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Microstructural investigation using synchrotron radiation X-ray microtomography reveals taste-masking mechanism of acetaminophen microspheres

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ABSTRACT

The structure of solid drug delivery systems has considerable influence on drug release behaviors from particles and granules and also impacts other properties relevant to release characteristics such as taste. In this study, lipid-based microspheres of acetaminophen were prepared to mask the undesirable taste of drug and therefore to identify the optimal formulation for drug release. Synchrotron radiation X-ray computed microtomography (SR-μCT) was used to investigate the fine structural architectures of microspheres non-destructively at different sampling times during drug release test, which were simultaneously determined to quantitatively correlate the structural data with drug release behaviors. The results demonstrated that the polymeric formulation component, namely, cationic polymethacrylate (Eudragit E100), was the key factor to mask the bitter taste of acetaminophen by inhibiting immediate drug release thereby reducing the interaction intensity of the bitter material with the oral cavity taste buds. The structure and morphology of the microspheres were found to be influenced by the shape and particle size of the drug, which was also an important factor for taste-masking performance. The quantitative analysis generated detailed structural information which was correlated well with drug release behaviors. Thus, SR-μCT has been proved as a powerful tool to investigate the fine microstructure of particles and provides a new approach in the design of particles for taste masking.

1. Introduction

Undesirable taste is one of the top factors governing patient compliance, especially in paediatric medicines or to the sensitive patient population. Therefore, many taste masking technologies have been developed and used to address the patient compliance problem. These include coating (Douroumis et al., 2011; Guffon et al., 2012; Guhmann et al., 2012; Hamashita et al., 2008; Menjoge and Kulkarni, 2007; Ostrowski et al., 2010), granulation (Guhmann et al., 2014), encapsulation into microcapsules and microspheres (Freitas et al., 2005), solid dispersions (Chiappetta et al., 2009; Gryczke et al., 2011; Haware et al., 2008; Kulkarni and Amin, 2008; Shah and Mashru, 2008; Shiino et al., 2012), ion exchange resins to sustain the release of drugs in saliva (Patra et al., 2010; Rahman et al., 2012; Roblegg et al., 2010), complex formation to shield drugs from taste buds (Mady et al., 2010; Patel and Vavia, 2008; Shah and Mashru, 2010; Tan et al., 2012), sweeteners to mask the bitter taste (Albertini et al., 2004; de Aguiar et al., 2010; Fini et al., 2008; Harada et al., 2010; Sheshala et al., 2011a), and taste suppressants to reduce the ability of taste buds to perceive bitter taste (Katsuragi et al., 1995). The microencapsulation and microspheres are valuable techniques applicable to mask the unpleasant taste as well as to protect materials from volatilizing and oxidation (Ayenew et al., 2009). Microencapsulation processes are generally based on the principle of solvent extraction or evaporation.

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However, residual organic solvents cause safety risk for their applications. Therefore, the other techniques such as spray drying and spray congealing are also utilized for microencapsulation (Singh et al., 2010). It is well known that many properties of materials are determined by their structures. At the particle level, it seems that there is an absence of reports about the relationship between taste and particle microstructure.

From another perspective, *in vitro* drug release testing approaches have been widely used to predict or quantify the effect of the taste-masking technique. Release characterization at mimic oral cavity conditions could effectively evaluate the taste masking effectiveness by reducing contact between the bitter active pharmaceutical ingredient (API) and oral cavity taste bud regions (Sheshala et al., 2011b; Shukla et al., 2009).

Moreover, the rate and mechanism of the drug release from solid dosage forms strongly depend upon the morphology such as shape and surface of the dosage form. For example, the rough pellets showed fast release rate than smooth or spherical pellets approximately after 2 h of release (Lorck et al., 1997). Yajima et al. (1999) prepared wax matrix of clarithromycin by different conditions. It was found that the morphology properties which were influenced by atomizer wheel speed affected the release behavior of the matrix to control the taste properties. However, the taste masking characteristics of drugs have not been quantitatively correlated with their internal microstructure.

The internal micro-structure of pharmaceutical tablets not only influences the mechanical strength of the tablets but also impacts the release rate of APIs (Gane et al., 2006). A good correlation has been also reported between the total porosity, mean pore diameter and drug release rate for erosion matrix drug loaded pellets, while these porosity parameters were important when evaluating the *in vitro* performance during the controlled release of an insoluble drug (Mehta et al., 2000). Recently, SR-μCT has been used for the microstructural investigation of pellet, it is reported that the release profile of single pellet correlated well with the steric features like drug loading, volume, and surface area (Yang et al., 2014). Therefore, it possibly indicates that the microstructure of taste masking particles or granules are closely relates to effectiveness in taste masking.

