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Design and characterization of loratadine nanosuspension prepared by ultrasonic-assisted precipitation

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ABSTRACT

Nanoparticle engineering is a well-defined technique employed as a novel and effective method in drug design and delivery. It is widely used to control particle size, as well as the morphological and physicochemical properties of active pharmaceutical ingredients. Furthermore, it serves as a method of pre-dispersion preparation for various dosage form developments. Nanotechnology produces nanomaterials with enhanced properties in terms of solubility, dissolution and permeability. In this work, ultrasonic-assisted precipitation was employed to produce nanosuspensions of poorly water-soluble loratadine, using different stabilizers. The objective of our study was attempting to prepare solid nanoparticles of loratadine to be used as a possible intermediate for designing various dosage forms. The effects of the type(s) and concentration(s) of stabilizer(s) on mean particle size were assessed. Optimal process parameters required to produce homogeneous nanoparticles with particle size below 500 nm and polydispersity less than 0.3 were determined both for precipitation and ultrasonication. Pre-dispersions were evaluated for their particle size, polydispersity index and zeta potential. Freeze-drying was employed to produce dry nanoparticles. Particle size, particle size distribution and zeta potential of the dried nanoparticles were measured after reconstitution in water. Besides thermal analysis using DSC and structural analyses (XRPD and FT-IR), the morphological characteristics and dissolution behaviors were also investigated. The selected freeze-dried nanoparticles had a mean particle size range of 353–441 nm, a polydispersity index ranging between 0.167 and 0.229 and a zeta potential between −25.7 and −20.7 mV. These results suggest that material and process parameters were successfully optimized. DSC and XRPD spectra confirmed interactions between the formulation's components during freeze-drying. The solid nanoparticles showed 30–42% of cumulative release after 10 min compared to less than 1% of dissolution characterizing loratadine without pre-processing. This study demonstrates that preparing dried loratadine nanoparticles suitable for designing effective drug preparations is a feasible approach.

1. Introduction

Nanotechnology is one of the most widely used approaches to overcome the inconveniences of solubility and poor bioavailability, as well as a method utilized to produce intermediate compounds for different dosage forms. Nanosuspensions have numerous outstanding advantages, including enhanced solubility and dissolution rate of otherwise poorly water-soluble drug compounds, high adhesiveness to biological surfaces, as well as easy formulation and scale up. Also, they allow reaching high drug concentrations and applicability in any types of drug formulations, such as preparations for oral, parenteral, dermal, pulmonary, ocular and nasal delivery (Bartos et al., 2015a; Chen et al., 2015; Merisko-Liversidge and Liversidge, 2008; Patravale et al., 2004; Pawar et al., 2014).

Nanosuspensions are colloidal dispersions of drug particles in the submicron size (mean particle size less than 1 μm) and need to be stabilized by a minimum amount of suitable ionic or/and steric stabilizer. The drug compounds (active pharmaceutical ingredients, APIs) included in nanosuspensions can exist in crystalline or amorphous forms. The produced liquid pre-dispersion can be converted into intermediate solid products, such as powder, by means of drying or into a semi-solid formulation, such as gel (Bartos et al., 2016; Hao et al., 2015; Lindfors et al., 2007; Rabinow, 2004).

Top-down and bottom-up procedures are generally applied for the preparation of nanosuspensions. The top-down approach includes comminution of large particles into nanoparticles, while the bottom-up approach employs the precipitation of nanoparticles from dissolved drug molecules. Although the top-down method is preferred in the pharmaceutical industry, the bottom-up method has the potential for producing homogenous nanoparticles with lower energy input

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(Agrawal and Patel, 2011; Du et al., 2015; Iurian et al., 2017; Möschwitzer, 2010; Müller et al., 2011; Rahim et al., 2017).

Antisolvent precipitation is the most common and effective bottom-up technique currently applied in nanosuspension preparation. Its advantages include simplicity and cost-effectiveness. The method of antisolvent precipitation is based on the principle that a compound's solubility in a water-miscible organic solvent can be modified by adding an antisolvent which promotes precipitation. During precipitation, stabilizers dissolved in the antisolvent get absorbed on the crystal surfaces to inhibit further crystal growth (Ambrus et al., 2009; Matteucci et al., 2006).

Ultrasonication has been introduced as an effective method to be combined with precipitation to achieve an enhanced particle size reduction and to control the processes of nucleation and crystallization. When applied on liquid, ultrasound waves are characterized by a cyclic succession of expansion and compression phases, with compression cycles exerting a positive pressure and pushing the liquid molecules together, while expansion cycles exert a negative pressure and pull the molecules apart. Besides, ultrasound waves intensify mass transfer by initiating cavitation. Cavitational bubbles are formed during the negative-pressure phase. The phenomena of the formation, growth and subsequent collapse of microbubbles release a large magnitude of energy. When a bubble collapses, a confined hot spot with high temperature and pressure is formed, releasing powerful shock waves. Thus, mixing of the solvent and the antisolvent is enhanced, leading supersaturation of the mixture. Furthermore, the implosion of vacuum bubbles breaks down particles. The final results of this process are dependent on sonication duration and intensity, on the sonotrode's length and depth of immersion, as well as on temperature (Anil et al., 2016; Bartos et al., 2015b; Dhumal et al., 2008; Jiang et al., 2012; Liu et al., 2012; Mishra et al., 2015; Wu et al., 2013; Xia et al., 2010; Zhang et al., 2006).

