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Spray drying of cefixime nanosuspension to form stabilized and fast dissolving powder

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ABSTRACT

Size reduction to a nanoscale is a relatively new approach to overcome solubility and bioavailability issues of many drugs such as cefixime (CFX). However, nanoparticles and specifically nanosuspensions are prone to many instabilities like aggregation and sedimentation. One of the main solutions is transforming liquid nanosuspension into dry powder.

In this study, cefixime (CFX) nanosuspension was co-spray dried in the presence of different carriers (lactose, mannitol and sorbitol) in 3 ratios of nanoparticles (NPs)/carriers (1, 1.5 and 4 (*w*/*w*)). Physicochemical properties of the obtained powders were assessed in terms of particle size, morphology, thermal behavior, flowability, dissolution profile and aggregation over 6 months.

Co-processing of NPs resulted in the formation of partially spherical particles with deeply wrinkled surfaces in the sizes ranging from 3.61 to 12.18 μm. Flowability showed improvement of all microparticles and thermal analysis demonstrated an amorphous state. Results suggest that among carriers, sorbitol based microparticles had the same dissolution profile as the initial NPs (29-fold increase in maximum solubility compared to unprocessed CFX) and could preserve reconstituted NPs' size efficiently after storage. This shows the feasibility of using sorbitol as a promising carrier for spray drying of nanosuspensions which was mostly used for co-processing of solid lipid nanoparticles, proteins and peptides before.

1. Introduction

Cefixime (CFX) is a third generation cephalosporin used orally to treat infections due to susceptible Gram positive and Gram negative bacteria, including gonorrhea and infections of the respiratory system and urinary tracts [1]. CFX has a very low aqueous solubility and thus a low bioavailability of 40–50% [2,3]. Its aqueous solubility is pH dependant and enhanced concurrently as the pH increase [4].

The poor water solubility of drugs such as CFX is a major hurdle for drug formulation. It results in poor bioavailability and therapeutic failure of the drugs due to their inability to adequately reach their target sites [5,6]. Nanosuspensions are promising candidates that can be used to enhance the dissolution rates of such poorly soluble drugs [7–11]. In nanosuspensions, the drug is maintained in the required crystalline state with reduced particle size which results in an increase in surface area and creation of high energy surfaces due to the disruption of drug microcrystals to nanoparticles (NPs). In addition, particle size reduction to the nanoscale decreases the diffusional distance on the surface of drug NPs, thus leading to an increased concentration gradient. Moreover, NPs tend to have an increased adhesiveness to surfaces, cell membranes and intestinal wall, thus increasing drug absorption and reducing inter-individual variation which can enhance drug bioavailability [9,11–15].

Despite recent progresses and numerous researches on nanosuspension technology, stability remains a limitation for their applications in pharmaceutical industries [16–18]. Aggregation is the main stability issue and can occur during either the preparation process or storage and it is due to the Ostwald ripening phenomenon [17,19]. Moreover, crystalline transformation can destabilize nanosuspensions because in many cases, nanoparticles are in the amorphous state and therefore, comparing to the crystalline state, they are thermodynamically unstable [18,20].

Among various ways to overcome nanosuspensions stability problem such as stabilizer addition [19,21], solidifying is one of the main solutions [16,17,20,22]. The solid state is preferred over the aqueous nanosuspensions, due to the fact that aggregation and other instability factors are significantly decreased. Therefore, nanosuspensions are commonly converted into the solid state and then formulated as other dosage forms [17,23,24].

Spray drying is a popular method to transform nanosuspensions into dry powders. It is more preferable over freeze-drying because it consumes less time and energy, so it is generally used by pharmaceutical industries [18,22]. Among variables affecting the quality of spray drying process, addition of a proper excipient is critical to ensure complete

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redispersion of NPs into their pre-drying state [9,23,25]. Sugars are common excipients playing a significant role in preventing NPs from aggregation and serving as protectants since they are concentrated during the spray drying process [9,16,26].

The aim of the present study was to convert CFX nanosuspension into the stable dry powder and evaluate the effects of sugar type and ratio on the powder properties and dissolution quality of spray dried NPs.

2. Materials and methods

2.1. Materials

Cefixime trihydrate was kindly supplied by Jaber Ebne Hayyan Pharmaceutical Co. (Iran). Polyvinylpyrrolidone (PVP) K-30 and sorbitol were obtained from Fluka (Germany). Lactose monohydrate, mannitol, monosodium phosphate, monopotassium phosphate and methanol of HPLC grade were purchased from Merck (Germany).

2.2. Methods

2.2.1. Preparation of CFX nanosuspension

CFX nanosuspension was prepared according to a previously optimized condition by the sonoprecipitation method. Briefly, 810.98 mg of CFX and 89.02 mg of PVP-K30 were dispersed in 20 mL distilled water. The pH of the mixture was raised by NaOH (1 M) to a final value of 11. At this pH, CFX was completely dissolved in the solvent. Then, the solution was placed in an ice–water bath and treated with an ultrasonic probe (Hielscher, Germany) at power input of 120 W and cycle of 1.0 per second. Meanwhile, precipitation initiated by the addition of phosphoric acid 85% drop-wise (one drop per 15 s).

