanolamine until pH 6.0 to 8.0. The gel was allowed to stand overnight to remove entrapped air. The preparation process of blank-gel (without NTZ) was the same as NTZ-nanogel.

2.7. Characterization of NTZ nanogel

2.7.1. Particle size and stability

The volume average particle size and polydispersity index (PDI) of NTZ-NS during process optimization were determined by photon correlation spectroscopy (PCS) using a laser particle size analyzer (Winner 801, Jinan Winner Particle Instrument Stock Co., Ltd. China).

The stability of NTZ-NS was evaluated by stability index (SI) [25], as follows:

Table 1
Independent factor and their coded levels of Box–Behnken design.

Independent factors		Design level	
Actual parameters	Coded	Actual value	Coded level
Conc. of SDS (%,w/v)	A	0.1%	−1
		0.2%	0
		0.3%	+1
Conc. of PVPK30 (%,w/v)	B	0.2%	−1
		0.3%	0
		0.4%	+1
Bead volume (mL)	C	3.5	−1
		4.0	0
		4.5	+1
Milling time (h)	D	2	−1
		4	0
		6	+1