Colloids and Surfaces B: Biointerfaces 143 (2016) 107–110

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

A new approach to produce drug nanosuspensions CO_2-assisted effervescence to produce drug nanosuspensions

Xiangfei Han, Menglin Wang, Zhihui Ma, Peng Xue, Yongjun Wang*

School of Pharmacy, Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenyang, 110016, China

ARTICLE INFO

Article history:
Received 12 January 2016
Received in revised form 4 March 2016
Accepted 5 March 2016
Available online 7 March 2016

Keywords:
Nanomedicine
Nanoamorphization
CO_2
Itraconazole
Cabazitaxel

ABSTRACT

The exploration of a simple and robust approach to produce nanosuspensions is a meaningful attempt for clinical translation. CO_2-assisted effervescence was firstly developed to prepare nanosuspensions and was found to be easy for scale-up. Drug nanosuspensions were easily obtained by adding aqueous carbonate to the pre-treated mixture of drug, stabilizer and organic acid. The burst of CO_2 bubbles resulted from the acid-base reaction insert a micro gas bubble smashing and mixing effect to the formation of nanosuspensions, leading to smaller sizes and a refined size distribution. We successfully prepared nanosuspensions with twelve structurally diverse drugs. Alternatively, solid carbonate blended with the mixture, allowing for later addition of water, also facilitates the formation of amorphous nanosuspensions. We defined this approach as *in situ* nanoamorphization (ISN). Intensive *in vitro* and *in vivo* investigations for itraconazole and cabazitaxel nanosuspensions validate the availability for administration.

1. Introduction

Nanosuspensions are liquid sub-micron colloidal dispersions of nanosized pure drug particles stabilized by polymer and/or surfactant. A nanosuspension platform is a very efficient drug delivery system for water-insoluble drugs because these platforms provide increased dissolution velocity and high mass per volume loading. [1] To date, existing techniques to produce nanosuspensions are divided into "bottom-up", "top-down" techniques, or a combination of both. The top-down technique utilizes mechanical attrition, high-pressure homogenization or media milling to invert coarse drugs into nanosized particles. When the "top-down" technique is used, the drug often exists in a crystalline state in the dispersion medium [2]. In contrast, the "bottom-up" process involves dissolving the drug in a solvent and precipitating it in a controlled manner to achieve nanosized particles at the addition of an antisolvent (so-called antisolvent precipitation technique). With this method, the drug can exist in either a needle-shaped crystalline state or amorphous state, depending on the applied technique [3]. The top-down technique is more widely employed in the pharmaceutical industry due to its straightforward process features. Six products based on the top-down technique have been successfully marketed in recent years [4]. However, many challenges remain as outlined below:

i) Nanosuspensions are thermodynamically unstable colloid dispersion systems with a high surface energy that inevitably induces growth of particle size, known as Ostwald ripening. In addition, nanosized systems tend to reduce the Gibbs free energy causing nanosuspensions to aggregate during the preparation process and storage. During the bottom-up process, stability issues are more severe because the drug nanoparticles are usually generated in a mestastable polymorphic form, which can cause transformation to occur. Therefore, although the amorphous form is more soluble and has a higher dissolution rate than the crystalline state, no products based on the bottom-up technique have yet appeared on the market.

ii) In comparison with conventional approaches that attempt to solubilize insoluble drugs using agents such as co-solvents and inclusion complexes, a high-pressure homogenization or media milling process consumes high energy and requires special equipment such as a homogenizer or ball grinder [5]. Furthermore, a solidification process using spray drying or freeze-drying method is typically required due to the instability of aqueous nanosuspensions [3]. This results in higher production costs and concerns over the ability to re-disperse the dried powder are also needed.

iii) The media milling process generates considerable heat, which may cause crystal defects or degradation of heat-sensitive drugs. Moreover, the erosion of milling pearls may contaminate the nanosuspension [6]. Because of these limitations, alternative

* Corresponding author at: Mailbox 59#, Department of Biopharmaceutics, School of Pharmacy, Shenyang Pharmaceutical University, No. 103, Wenhua Road, Shenyang, 110016, China.
E-mail address: wangyjspu@163.com (Y. Wang).

