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Feasability of a new process to produce fast disintegrating pellets as novel multiparticulate dosage form for pediatric use

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ABSTRACT

Novel orally disintegrating system based on multiparticulate form was developed, offering an alternative to encounter major issues in the design of dosage form for pediatric patients, i.e., the difficulty in swallowing large solid dosage form (tablet or capsule), and the requirement to cover a broad range of doses for different age groups. Microcrystalline cellulose-based pellets containing acetaminophen were prepared via extrusion/spheronization followed by freeze-drying. The in vitro disintegration behavior of these pellets was quantitatively measured with a texture analyzer. Mercury intrusion and gas adsorption techniques, scanning electron microscopy of pellet surface and cross-section were performed in order to characterize their internal porous structure. Pellets characteristics such as size distribution, sphericity, friability and drug release were also determined. The developing process was able to produce pellets containing high drug loading (25, 50 and up to 75%, w/w) with good sphericity (aspect ratio ~1) and low friability. The pellets exhibited an instantaneous disintegration upon contact with water, which was indicated by two parameters: the disintegration onset was approximating to 0, and the disintegration time less than 5 s. The fast disintegration behavior is correlated with the pellet internal structure characterized by a capillary network with pore diameter varying from 0.1 to 10 μm. Such a structure not only ensured a rapid disintegration but it also offers to freeze-dried pellets adequate mechanical properties in comparison with conventional freeze-dried forms. Due to pellet disintegration, fast dissolution of acetaminophen was achieved, i.e., more than 90% of drug released within 15 min. This novel multiparticulate system offers novel age-appropriate dosage form for pediatric population owing to their facility of administration (fast disintegration) and dosing flexibility (divided and reduced-size solid form).

1. Introduction

Due to the lack of approved drugs and appropriate formulations, children represent the most vulnerable patients. The World Health Organization (WHO) estimates that ~50% of the medicines prescribed for children are not commercially available in pediatric form (Nahata and Allen, 2008). To ensure a simple and safe drug administration, a dosage form intended for pediatric use requires a particular design because of specific characteristics of this population. Main challenges in the design of such dosage form include how to encounter the dosing issues and to facilitate the medicine administration (Breitkreutz and Boos, 2007; Nunn and Williams, 2005; Schirm et al., 2003). Indeed, pediatric patients constitute a heterogeneous population of widely varying ages that is going through periods of rapid growth, maturation and development (Bowles et al., 2010; Dotta et al., 2011). The magnitude of dose required must be consequently adapted to this change and usually related to children's body weight. There are also significant changes in the ability to handle different dosage forms. Age-adapted dosage forms are essential for younger age groups. Children under six years old have difficulties in swallowing conventional solid dosage forms such as tablets and capsules because of their size and hardness. Liquid dosage forms often prescribed are easier to administer but may be limited in use due to their stability, packaging, inaccurate dosing and cost (Sosnik et al.,

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2012). In a report of the informal expert meeting on dosage forms of medicines for children, WHO recommended that small sized solid forms and/or orally disintegrating solid forms should be favored (WHO, 2008).

Pellets are small spherical solid dosage form having a mean size between 0.5 and 2 mm (in diameter). Pellets have been readily investigated as controlled drug delivery system because they offer advantages over single-unit dosage form, such as less irritation of the gastrointestinal tract, lowered risk of side effects due to dose dumping, reproducible drug blood levels (Wang et al., 2015; Qi et al., 2015; Hung et al., 2015; De Barros et al., 2015; Vervaet et al., 1995). As multiparticulate dosage form, pellets are particularly interesting in the development of medicines for children. Since each individual unit contains a small amount of drug, dose adjustment can be accurately achieved by means of dosing device e.g., particulate counting devices or volume/weight measuring devices. Flexible dosing dosage form allows therefore covering a broad range of doses for different age groups and especially for children suffering chronic diseases. The most commonly used pelletization technique is extrusion/spheronization because it offers a number of technological advantages: ease of operation, high throughput process, pellets produced having narrow size distribution and low friability, ability of high drug loading, etc. (Vervaet et al., 1995). Microcrystalline cellulose is considered as standard pelletization aid in extrusion/spheronization because it provides the most suitable plasticity and cohesiveness to the wet mass prior to extrusion and spheronization (Law and Deasy, 1998; Mastropietro and Omidian, 2013; Thommes and Kleinebudde, 2006). However, microcrystalline cellulose based pellets have a prolonged disintegration time (Kleinebudde, 1994; Zimm et al., 1996). Various approaches have been evaluated to overcome this limitation e.g., partial or total substitution of microcrystalline cellulose with soluble diluents (Fielden et al., 1993; Ku et al., 1993; Sousa et al., 2002; Baert et al., 1992; Goyanes et al., 2010), incorporation of superdisintegrants (Souto et al., 2005; Schröder and Kleinebudde, 1995; Goyanes et al., 2011, 2013). The production of orally disintegrating pellets constitutes therefore a great challenge.

