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Fabrication of drug-loaded edible carrier substrates from nanosuspensions by flexographic printing

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ABSTRACT

The main goal of the current work was to investigate the possible use of flexographic printing for the conversion of nanosuspensions into solid dosage forms. Aqueous nanosuspensions of indomethacin (IND) and itraconazole (ITR) with Poloxamer 407 as the stabilizer agent were prepared by wet ball-milling. The nanosuspensions were flexographically printed on three different substrates, including two commercially available edible substrates. The printed formulations were characterized with X-ray diffractometry (XRD) and scanning electron microscopy (SEM). In addition, dissolution studies for the printed IND and ITR formulations were conducted. The mean particle size of milled nanosuspensions of IND and ITR was 422.6 ± 7.7 nm and 698.1 ± 14.0 nm, respectively. The SEM imaging showed even distribution of nanosuspensions on the substrates after printing without any evident agglomeration. The printed formulations contained drug at least partially in crystalline form. The drug dissolution rate from the prepared formulations was improved compared to the pure drug. The drug release from the preparations on edible substrates was slightly slower due to the incorporation of the drug particles into the substrate matrix. In conclusion, the results indicated that flexographic printing can be considered as a promising fabrication method of solid nanoparticulate systems with enhanced dissolution behavior.

1. Introduction

The majority of new active pharmaceutical ingredients (APIs) under development possess insufficient water solubility and/or low dissolution rate (Gursoy and Benita, 2004; Hauss, 2007; Lipinski, 2000). These properties cause challenges to achieve desired bioavailability in formulations, where poor solubility of APIs is the limiting step of drug absorption.

Production of nanosuspensions allows obtaining particles in the sub-micron size range. It is a common method to enhance the solubility and dissolution rate of poorly water-soluble APIs. Nanoparticles can be obtained either by "bottom–up" or "top–down" approaches. "Bottom–up" approaches are based on the crystallization or precipitation of drug molecules into nano-size particles. For pharmaceutical applications "top–down" methods, such as high pressure homogenization and wet media milling with pearl mill are most commonly used in the nano-sizing of particles (Ali at al, 2011; Kakran et al., 2012; Keck and Müller, 2006; Müller and Peters, 1998; Van Eerdenbrugh et al., 2008b). In wet ball-milling technique particle size of the drug is reduced by mechanical grinding of aqueous mixture of a drug and a stabilizing polymer with the aid of milling pearls (Liu et al., 2011). The model compounds indomethacin (IND) and itraconazole (ITR) used in this study belong to the II class of the biopharmaceutical classification system (BCS) and therefore have low solubility and high permeability (Amidon et al., 1995). Reduction in the particle size is directly connected to the increase in the available surface area. Based on the Noyes–Whitney equation, an increase in the available surface area affects proportionally the dissolution rate of the active compound (Merisko-Liversidge and Liversidge, 2008; Noyes and Whitney, 1897).

Numerous studies have been conducted to show the benefits of wet ball-milling technique for the preparation of pharmaceutical

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formulations with improved dissolution rate. Several stabilizing agents, such as hydroxypropyl cellulose (HPC) (Cerdeira et al., 2010, 2013; Chung et al., 2012; Figueroa and Bose, 2013; Lee 2003), polyvinylpyrrolidone (PVP) (Ali et al., 2011; Cerdeira et al., 2010; Ghosh et al., 2011), poloxamers (Cerdeira et al., 2010, 2013; George and Ghosh, 2013; Ghosh et al., 2011; Liu et al., 2011; Nakarani et al., 2010; Van Eerdenbrugh et al., 2008c), D-α-tocopherol polyethylene glycol succinate (TPGS) (George and Ghosh, 2013; Ghosh et al., 2011a,b) and others have been used in the production of nanosuspensions by wet ball-milling technique. The addition of ionic surfactants has also been investigated in several studies (Cerdeira et al., 2010, 2013; Figueroa and Bose, 2013; George and Ghosh, 2013; Ghosh et al., 2011; Van Eerdenbrugh et al., 2008c).

Despite evident benefits of nanosuspensions, challenges remain in ensuring the stability of nanosuspensions. One of the main problems is maintaining the size of the particles upon storage. This is due to their tendency to aggregate into thermodynamically stable state due to the high surface energy that promotes attraction interactions between the particles (Merisko-Liversidge and Liversidge, 2008; Van Eerdenbrugh et al., 2008a). In addition, preserving microbial stability of aqueous nanosuspensions can be a problem in providing a long-term shelf-life of the preparations.

Freeze-drying (Chung et al., 2012; Nakarani et al., 2010; Van Eerdenbrugh et al., 2008b) and spray-drying (Figueroa and Bose, 2013; Kayaert and Van den Mooter, 2012; Lee 2003) have been exploited to improve the stability of those nanoparticulate systems by converting nanosuspensions into more stable solid dosage forms. However, these methods are time-consuming and require additional excipients for the stabilization of formulations during the production process. Therefore, there is still a need for more cost-effective and feasible methods that are able to convert nanosuspensions into solid dosage forms, which possess the unique characteristics of nanosuspensions upon re-dispersion, such as the nano-size range of the drug particles and a desired dissolution profile.