http://dx.doi.org/10.1016/j.colsurfb.2016.03.017
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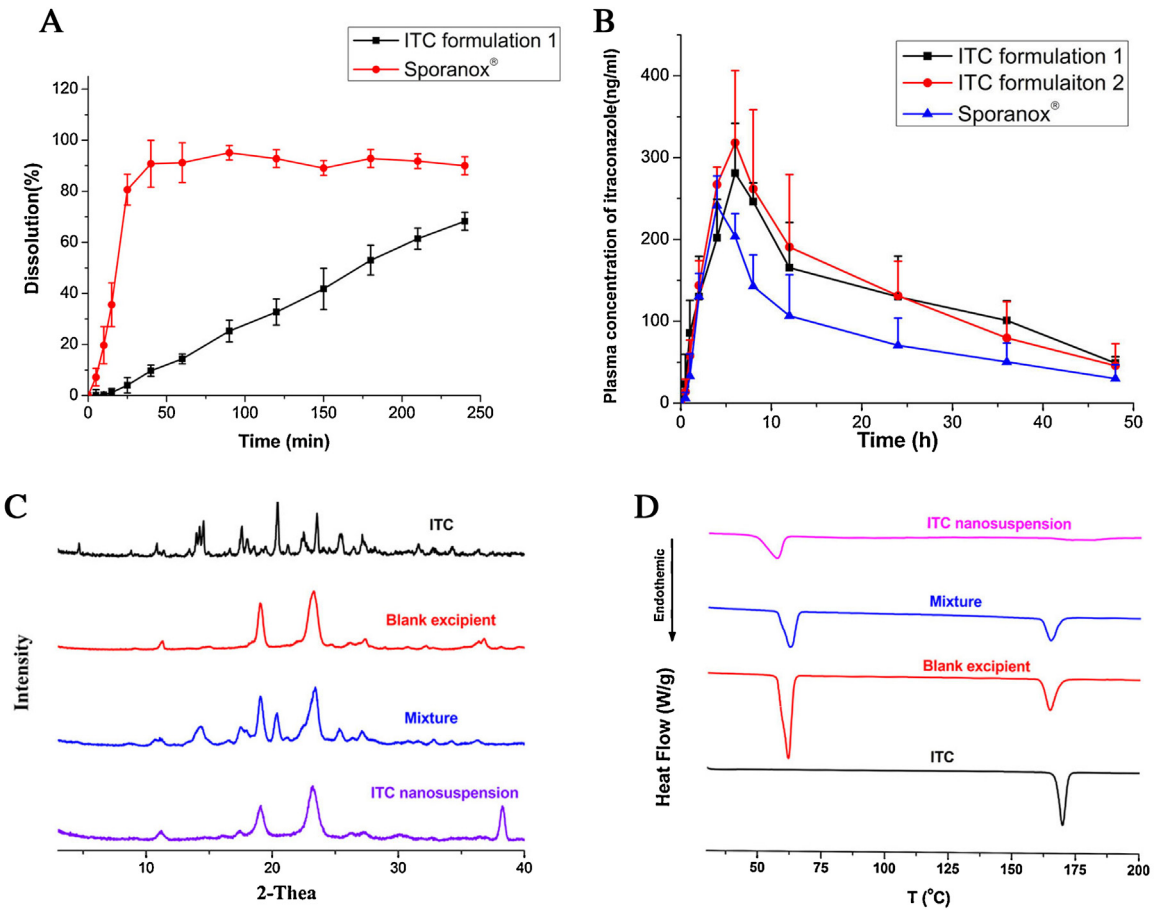

Fig. 1. (A) The dissolution profiles of ITC formulation 1 and Sporanox® in pH 1.2 with 0.6% SDS (mean ± SD, n = 3). (B) Plasma concentration profiles of ITC after oral administration of ITC formulation 1, ITC formulation 2 and Sporanox® (mean ± SD, n = 6). (C) XRD and (D) DSC images for ITC, blank excipient, the mixture of ITC and excipients and ITC/soluplus (1:3, w/w) nanosuspension.

nanosuspension production processes are attractive to the pharmaceutical industry.

In this study, we explored a simple but robust approach to prepare nanosuspensions (Scheme). The process utilizes an organic solvent to dissolve water-insoluble drugs along with organic acids and stabilizers. Then, the organic solvent is evaporated—leaving an organic acid-phase material. Finally, drug nanosuspensions are obtained following the addition of aqueous carbonate, which rapidly generates CO_2 bubbles by acid-base reaction. Alternatively, the solid acid-phase material can be blended with dry carbonate and prepared into final solid dosage forms at a later time. Of importance, the nanosuspensions could not be produced in the absence of the organic acid or carbonate; rather, the drugs gradually aggregated together and precipitated over time. In this new approach, CO_2 bubbles exert a rapid micro-mixing effect to suppress crystal growth while stabilizers simultaneously absorb onto the hydrophobic surface of the drugs and prevent aggregation and agglomeration. Unlike the top-down and bottom-up techniques, it was demonstrated that the drugs of final nanosuspensions existed as amorphous form. Ideally, formulated nanosuspensions occur in the amorphous form to improve solubility and the dissolution rate. However, limited commercialization of nanosuspensions in the amorphous state has occurred due to stability issues. The method described here bypasses concerns over stability because the final products can be produced in a sub-packaging form consisting of the organic-acid phase with drug and stabilizer separated from the aqueous carbonate. Consequently, the nanosuspensions could be achieved by combining the aqueous carbonate with the organic acid-phase. In this new approach, the nanosuspension is prepared only at the time of usage. We define this new technique as in situ nanoamorphization (ISN). ISN may not only solve the stability issues associated with current manufacturing techniques, but is also a low-energy consumption process.

2. Results and discussion

Here, we show that this approach is suitable for the preparation of nanosuspensions of structurally diverse drugs with different physicochemical properties (Molucular weight, MW, from 206.28 to 1202.62; logP, from 3.07 to 9.05; melting point, from 75 to 213 °C) (Table S1). As shown in Table 1, the particle size of the nanosuspended drugs range from 92.21 nm (cabazitaxel) to 653.9 nm (loratadine) (Table 1). Due to the different steric stabilization effects, the use of different stabilizers resulted in varying particle sizes with the nanosuspensions. For example, the stabilizers Soluplus (a polyvinyl caprolactam – polyvinyl acetate – polyethylene glycol graft copolymer), TPGS (D-alpha tocopheryl polyethylene glycol 1000 succinate), and HPMC E5 (a hydroxypropyl methyl cellulose) resulted in cyclosporin A particle sizes of 128.9 nm (polydispersity index, PDI, 0.234), 290.3 nm (PDI, 0.191) and 510.9 nm (PDI, 0.214), respectively. In short, nanosuspensions prepared by ISN present favorable small particle sizes and narrow particle size distributions. In comparison, the bottom-up technique is usually followed by an ultrasonication or homogenization step due to the difficulty in controlling particle growth, which is the