The European Pharmacopoeia describes orally disintegrating tablets as uncoated tablets intended to be placed in the mouth where they disperse rapidly i.e., within 3 min before being swallowed. FDA defines orally disintegrating tablet as a solid dosage form which disintegrates rapidly within a matter of seconds when placed upon a tongue. Hence, this kind of dosage form is claimed to be the most convenient mode of medicine administration for pediatric population and other patients with dysphagia. It can disintegrate and/or dissolve spontaneously in the oral cavity, resulting in a suspension or solution that can be easily swallowed. Also, fast disintegrating systems have all advantages of solid dosage forms e.g., good stability, accurate dosing, easy handling by patients and advantages of liquid formulations e.g., easy administration, no risk of suffocation due to physical obstruction (Habib et al., 2000; Saigal et al., 2008). Different technologies have been investigated to develop orally disintegrating tablets with a particular shift to freeze-drying (Saigal et al., 2008; Parkash et al., 2011; AlHusban et al., 2010). Indeed, tablets prepared by freeze-drying technique possess highly porous structure that enhances the water adsorption and hence facilitates rapid disintegration (Schwegman et al., 2005; Liu, 2006). However, due to a very large pore size (>10 μm), freeze-dried products are extremely brittle and difficult to handle (Lafon, 1986; Kearney and Wong, 1997; Green and Kearney, 1999; Corveleyn and Remon, 1997). Achieving a better mechanical strength that is suitable for packaging and handling is therefore a critical factor during the development of orally disintegrating systems. The association of extrusion-spheronization and freeze-drying was also applied to pellets (Balaxi et al., 2010; Lutchman et al., 2005). Pellets of high porosity could be obtained by varying the operating conditions. Since porosity and pore size distribution are known to affect drug release, these findings may be useful in the delivery of drugs (Balaxi et al., 2010). High porosity could also improve the penetration of water in the pellets and then the disintegration of pellets which is important for orodispersible solid dosage forms.

The aim of this study is to evaluate the feasibility of combining these two well-established technologies i.e., extrusion/spheronization and freeze-drying in order to produce pellets that have fast disintegration and better mechanical strength as a novel dosage form for pediatric use. An instantaneous disintegration of the pellets while maintaining their mechanical strength would be interesting for paediatric orodispersible solid dosage forms. Acetaminophen was used as a model drug.

2. Materials and methods

2.1. Materials

Pulverized acetaminophen from Cooper (Melun, France); microcrystalline cellulose Avicel PH 101 from FMC (Cork, Ireland); acetonitrile HPLC grade (99.9%), trimethylamine HPLC grade (99.9%) and monobasic potassium phosphate crystalline (KH_2PO_4) from Fischer Chemical (Leicestershire, UK); phosphoric acid powder analytical grade (99.9%) from Merck (Darmstadt, Germany). All materials were used as received. Particle size distribution of acetaminophen and microcrystalline cellulose (MCC) were determined by Mastersizer S (Malvern Instrument, Orsay, France) and were presented in Table 1.

2.2. Methods

2.2.1. Pellet manufacturing process

Fig. 1 illustrates the manufacturing process of the pellets developped. 100 g of microcrystalline cellulose or blends of microcrystalline cellulose and acetaminophen (25, 50 and 75%, w/w) previously mixed for 10 min in a Turbula mixer (Bachofen Maschinenfabrik, Basel, Switzerland) was granulated by means of a planetary mixer fitted with a K-beater attachment (Kenwood, Croydon, UK). Demineralized water was gradually added into the powder blend during 1 min and the mixer was stirring at minimum speed for further 5 min. Any caked paste was regularly removed from the wall of the mixing bowl and the K-mixing arm to ensure uniform water distribution through the wet mass. The extrusion was performed on an Alexanderwerk GA 65 cylinder extruder (Remscheid, Germany) equipped with two counter-rotating cylinders: the granulating cylinder is perforated (1-mm diameter hole) and the other cylinder is solid. The rotation speed was 96 rpm and the wet mass was introduced between the two cylinders by gravity. The extrudates were spheronized for 1 min in a Caleva 15 spheronizer (Dorset, England) rotating at 765 rpm. Pellets were subsequently dried in an Epsilon 2–4 freeze-dryer (Martin Christ, Osterode am Harz, Germany). The freeze-drying included a freezing at −45 °C for 2 h, a primary drying (0.014 mbar, −10 °C shelf temperature, for 10 h) and a secondary drying (0.0014 mbar, 20 °C shelf temperature, for 10 h). Pellets were also dried by oven at

Table 1
Particle size distribution of raw materials (in micrometers).

	$D(4, 3)$	$D(v, 0.1)$	$D(v, 0.5)$	$D(v, 0.9)$
Acetaminophen	11.6	1.9	7.2	27.9
Avicel PH 101	62.3	14.5	53.6	122.8

$D(4, 3)$ is the volume mean diameter; $D(v, 0.5)$ is the size of particle at which 50% of the sample is smaller and 50% is larger than this size; $D(v, 0.1)$ and $D(v, 0.9)$ the size of particle for which 10% and 90% of the sample is below this size, respectively.