2.2.2. Spray drying of CFX nanosuspension

Freshly prepared CFX nanosuspensions were spray dried in the presence of different carriers as shown in Table 1. Carriers were dispersed in distilled water and then CFX nanosuspension was added to a final volume of 400 mL and solid content of 10 g with relative ratios of NPs/carriers (W/W) according to Table 1. Spray drying conducted using a B-191 mini spray drier (Büchi labortechnik AG, Switzerland), at inlet temperature of 100 °C, aspiration rate of 85%, air flow rate of 550–600 L/h, solution flow rates of 10 mL/min and outlet temperature in the range of 50 °C to 60 °C. After collecting powders from receiving chamber and evaluating the yield percentage, they were stored in glass desiccators at room temperature for further investigations. Yield (%) of the obtained powders was calculated using Eq. (1).

$$\text{Yield}\ (\%) = \frac{\text{Collected dry powder}}{\text{Dry mass in the feed solution}} \times 100 \quad (1)$$

2.2.3. Particle characterization

2.2.3.1. Size distribution of the NPs. Particle sizes of the nanosuspensions were determined using photon correlation spectroscopy (PCS). Additionally, spray dried microparticles (MPs) immediately after spray drying and again after 6 months of storage in 25 ± 2 °C/60 ± 5% relative humidity, were reconstituted to determine the size of the NPs. For this purpose, excess amount of MPs were redispersed in 2 mL of distilled water to form suspensions and were shortly sonicated in a water bath sonicator (Starsonic 60, Italy) prior to analysis. Mean particle size (Z average) and poly dispersity index (PDI) of NPs were assessed by a Malvern Zetasizer 3000 (Malvern Instruments, UK) at 25 °C. Each value resulted from triplicate determinations.

2.2.3.2. Size distribution of the spray dried MPs. Size of the MPs measured by laser diffraction method (Mastersizer X, Malvern Instruments, UK) at obscurations between 0.18 and 0.20 at 25 °C. For each sample, 5 mg of the powder was dispersed in 5 mL ethyl acetate with the aid of sonication (Starsonic 60, Italy) for 2 min. All measurements were carried out in triplicate.

2.2.3.3. Scanning electron microscopy (SEM). Morphology of the NPs and spray dried MPs were examined using SEM (S-4160, Hitachi, Japan) at an acceleration voltage of 20 kV. Samples were mounted onto aluminum stubs with double-sided adhesive tape and sputter-coated for 90 s with gold DS-sputtering (BAL-TEC, Switzerland) under vacuum in an argon atmosphere at room temperature before the examination.

2.2.3.4. Drug content. Although spray drying process is an efficient drying method capable of rapid transforming solutions or suspensions into solid products, it utilizes high inlet temperature which can lead to the destruction of drug molecules. Therefore, CFX content of the MPs and subsequently percent of CFX loss was determined according to a validated method using HPLC system (Waters, USA) equipped with a Nucleodur® C18 gravity column (4.6 × 150 mm, 5 μm, USP L1 Macherey-Nagel, Germany) at 25 °C [27]. The mobile phase consisted of a mixture of 12.5 mM monosodium phosphate aqueous solution and methanol (65:35, V/V) with pH adjusted to 2.75 using orthophosphoric acid 85%. It was filtered and degassed prior to delivery to the system and used at a constant flow rate of 1 mL/min. The injection volume was 20 μL and the eluent was monitored at 288 nm. Drug loss calculated based on Eq. (2).

$$\text{Drug loss}\ (\%) = \left(\frac{\text{CFX content before spray drying} - \text{CFX content after spray drying}}{\text{CFX content before spray drying}}\right) \times 100 \quad (2)$$

Table 1
Physicochemical characteristics of spray dried NP-embedded microcarriers.

Formulation	NP/carrier ratio	Carrier type	Viscosity of feed solution (mPa·s)	Size[a] (μm)	Yield (%)	Cefixime loss (%)	Similarity factor (f_2)	Difference factor (f_1)
Run_1	1	Lactose	1.37	12.18*	54.99*	9.74*	51.4	5.94
Run_2	1.5	Lactose	1.85	9.25	54.08(ns)	14.59	72.4	2.84
Run_3	4	Lactose	1.96	5.15	49.26	16.35	72.2	3.13
Run_4	1	Mannitol	1.37	5.1*	60.21*	7.25*	82.3	1.60
Run_5	1.5	Mannitol	1.84	4.81	55.82	9.12	50.0	7.43
Run_6	4	Mannitol	1.92	3.61	47.39	11.72	86.6	1.11
Run_7	1	Sorbitol	1.37	6.56*	66.19*,**	3.99*	63.8	3.60
Run_8	1.5	Sorbitol	1.85	6.19	62.47	5.56	85.2	1.29
Run_9	4	Sorbitol	1.95	5.17	47.49	8.85	85.3	1.46

Ns: not significant.
[a] Median **p**article size 50% (d50) (μm).
* $p < 0.05$, in com**p**a**r**i**s**on of different ratio**s** of NPs to each carrier.
** $p < 0.05$, in comparison of all formulation.