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Hot-melt extrusion of sugar-starch-pellets

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ABSTRACT

Sugar-starch-pellets (syn. sugar spheres) are usually manufactured through fluidized bed granulation or wet extrusion techniques. This paper introduces hot-melt extrusion (HME) as an alternative method to manufacture sugar-starch-pellets. A twin-screw extruder coupled with a Leistritz Micro Pelletizer (LMP) cutting machine was utilized for the extrusion of different types (normal-, waxy-, and high-amlyose) of corn starch, blended with varying amounts of sucrose. Pellets were characterized for their physicochemical properties including crystallinity, particle size distribution, tensile strength, and swelling expansion. Furthermore, the influence of sugar content and humidity on the product was investigated. Both sucrose and water lowered the T_g of the starch system allowing a convenient extrusion process. Mechanical strength and swelling behavior could be associated with varying amylose and amylopectin. X-ray powder diffractometric (XRPD) peaks of increasing sucrose contents appeared above 30%. This signified the oversaturation of the extruded starch matrix system with sucrose. Otherwise, had the dissolved sucrose been embedded into the molten starch matrix, no crystalline peak could have been recognized. The replacement of starch with sucrose reduced the starch pellets' swelling effect, which resulted in less sectional expansion (SEI) and changed the surface appearance. Further, a nearly equal tensile strength could be detected for sugar spheres with more than 40% sucrose. This observation stands in good relation with the analyzed values of the commercial pellets. Both techniques (fluidized bed and HME) allowed a high yield of spherical pellets (less friability) for further layering processes. Thermal influence on the sugar-starch system is still an obstacle to be controlled.

1. Introduction

Multi-particulate oral dosage forms (e.g., pellets) offer several advantages over the commonly used single unit solid dosage forms. They demonstrate good flowability, less decomposition and a more narrow particle size distribution (Bracher et al., 2015), which is important for a dosing accuracy complying with Ph. Eur. and USP requirements. In general, multi-particulate dosage forms decrease the risk of burst-releasing the active pharmaceutical ingredient (API), thereby minimizing the possibility of unwanted side effects. In comparison to granulates, pellets show a more uniform particle size distribution and a smoother surface. Besides the lower specific surface area, the spherical shape and smooth surface render the pellets ideal for applying additional processing steps (e.g., layering), resulting in advantages such as a lower consumption of coating material and increasing the procedural cost-effectiveness. Following the coating procedure, the pellets can be filled into capsules or compressed into tablets. Once the tablet disintegrated or the capsule dissolved, sufficiently small pellets pass quickly from the stomach to the intestine.

Pellets are generally classified in two groups based on their application: API containing pellets and neutral pellets (non-pareilles, sugar spheres), which are used for API-layering processes. Several methods have been hitherto established for the manufacture of sugar-starch-pellets. The most common ones are fluidized bed granulation or pan coating system and wet-extrusion with subsequent spheronization (Werner, 2006).

The past two decades have witnessed an increased interest in hot-melt extrusion (HME) as a suitable method for the preparation of solid oral dosage forms. It is utilized to improve the bioavailability of drugs of class II and IV according to Biopharmaceutics Classification System (BCS), which show poor solubility and good or bad permeability, respectively. Within this technique, a twin-screw extruder with temperature-controlled barrel zones is used for the melting process. Excipients are fed into the screws by a hopper, located at the first barrel segment. High temperature as well as energy imparted by the movement of the screws melts the materials. The materials are then conveyed along a cone through a die-plate with several orifices to form strands. After exiting from the orifices, the melt is exposed to a cooling airflow produced by

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the die-face pelletizer, which facilitates solidification of the strands, so they can be chopped into pellets by a die-face pelletizer (Bialleck and Rein, 2011). The pelletizing machine has a rotating knife system adjoining to the exit of the extruder barrel. This technique is primarily appropriate for viscoelastic polymers with a high molecular mass. One of its advantages is that the pellets swell to their spherical shapes without a spheronization process. Furthermore, the mild cooling airflow carries the pellets to the cooling tower, where they fall from one cooling station onto the next until the pellet-bulks can be collected after exiting this tower station.

Compared to wet-extrusion techniques, HME offers additional advantages such as minimization or even elimination of the amount of solvent needed during the manufacturing process (Chokshi and Zia, 2010). This consequently shortens the time required for drying. In addition, given the HME's unique melting procedure changing the structure of the raw materials, HME products can reveal a higher mechanical stability than products obtained from fluidized bed or pan coater. HME can help reducing or even avoiding the use of organic solvents.

Bialleck and Rein (2011) introduced starches as suitable matrix-forming polymers for HME. Extruded starch forms solid solutions dissolving, or dispersing the API. It is established that the melting of starch is associated with a gelatinization process. Starch is non-toxic and biodegradable, and is thus convenient as a matrix-forming material for pharmaceutical applications (Henrist et al., 1999). The products' properties are controlled by the varying ratios of amylose and amylopectin, which results in distinct swelling behaviors. Higher amylopectin content correlates with a quicker erosion of the matrix core, which correlates to a more rapid release of the API. Conversely, high amylose contents lead to a different swelling behavior, keeping the inner core intact, thus leading to a more prolonged release. In order to modify the properties of the resulted matrix, starches can be blended with other excipients such as sucrose. When immediate release formulations are desired, a sucrose blend is advantageous due to accelerating the release of the API from the starch matrix.

