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Optimization of the formulation of solid multiparticulate dosage forms containing pancreatin

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ABSTRACT

The objective of this study was to investigate the changes in the starch-hydrolysing activity of pancreatin under conditions that can occur during the formulation of multiparticulate systems (granulation, direct compression for the preparation of minitablets and coating). Direct compression did not induce a significant alteration in the starch-hydrolysing activity. A factorial design was applied in the testing of the wet conditions ensured by water and ethanol. These had a significant impact, though ethanol caused a more relevant decrease. An increased content of liquid was necessary for unwanted effects, but the changes of its amount in the tested range were not highly relevant. In both cases, the most important factor in the investigation of wet conditions was temperature. During the study of the effects of modelling of the circumstances of tabletting, elevated temperature did not cause alterations in the relatively dry material. This information can promote an improved design for the preparation of the dosage form. Pelletization is not appropriate for the preparation of an intermediate. Direct compression is the most suitable formulation step. Coating must be performed at low temperature with aqueous systems, but rapid drying is also advisable for the first separating layer. A mathematically based optimization can be necessary for the preformulation study of the preparation of dosage forms containing sensitive enzymes.

Keywords: Direct compression; Factorial design; Pancreatin; Starch-hydrolysing activity; Wet conditions

1. Introduction

Pancreatin (PAN) is a combination of digestive enzymes secreted by the pancreas. It is prepared from the pancreas of pig or ox and consists of lipases, amylases and proteases; it is therefore able to break down fats, starch and proteins. It is administered in cases of a chronic pancreatic insufficiency to restore normal digestive conditions in the intestines (Parfitt, 1999) and for the treatment of cystic fibrosis (Patchell et al., 2002), and it is also used as an additive in the food industry (Kong et al., 2007).

The components of PAN are proteins (Reetz, 2002; Hill et al., 2008; Tripathi et al., 2008). These have complex internal structures which determine their biological activities. Therapeutically applied PAN is mainly incorporated in coated multiparticulate solid dosage forms. Popular multiparticulate systems are minitablets or granules/pellets filled into capsules (van der Merwe et al., 2004). Different methods are available for the formulation of tablets (Ritschel and Bauer-Brandl, 2002; Aulton, 2007), while a widely used possibility for the preparation of minitablets is direct compression. For this active agent, it is necessary to consider not only the conventional parameters, such as the properties of the surface, homogeneity, good flowability and good compressibility of the powder mixture (Rubinstein, 1987), but also the high pressure on the special internal structure of the active component and the thermal stress generated during high-speed compression performed under high pressure. It is well known that the generation of heat is unavoidable during the preparation of tablets (Lieberman et al., 1989; Rankell and Higuchi, 1968). The heat generated is high for tablets prepared by direct compression, since a high compression force must be applied. It is also well known that if crystals are arranged side to side with a high thermal conductivity edge, then this promotes the attainment of a higher temperature in a very small volume. This increased temperature can be higher than the melting point of the material and the crystals will melt (nearly 100 °C can be reached). Since melted materials recrystallize after com-

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pression, the particles lose their individuality. Such sites in the texture are called "hot spots" (Kedvessy and Garamvölgyi-Horvát, 1973; Fuhrer and Parmentier, 1977; Bogs and Lenhardt, 1971). Other intermediates for the formulation of multiparticulate systems are granules and pellets (Ghebre-Selassie, 1994). Moisture and heat can damage PAN, and accordingly the application of wet granulation must be considered carefully (Thoma and Bechtold, 1999). The use of melt granulation is also questionable since enzymes can then undergo thermal damage.

PAN is digested in the gastric juice and acts in the ileum, and an intestinosolvent coating is therefore necessary (Thoma and Bechtold, 1999). Accordingly, the optimization process for the dosage form containing this component must involve the coating step. We previously studied the properties of the surface of tablets containing PAN. The surface enrichment of PAN was detected on tablets containing microcrystalline cellulose as a conventional binder (Kristó et al., in press). Investigation of the influence of moisture on the starch-hydrolysing activity of PAN is important, because the possibility of modification is higher in response to liquids.

