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Optimizing the taste-masked formulation of acetaminophen using sodium caseinate and lecithin by experimental design

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ABSTRACT

In a previous study of ours, the association of sodium caseinate and lecithin was demonstrated to be promising for masking the bitterness of acetaminophen via drug encapsulation. The encapsulating mechanisms were suggested to be based on the segregation of multicomponent droplets occurring during spray-drying. The spray-dried particles delayed the drug release within the mouth during the early time upon administration and hence masked the bitterness. Indeed, taste-masking is achieved if, within the frame of 1–2 min, drug substance is either not released or the released amount is below the human threshold for identifying its bad taste. The aim of this work was (i) to evaluate the effect of various processing and formulation parameters on the taste-masking efficiency and (ii) to determine the optimal formulation for optimal taste-masking effect. Four investigated input variables included inlet temperature (X_1), spray flow (X_2), sodium caseinate amount (X_3) and lecithin amount (X_4). The percentage of drug release amount during the first 2 min was considered as the response variable (Y). A 2^4-full factorial design was applied and allowed screening for the most influential variables i.e. sodium caseinate amount and lecithin amount. Optimizing these two variables was therefore conducted by a simplex approach. The SEM and DSC results of spray-dried powder prepared under optimal conditions showed that drug seemed to be well encapsulated. The drug release during the first 2 min significantly decreased, 7-fold less than the unmasked drug particles. Therefore, the optimal formulation that performed the best taste-masking effect was successfully achieved.

1. Introduction

Spray-drying is an inexpensive and straightforward technology that has been widely used in chemical, food and pharmaceutical industry. The process involves the dispersion of a feed preparation into small droplets that come into contact with drying air, so that the droplet moisture removal takes place. This is not only a technique to transform a liquid into a dried particulate form, but also gains interest in particle engineering, e.g. microencapsulation (Columbano et al., 2003; Youan, 2004; Blanco et al., 2005; Elversson and Millqvist-Fureby, 2006; Vega et al., 2007). These works emphasize a beneficial phenomenon in which, some components have tendency to accumulate on the surface of a multicomponent droplet and hence enable to encapsulate other components as dried particle forms. It is attributed to the component segregation within the droplet prior to complete dehydration. A number of mechanisms are discussed in the literature wherein three mechanisms are mentioned by Kim (2008): (i) the first mechanism suggests that an initial layer of crust forms on the outermost layer of the droplet. Since the evaporation continues to occur, the crust increases in thickness toward the center of droplet. For this hypothesis, the segregation cannot be explained. However, the formation of crust can happen during the segregation of different components; (ii) the second mechanism suggests that the solvent and/or water migrates toward the surface while the solutes migrate to the center of the droplet. At the surface where evaporation occurs, the concentration of solutes increases. The gradient of concentration results in diffusion of solutes toward the center. As the diffusivity differs from each component, some may travel to the center at a faster rate than others; (iii) the third mechanism assumes that surface-active component moves preferentially to the liquid/air interface. As the droplet is generated, the surface-active component may quickly form a monolayer on its surface and almost instantly precipitate out by initial heating. This causes a drop in the local concentration

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near the surface of the droplets. The gradient of concentration further drives the diffusion of the surface-active component from the inner region to the surface of the droplet. Numerous works studied the effect of various factors on the drying process and therefore the particle formation, e.g. feed concentration, drying temperature, spray flow, etc. (Baras et al., 2000; Fu et al., 2001; Danviriyakul et al., 2002; Wang and Wang, 2002; Nijdam and Langrish, 2006; Raffin et al., 2006; Rattes and Oliveira, 2007; Gaiani et al., 2010, 2011). Also, some authors proposed the modeling of drying kinetics associated with spray-drying in an attempt to assess the conditions under which the aforementioned mechanisms are dominant (Meerdink and Van't Riet, 1995; Vehring et al., 2007; Wang and Langrish, 2009; Chen et al., 2011). Nevertheless, how to determine the advantageous conditions for investigated system and therefore the desired quality for final product is not thoroughly justified and is commonly case-dependent.

In the previous study, the association of sodium caseinate and lecithin was demonstrated to be promising to mask the bitterness of acetaminophen by drug encapsulation via spray-drying, since no drug was detected on the particle surface (Hoang Thi et al., 2012). The surface composition of spray-dried particles assumed that an appropriate ratio of encapsulating agents might effectively encapsulate the drug, and hence exhibits a better taste-masking efficiency. To improve the process understanding, experimental designs are adopted, which aim to simultaneously examine the effect of several input variables and their possible interactions on the output variable. This approach gives the advantage of gaining systematically the maximum informative data with a minimum number of experiments during the early stage of drug development (Huang et al., 2011; Lourenço et al., 2012). The aim of the present work is therefore (i) to evaluate the effects of various processing and formulation parameters on the taste-masking efficiency, i.e. inlet temperature, spray flow, sodium caseinate amount, lecithin amount, by using a full factorial design and (ii) to determine the optimal formulation for optimal taste-masking effect by means of a simplex design.