In terms of stability, liquid nanosuspensions are characterized by physical and chemical instability attributed to aggregation, agglomeration, Ostwald ripening and changes of the crystalline state (Lindfors et al., 2007). Thus, an immediate transformation of nanosuspensions into solid nanoparticles facilitates stability and allows processing to produce various dosage forms. Freeze-drying is one of the most widely used methods for drying nanosuspensions. However, even the freeze-drying process may induce stress, which in turn influences the physical stability of nanosuspensions. The stress evoked during the freezing and drying phases can destabilize the colloidal system. During freezing, a phase separation is experienced, yielding ice and a cryo-concentrated solution phase. This highly concentrated system may promote aggregation of the particles. Moreover, the crystallization of ice may produce a mechanical stress on the nanosized particles, also leading to their destabilization. On the other hand, the dehydration phase involves the removal of ice and unfrozen water which remained dissolved or adsorbed on the solid phase (Abdelwahed et al., 2006a, 2006b; Beirowski et al., 2011; Quintanar-Guerrero et al., 1998; Van Eerdenbrugh et al., 2008; Wu et al., 2011).

Consequently, numerous parameters play a significant role in the particle size and properties of nanosuspension-based freeze-dried nanoparticles, including drug concentration, type(s) and concentration(s) of stabilizer(s), solvent type and solvent to antisolvent ratio, as well as sonication and drying conditions and additives. Thus, nanosuspension preparation with ultrasonic-assisted precipitation and freeze-drying of these nanosuspensions are complex asks that require a careful selection of both process and material parameters.

Loratadine (LOR), a second-generation histamine H_1 receptor antagonist, is the most frequently prescribed antihistamine drug for the treatment of allergic conditions, such as rhinitis, urticaria and atopic dermatitis. Recent studies have also reported LOR as a safe and effective emergency therapy for the management of bone pain induced by granulocyte-colony stimulating factors (G-CSFs). It is reported that10 mg of LOR is effective against NSAID-resistant severe G-CSF-induced bone pain (Moore and Haroz, 2016; Romeo et al., 2015). The compound's properties classify LOR as a class II agent according to the biopharmaceutical classification system, characterized by poor water solubility (3.03 µg/ml) and high permeability (logP = 5). It is a weak base with a reported pKa value of 5.25 at 25 °C, responsible for its pH-dependent solubility, and consequent variability in bioavailability (Dagenais et al., 2009; Han et al., 2004; Popović et al., 2009). Various techniques have been applied to enhance the solubility and dissolution properties of LOR, including solid dispersion, inclusion with ß-cyclodextrin derivatives, micellar solubilization and self-microemulsifying systems. Other studies have also reported the preparation of a LOR in situ gel as niosomes, as well as a nanoparticle loaded thermosensitive in situ gel for nasal delivery(Frizon et al., 2013; Hin Teng et al., 2015; Li et al., 2015; Nacsa et al., 2008, 2009; Popović et al., 2009; Vyshnavi et al., 2015).

The present research is known to be the first work to utilize the ultrasonic-assisted antisolvent precipitation approach to prepare LOR nanosuspensions (LNs), using cellulose derivatives (i.e. hydroxylpropylmethylcellulose, HPMC), polyvinylpyrrolidone (PVP-K25), Poloxamer 188 (Pluronic F 68), polysorbate (Tween 80) and sodium lauryl sulfate (SLS) either as a single stabilizer or in combination. The effects of the type(s) and concentration(s) of the stabilizer(s) on mean particle size were investigated. The novelty of our research includes the preparation of a nanoscale LOR powder that can be used as an intermediate for designing different dosage forms.

2. Materials and methods

2.1. Materials

LOR was purchased from Teva Ltd. (Budapest, Hungary). Hydrophilic polymers; Polyvinylpyrrolidone K-25 (PVP-K25) was supplied by ISP Customer Service GmBH (Cologne, Germany) and hydroxypropylmethylcellulose E50LV (HPMC) was supplied by Colorcon (Budapest, Hungary). Pluronic F68, a synthetic tri-block copolymer, was purchased from BASF (Ludwigshafen, Germany). The non-ionic surfactant Tween 80 was supplied by Fluka Chemika (Buchs, Switzerland), the anionic surfactant sodium lauryl sulfate (SLS) was supplied by Molar Chemicals Ltd. (Budapest, Hungary), methanol was purchased from FreeHand Ltd. (Pecs, Hungary), ethanol was supplied by Spectrum-3D (Debrecen, Hungary), and D-(+)-trehalose (TRE) was supplied by Sigma-Aldrich (New York, USA). Water was purified by double distillation.

2.2. Methods

2.2.1. Preliminary studies with LOR: solubility tests

Excess drug amount was added into 5 ml of distilled water or phosphate buffer solution (PBS; pH 7.4), followed by shaking at 25 °C for 24 h. A sample was taken, filtered and the amount of dissolved LOR was measured spectrophotometrically (Unicam UV/VIS Spectrophotometer, Cambridge, UK). Solubility in other solvents was determined gravimetrically by adding an excess amount of LOR into 5 ml of different water-miscible solvents, such as ethanol, acetone and methanol. The drug-containing solution was stirred at 4000 rpm for 1 h at room temperature (25 °C), and then 1 ml of each solution was filtered into a drying dish. The filtrate was allowed to stand for solvent evaporation, and the residual mass was weighed on a daily basis, using an analytical balance (Mettler Toledo Ax 205, d = 0.01 mg) to make sure of the total removal of the solvent. Constant mass indicates the solubility in 1 ml of the solvent used.

2.2.2. Preparation of loratadine nanosuspension (LN)

After the preliminary studies, LNs were prepared using the precipitation-ultrasonication method. LOR was dissolved in ethanol according to its solubility, while the stabilizer(s) was (were) dissolved in