Moreover, characterization and evaluation of taste masked products are of significant interest. In addition to drug release testing, conventional methods have been employed for powders, including particle size analysis, porosity measurement, morphology analysis, differential scanning calorimetry (DSC) and X-ray diffraction (XRD) (Hu et al., 2009; Malik et al., 2011; Qi et al., 2008; Shah et al., 2012; Tange et al., 2013; Xu et al., 2008; Yan et al., 2010). However, these methods are not able to directly investigate the internal fine structures and identify their roles in taste masking of the various ingredients. Therefore, a quantitative method to correlate the detailed structural information with the drug release behavior will provide mechanistic and new knowledge for taste-masking technologies.

Synchrotron radiation X-ray computed microtomography (SR-μCT), a novel technique for investigation of the internal three dimensional (3D) structures for various objects, shows great possibilities for quantitative evaluation and design for solid drug delivery systems. Our previous studies have shown that the interior porous channels and irregular structures can be quantified by the fractal dimensions, which were also well correlated with the drug release kinetics of felodipine osmotic pump tablets (Yin et al., 2013). After the surface morphology and the internal 3D structure of felodipine osmotic pump tablets was visualized, the intrinsic drug release kinetics and 3D parameters, such as surface areas of the remaining core, were quantitatively elucidated using SR-μCT (Li et al., 2012). SR-μCT has also been used non-destructively to investigate the mixing and segregation of granular materials in three-dimensions combined with statistic method (Liu et al., 2013). Additionally, Noguchi et al. (2013) applied CT using synchrotron X-ray radiation for the structural analysis of fine granules containing drugs prepared by melt granulation with irregular shape.

In this study, acetaminophen was used as a model for drugs with the bitter taste. Acetaminophen lipid microspheres prepared by spray congealing were examined by SR-μCT to give quantitative analysis for the internal 3D structure and taste masking. The primary objectives were to study the micro-structural basis of lipid microspheres for taste-masking by sustaining the release of drug and further to provide new knowledge and method for evaluation of taste-masking formulations.

2. Materials and methods

2.1. Materials

Acetaminophen with purity of 99.45% was provided by Anhui Fengyuanlikang Pharmaceutical Co., Ltd., China. Octadecanol and Eudragit E100 (PMA), as the excipients for taste masking were supplied by Hunan Erkang Pharmaceutical Co., Ltd., and Hanghai Chineway Pharmaceutical Tech. Co., Ltd., respectively. Sodium phosphate monobasic dehydrate, sodium hydrogen phosphate and phosphoric acid, used for dissolution test, were provided from Sinopharm Chemical Reagent Co., Ltd., China.

Taste masking microspheres were prepared using a spraying technique (Spray gun, W-71, Iwata, Japan). Inverted phase contrast microscopy (TS-100F, Nikon, Japan) and a particle sizing system (Camsizer XT, Retsch, Germany) were used for morphology characterization. Dissolution test was performed using a dissolution apparatus (ZRS-8G, Tianjin Haiyida Co., Ltd., China). The Synchrotron radiation X-ray microtomography scans were carried out at the Shanghai Synchrotron Radiation Facility (SSRF) in Shanghai Institute of Applied Physics, Chinese Academy of Sciences (Shanghai, China). Data were analyzed using the commercially available software VGStudio Max (Version 2.1, Volume Graphics GmbH, Germany) and Image Pro analyzer 3D (version 7.0, Media Cybernetics, Inc., Bethesda, MD, USA).

2.2. Preparation of acetaminophen lipid microspheres

Acetaminophen lipid microspheres were prepared by the addition of an appropriate amount of PMA, which can only dissolve at pH ≤ 5, into octadecanol at 100 °C. The various formulations are shown in Table 1. Acetaminophen as a micronized powder was gradually added whilst stirring the system at 1000 rpm and 100 °C to produce a uniform mixture. The mixture was then immediately poured into the reservoir of a spray gun preheated to 90 °C in a drying oven and sprayed such that the air dried microspheres at room temperature were collected from stainless steel trays. Batch sizes were between 30 and 50 g. The solid microspheres were sieved and the fraction sizes between 160 and 200 mesh (~75–96 μm) and 80–100 mesh (~150–180 μm) were collected for further study.

Table 1
Formulation of microspheres.

Ingredients	Formulation codes and compositions (% w/w)				
	F1	F2	F3	F4	F5
Acetaminophen	33.3	32.3	31.7	30.8	30
Octadecanol	66.7	64.5	63.3	61.7	60
PMA	–	3.2	5.0	7.5	10