Printing technology offers several opportunities in the production of solid dosage forms (Sandler et al., 2011). Inkjet and flexographic printing are two technologies that can be used in the deposition of drug solutions, suspensions, emulsions etc. on the substrates in a controlled manner (Genina et al., 2012; Janßen et al., 2013; Pardeike et al., 2011; Raijada et al., 2013). Both techniques have been used in the manufacturing of personalized medicines (Genina et al., 2012, 2013; Janßen et al., 2013; Raijada et al., 2013). Inkjet printing of suspensions with micro-sized drug particles has been reported to be problematic due to nozzle clogging, whereas printing of nano-sized folic acid suspension with Tween 20 has been conducted previously by inkjet printing and formed micro-sized droplets with the diameter $\leq 5\,\mu m$ without any clogging (Pardeike et al., 2011). Robust and fast flexographic printing has been successfully applied to print solutions of rasagiline mesylate (Janßen et al., 2013) and piroxicam (Raijada et al., 2013) as well as micro-sized suspension of tadalafil (Janßen et al., 2013). Flexographic printing is a roll-to-roll imprinting method, where an uniform layer of printing ink is transferred from the an anilox roll to a patterned printing plate that further carries the ink to a substrate that is attached to an impression roll (Genina et al., 2012; Janßen et al., 2013). The volume of the cells on the anilox roll determines the amount of the ink printed and a doctor blade on the anilox roll ensures the removal of the excess ink. Flexography can be used to print various ink formulations on several substrates. One major challenge of flexographic printing is dosing precision (Genina et al., 2012). The exploitation of flexography was mentioned by Janßen et al. (2013) as a potential option to enable a flexible and continuous manufacturing process of nanoparticulate solid dosage forms.

The goal of this research was to investigate the use of flexographic printing as an alternative production method of solid dosage forms from nanosuspensions prepared by ball-milling. Two drug compounds with poor water solubility – itraconazole (ITR) and indomethacin (IND) – were chosen as model agents for the deposition of nanosuspensions by flexographic printing on different substrates. Commercially available edible substrates were used as carrier material while transparency film was used as a non-porous reference material. This approach could be beneficial to enhance the dissolution rate of poorly water-soluble low-dose drugs and increase their stability against aggregation.

2. Materials and methods

2.1. Materials

Indomethacin (IND) (Hawkins, MN, USA) and itraconazole (ITR) (Orion Pharma, Finland) were used as poorly water-soluble model compounds. A non-ionic surfactant Poloxamer 407 (Pluronic® F-127) (BASF Co., Ludwigshafen, Germany) was used as a stabilizer in the preparation of aqueous nanosuspensions.

Potassium dihydrogen phosphate (Sigma–Aldrich Inc., USA) and hydrochloric acid (≥37%, Sigma–Aldrich Inc., USA) were used for the preparation of dissolution media. Trifluoroacetic acid (TFA) (99%, Sigma–Aldrich Inc., USA) and acetonitrile (ACN) (≥99.9%, Fisher Scientific UK Ltd., UK) were of analytical grade and used for the mobile phase preparation in high performance liquid chromatography (HPLC) analysis. Purified water (Milli-Q) was used as a solvent.

The nanosuspensions were printed on three different substrates – transparency film (TF) (Dataline™, Esselte Office Products Oy, Finland), rice sheet (RS) (Easybake® edible rice paper, N.J. Products Ltd., UK) and rice paper (RP) (Blue Dragon® Spring Roll Wrappers, UK).

2.2. Preparation of nanosuspensions

Aqueous nanosuspensions with ITR and IND were made by a wet ball-milling technique, using a planetary ball mill (Pulverisette 7 Premium, FritschCo., Idar-Oberstein, Germany). Poloxamer 407 with the concentration of 60 wt% of the drug amount was used as a stabilizer. The solid ingredients of the mixture were inserted into a zirconium oxide milling vessel with 70 g of milling pearls (zirconium oxide, diameter 1 mm) and 10 ml of water was added. The grinding was performed at 1100 rpm with 10 cycles, each cycle consisting of 3 min of grinding and 10 min pause. The nanosuspensions were separated from the grinding pearls by sieving with additional 10 ml of water to collect the residual suspension. The concentrations of the prepared nanosuspensions with IND and ITR were 145.1 mg/ml and 112.2 mg/ml, respectively.

2.3. Particle size distribution

The mean particle size and polydispersity index (PI) of the nanosuspensions were measured by dynamic light scattering (DLS) (Malvern Zetasizer Nano ZS, Malvern Instrument, Malvern, UK). A part of the fresh nanosuspension was diluted with water in order to achieve a suitable concentration for the measurements by DLS. Before the analysis the nanosuspensions were sonicated for 4 min. The measurements were performed in triplicate.

2.4. Flexographic printing

A laboratory scale printability tester (IGT Global Standard Tester 2, IGT Testing system, the Netherlands) was used for the preparation of flexographically printed formulations. A relief

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