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Review

Nanosuspensions of poorly water-soluble drugs prepared by bottom-up technologies

Juan Du[a], Xiaoguang Li[b], Huanxin Zhao[c], Yuqi Zhou[a], Lulu Wang[a], Shushu Tian[a], Yancai Wang[a,*]

[a] School of Chemistry and Pharmaceutical Engineering, Qilu University of Technology, Jinan 250353, Shandong, PR China
[b] Hospital, Qilu University of Technology, Jinan 250353, Shandong, PR China
[c] Institute of Materia Medica, Shandong Academy of Medical Sciences, Jinan 250062, Shandong, PR China

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ABSTRACT

In recent years, nanosuspension has been considered effective in the delivery of water-soluble drugs. One of the main challenges to effective drug delivery is designing an appropriate nanosuspension preparation approach with low energy input and erosion contamination, such as the bottom-up method. This review focuses on bottom-up technologies for preparation of nanosuspensions. The features and advantages of drug nanosuspension, including bottom-up methods as well as the corresponding characterization techniques, solidification methods, and drug delivery dosage forms, are discussed in detail. Certain limitations of commercial nanosuspension products are also reviewed.

Contents

* Corresponding author. Fax: +86 531 89631208.
E-mail address: wangyancai1999@163.com (L. Wang).

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1. Introduction

In recent years, active chemical entities have been increasingly studied, although most of them are poorly soluble or insoluble in water (Al-Qadi et al., 2011). More than 40% of the potential drugs are poorly soluble in water, which, although important, are thus excluded from further study (Gebremedhin et al., 2014). It is estimated that annually about $65 billion is spent on treatment of disease worldwide due to the poor bioavailability of drugs, with little curative effect. In particular, some drugs have also been proven to exert severe or even fatal effects. The low bioavailability of poorly soluble drugs prepared by traditional methods for oral or intravenous administration greatly limits their application (Zhu et al., 2014). To overcome this limitation, preparation workers use methods such as using mixed solvents, adopting inclusion technology and micronization, or converting into intravenous emulsion (Merisko-Liversidge and Liversidge, 2011). However, these methods have certain drawbacks: the mixed solvent method requires drugs with particular physical and chemical properties, capable of being dissolved in some organic solvents; the inclusion technology requires drugs of suitable molecular size; and the micronization method does not increase bioavailability significantly (Tran et al., 2015).

In fact, exploiting the density and solid state is beneficial in producing drug–polymer complexes of large unit volume, especially in preparing pharmaceuticals in large doses (Sievens-Figueroa et al., 2012). However, molecular complexation approaches have often failed, as complex materials with large mole ratio are used (Rabinow, 2004). A high loading dose is used to reduce the administration volume, which is important in the case of small-volume intramuscular and ophthalmic injections (Deng et al., 2014).

Furthermore, in order to increase the solubility of insoluble drugs, conventional preparation methods often require large amounts of cosolvent, although this could result in a toxic effect (Jeon et al., 2000). Subsequently, an increasing number of experimental animals were used in studies investigating the optimal, safe dose (Alhassan et al., 2014).

Therefore, researchers abroad have developed a new kind of preparation nanosuspension to improve the bioavailability of poorly soluble drugs (George and Ghosh, 2013). Nanosuspension is a kind of pure particle–drug system that is composed of submicron colloidal dispersions, with a surfactant as the suspension agent (Kuntsche and Bunjes, 2007). Nanosuspensions can be used to prepare water-insoluble but oil-soluble drugs, although lipid systems such as liposome and emulsion preparations can also be used (Mengersen and Bunjes, 2012). In comparison to the lipid systems, nanosuspensions can also successfully formulate drug preparations that are poorly soluble in both water and oil. Nanosuspensions helps prevent the dissolution of the drug before preparation, as it must be maintained under the optimum crystallization conditions and at sufficiently small sizes (Yao et al., 2012).

Therefore, nanosuspensions have several benefits in disease treatment. For instance, intravenous administration of drugs can reduce toxicity and increase the curative effect; further, pulmonary drug delivery can increase lung-deep penetration of the medication (Wu et al., 2011). Nanosuspensions also reduce the size of solid drugs to improve their solubility, especially in the case of poorly soluble oral drugs. The solid state is superior to the liquid state, and small size can increase the physical stability of sedimentation. Therefore, nanosuspensions differ significantly from drug carriers such as colloidal polymer nanoparticles (Wu et al., 2011).

This dosage form has also shown other advantages such as the production of biological adhesion and improvements in chemical stability (Otsuka et al., 2012). In 2000, nanosuspensions were made commercially available in the pharmaceutical market with its special features of increased saturation velocity, increased adhesiveness to surfaces/cell membranes, and increased dissolution velocity (Müller et al., 2011).

2. Bottom-up technologies for preparing nanosuspension

2.1. Precipitation–ultrasonication method

In recent years, ultrasound has emerged as an effective method of controlling the process of nucleation and crystallization. Further, ultrasound irradiation helps intensify mass transfer and accelerate

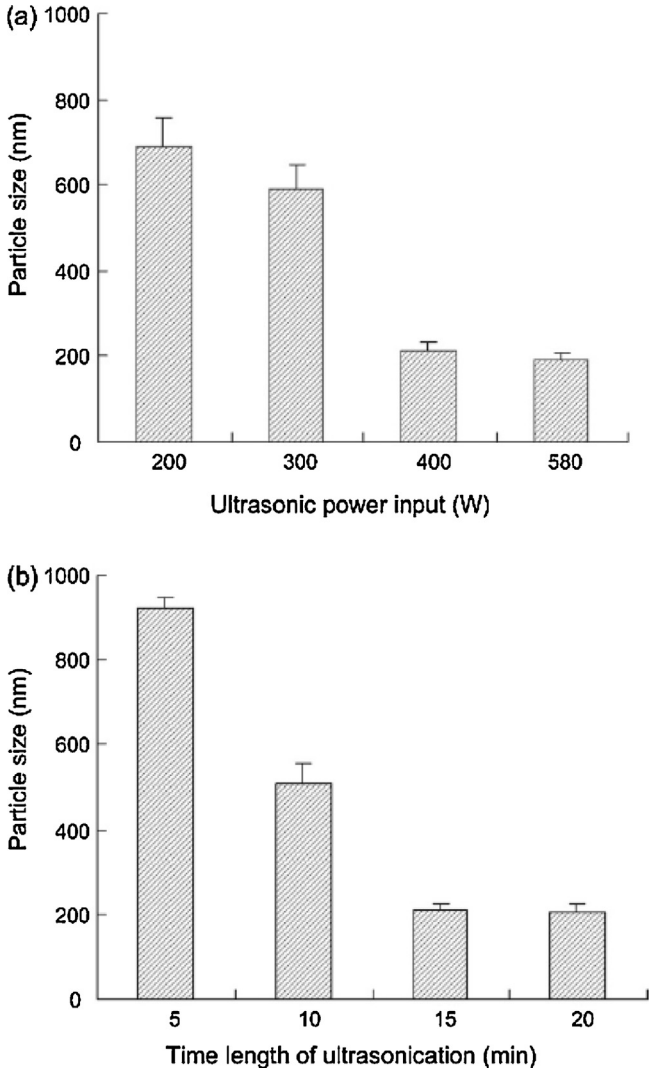

Fig. 1. Effects of ultrasonic power input (a), and duration of ultrasonic treatment (b) on the particle size of nanosuspension (Xia et al., 2010).