2. Materials and methods

2.1. Materials

Pulverized acetaminophen from Cooper (Melun, France); casein sodium salt from bovine milk (sodium caseinate) from Sigma–Aldrich (Missouri, USA); refined soybean lecithin from Alfa Aesar (Massachusetts, USA); acetonitrile HPLC grade (99.9%), triethylamine HPLC grade (99.9%) and monobasic potassium phosphate crystalline (KH_2PO_4) from Fischer Scientific (Leicestershire, England); phosphoric acid powder analytical grade (99.9%) from Merck (Darmstadt, Germany). The materials were used as received.

2.2. Methods

2.2.1. Spray-drying experiments

The feed dispersion was prepared by dissolving acetaminophen (1%, w/v), sodium caseinate and lecithin in distilled water and stirring overnight before being spray-dried in a Mini Spray Dryer B-190 (Büchi Labortechnik, Flawil, Switzerland). The spray-dryer equipped with a 0.5-mm-orifice spray nozzle was a co-current model, using compressed air as atomizing and drying air. The feed rate was set at 4 mL/min with maximum aspiration. Sodium caseinate amount and lecithin amount in the feed dispersion, the inlet temperature and the spray flow were defined by experimental design as described further. The spray-dried powders were stored at 20 °C and 12% relative humidity before analysis.

2.2.2. Determination of the drug content

A quantity of powder equivalent to 10 mg of drug was completely dissolved in distilled water and analyzed by HPLC in order to determine the drug content in the spray-dried powders. The analysis was performed on six replicates. The average content and the recovery rate related to the nominal dose were calculated.

The HPLC system was equipped with a ProStar 230 pump, a ProStar 410 auto-sampler, a ProStar 325 UV-Vis detector (Varian Inc., Les Ulis, France). The separation was performed on a Synergi Hydro-RP column (4 μm, 250 mm × 4.6 mm i.d.) (Phenomenex Inc., Le Pecq, France) conditioned at 30 °C. The mobile phase was a 16:84 (v/v) mixture of acetonitrile and an aqueous phosphate buffer containing monobasic potassium phosphate (20 mM), triethylamine (0.2 mL/L) which was adjusted to pH 3.3 with phosphoric acid solution (3 N). The flow rate was 1.0 mL/min and the injection volume was 15 μL. The effluent peak was monitored at 243 nm. Chromatographic data were integrated by a Galaxie Software.

A stock solution of acetaminophen (200 mg/L) was used to prepare seven standard solutions in the range from 1–100 mg/L with milliQ water. The method is specific since no interference between acetaminophen and excipients was detected; the recovery rate was 99.6% ($n = 9$). The calibration curve was linear in the investigated range ($y = 0.860x + 0.325$, $r^2 = 0.9999$). The limits of detection and quantification were 0.30 and 0.90 mg/L, respectively. 10 mg acetaminophen was completely dissolved in 100 mL milliQ water; 5 mL of the solution was then diluted to 50 mL milliQ water and the resulting solution marked as laboratory standard solution (10 mg/L). The precision determined by the relative standard deviation of inter-day analysis of laboratory standard solution was 1.54%.

During sample measurement, the laboratory standard solution was injected twice before sample measurement started and after every fifth sample. Result data were only taken into account if the relative standard deviation was inferior to 5%.

2.2.3. Particle size distribution by laser diffraction

The particle size distribution of spray-dried powder was measured by a Mastersizer S (Malvern Instruments, Orsay, France) using a 300 mm lens. The sample was dispersed in the dry state with compressed air at 4 bars by a powder feeder.

2.2.4. Scanning electronic microscopy (SEM)

The morphology of spray-dried particles was visualized by a Hitachi S4700 apparatus (Tokyo, Japan) operating at an accelerating voltage of 3 kV. The micrographs were taken from the powder surface previously coated with carbon.

2.2.5. Differential scanning calorimetry (DSC)

The experiment was performed on a DSC 1 (Mettler Toledo, Greifensee, Switzerland). Samples were placed into non-hermetic aluminum pans and heated from 25 to 250 °C at 10 °C/min under a nitrogen purge. The reference was an empty aluminum pan. Temperature and enthalpy readings were calibrated using pure indium and zinc.

2.2.6. In vitro drug release measurements

The experiment was performed on a continuous flow system as previously described in our study (Hoang Thi et al., 2012). A quantity of powder equivalent to 10 mg of drug was placed in an unpacked Omega column tube (4.6 mm × 5 cm) fitted with 0.5 μm frits and connected with 1.6 mm o.d. tubing at each end. The column assembly, frits and tubing consisted in PEEK polymer were purchased from Upchurch Scientific (Washington, USA). The phosphate buffer saline pH 7.4 (European Pharmacopeia 7.5) was supplied to the column inlet at 1 mL/min by a PhD 2000 syringe pump (Harvard Apparatus, Massachusetts, USA) that simulates the stimulation rate of saliva in human (Preetha and Banerjee, 2005).