Sugar-starch-pellets are monographed within the European (Ph. Eur. 7.0/1570) and the United States (USP 36 NF 31 Volume 1) Pharmacopoeia. The European Pharmacopeia requires an upper limit of 92% sucrose and a diameter of 200–2000 μm. On the contrary, the USP describes pellet sizes ranging from 700 μm–2.36 mm with a sucrose content between 62.5% and 91.5%. Both pharmacopoeiae mandate the use of corn starch.

The aim of this study was to demonstrate the feasibility of HME as a novel manufacturing platform for sugar-starch-pellets. The produced pellets were then evaluated for their appropriateness as neutral cores for layering processes. Furthermore, the manufactured pellets were compared to starch pellets and commercially available sugar spheres.

2. Materials and methods

2.1. Materials

Different types of corn starch (Corn Starch B®, Waxilys®, Amylo-N400®) were kind gifts from Roquette (Lestrem, France). Sucrose was obtained from Südzucker Group (Mannheim, Germany) and was combined with various amounts of starch for the extrusion process. Commercially available sugar spheres were provided by Hanns G. Werner GmbH + Co. KG (Hamburg, Germany).

2.2. Preparation of pellets

A co-rotating twin-screw extruder model ZSE 27HP-PH equipped with a die-face pelletizer model Leistritz Micro Pelletiser LMP (Leistritz Extrusionstechnik GmbH, Nuremberg, Germany) was used for HME (Fig. 1). A gravimetrical dosing unit K-SFS-24 (K-Tron AG, Niederflenz, Switzerland) dispensed the powder

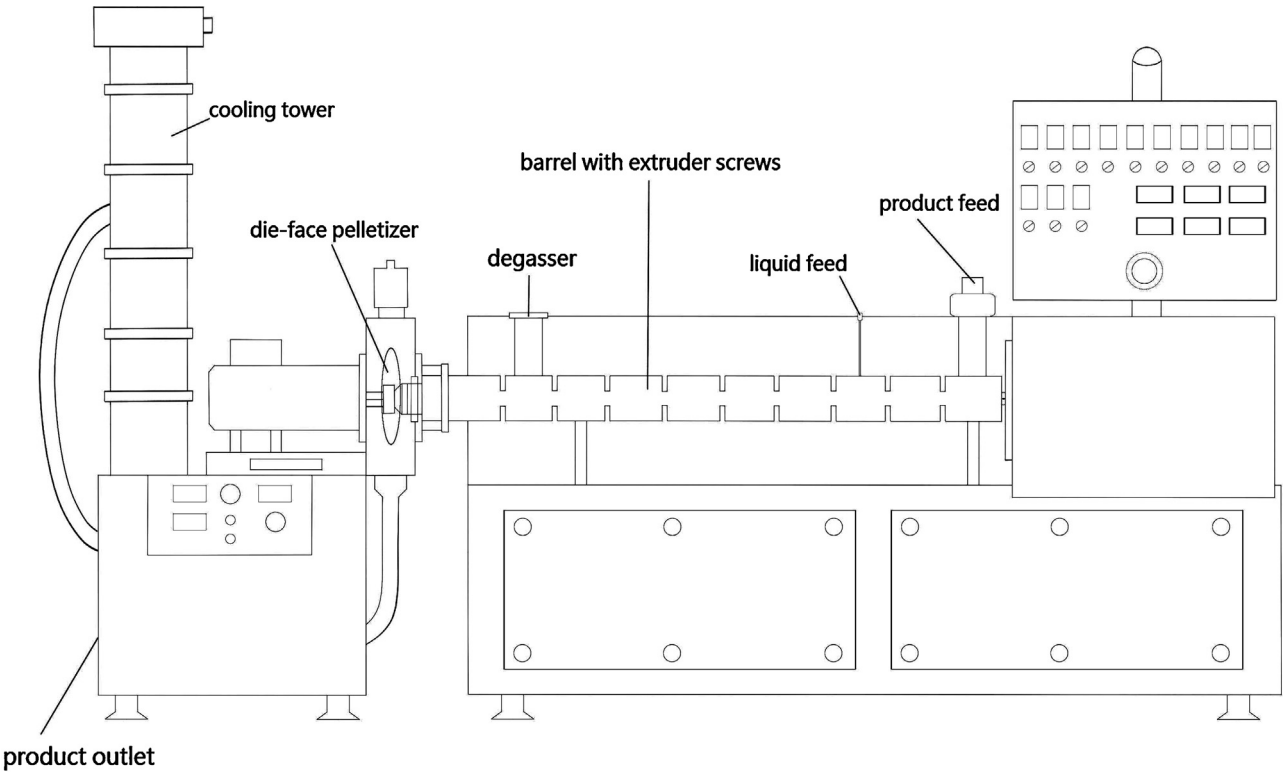

Fig. 1. Schematic demonstration of the experimental set-up.