Our present aims were therefore to study the effects of direct compression, granulation and coating on the starch-hydrolysing activity of PAN. The starch-hydrolysing activity of PAN was investigated during the modelling of circumstances of direct compression and wet granulation. Measurements of starch-hydrolysing activity were made according to Ph. Eur. In the first part of this study, the effects of direct compression were evaluated. Meat is generated during direct compression. The thermal stress of the dry material was studied separately, with the objective of an evaluation of the behaviour of this component in the possible "hot spots". Additives were not applied in this study; on the other hand, the effects of interactions on the starch-hydrolysing activity should be taken into consideration during tabletting. In the second step, the simultaneous effects of moisture and elevated temperature on the starch-hydrolysing activity of PAN were tested by means of a factorial design. Combinations of these factors can occur during granulation and coating. Aqueous and ethanolic coating liquids are typically used for the surface treatment of the solid dosage form (Cole et al., 1995; Bauer et al., 1988), and thus these liquids were applied. This approach for the assessment of the effects of different factors is not conventional for enzyme-containing dosage forms. This information can broaden the understanding of the effects of different technological processes, which is inevitable for the determination of the critical control point in the preparation of solids containing proteins. Its relevance is constantly increasing because of the spreading of biotechnology and protein-type active agents.

2. Materials and methods

2.1. Materials

Pancreatin (PAN) (Ph. Eur. Richter Gedeon Plc., Budapest, Hungary) (starch-hydrolysing activity: 18 EPU/mg; proteolytic activity: 3.6 EPU/mg; lipolytic activity: 41 EPU/mg; fat content: 2.2%) was applied as active agent. The moisture content of the untreated PAN was 6.68%. Water-soluble starch (Spektrum-3D, Debrecen, Hungary) was applied for measurement of the starch-hydrolysing activity. Distilled water and 96% ethanol (Spektrum-3D, Debrecen, Hungary) were applied for the study of the effects of wet conditions.

2.2. Measurement of starch-hydrolysing activity

The starch-hydrolysing activity of PAN was measured according to Ph. Eur. The concentration of the iodine-starch complex was determined at 576 nm with a UV spectrophotometer (Unicam Helios Alpha, Spectronic Unicam, UK). The amount of starch hydrolysed was calculated via the amount of the iodine–starch complex. The measurement was performed in consecutive steps. The first mixture contained 1250 μl 2% aqueous solution of starch, 500 μl pH 6.8 phosphate buffer, 50 μl 11.7 g/l sodium chloride solution and 50 μl PAN solution. It was incubated for 10 min at 37 °C in a water bath. After this, 100 μl 1 M hydrochloric acid, 500 μl 0.05 M iodine solution containing potassium iodide, and 2250 μl 0.1 M sodium hydroxide solution were added, the mixture was left to stand for 15 min at room temperature, and finally 200 ml diluted sulphuric acid (20%) was added. The starch-hydrolysing activity was determined; the starch-hydrolysing activity of the untreated PAN was taken as 100%.

2.3. Determination of effect of compression

The starch-hydrolysing activity was investigated during the modelling of the circumstances of tabletting. Comprimates 12 mm in diameter were prepared with a hydraulic press (Specac Inc., Graseby) at loads of 2, 4, 6, 8 or 10 t (19.62, 39.24, 58.86, 78.48 or 98.1 kN). The surface of the comprimates was flat. The resulting tablets were pulverized in a mortar before the starch-hydrolysing activity testing. Not only the effect of the pressure was examined. High pressure is known to induce the generation of heat. This occurs as a very rapid phenomenon during compression. For clarification of this situation, elevated temperatures (40, 50, 60, 70, 80, 90 and 100 °C) were applied in independent tests. In order to study the starch-hydrolysing activity during elevated temperature, the untreated PAN was stored for 2 h under dry air conditions in a thermostat (Hereaus Instruments, Hanau, Germany) in which the heat was distributed homogeneously.

2.4. Determination of effects of wet conditions

The 2^3 full factorial design was applied with 2 central points (Statistica for Windows) to evaluate the effects of the factors on the starch-hydrolysing activity of PAN. The factors investigated were temperature, time and liquid content (Table 1). The liquid was ethanol or distilled water. Homogeneous mixtures were prepared in a mortar and the resulting wet masses were stored in hermetically closed containers for a given time. The amount of liquid added to the powder is given as a percentage of the mass of wet mass. The content of liquid utilized during wet granulation is ~30–60%; hence, this range of liquid content was applied in these evaluations. During the calculation of the starch-hydrolysing activity, the exact liquid contents were considered.

The following approach, involving the interactions of the factors, was used to determine the response surface and the

Table 1 – Values of factors.

Factor	Low level (−)	Zero level (0)	High level (+)
Temperature (x_1)	40 °C	50 °C	60 °C
Time (x_2)	1 h	1.5 h	2 h
Content of liquid (x_3)	30%	45%	60%