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Summary of Ph. D. thesis

INVESTIGATION OF PROTEINS DURING PROCESSING INTO SOLID DOSAGE FORMS

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INTRODUCTION

Biologically active peptides and proteins are increasingly becoming a very important class of therapeutic agents because of their extremely specific activity and high tolerability by the human organism. Their rapid clearance in the body necessitates repeated injections, which is an inconvenient form of therapy, and additionally painful. It is therefore reasonable to formulate dosage forms which can be applied by the patient in a pain-free manner. Alternative routes for the systemic effect are currently becoming widespread. Thus, transdermal, rectal, nasal and buccal therapeutic systems can be used without the destructive effects of the gastrointestinal tract on the proteins. The dosage forms can be liquid, semisolid or solid with an appropriate bioadhesive effect. The applicability of these solids (e.g. oral tablets for buccal or sublingual use) is easier, and their formulation is therefore a promising method, though with many challenges. The proteins are very sensitive materials, and accordingly their formulation into solid dosage forms is difficult. The pharmaceutical technological methods applied in the case of active agents with low molecular weights for the formulation of solid dosage forms containing proteins are not appropriate as the proteins can be destroyed or their activity can decrease.

Preservation of the activity of proteins and enzymes should be taken into consideration during formulation. This study emphasizes the importance of special aspects in the processing of solid dosage forms containing proteins. Its relevance is constantly increasing because of the spreading of biotechnology and protein-type active agents. In the case of the formulation of solid dosage forms containing proteins the definition of critical control points is important. Process analytical technology (PAT) is currently becoming widely used. The definition of critical control points during the formulation is important in PAT.

In this study, some examples are demonstrated which must be taken into consideration during the formulation of solid dosage forms containing proteins.

AIMS

The two main aims of this study were to investigate of applicability of proteins during pharmaceutical technology prosesses and to investigate the activity of the proteins in the course of processing into conventional solid dosage form. Main purpose was the use of the technologies and apparatuses that can be applied during the formulation of these conventional forms.

Our purpose was to study the spreading of a coating liquid on the surfaces of different tablets containing PAN and different amounts of microcrystalline cellulose (MCC) and magnesium-stearate (Mg st.) as excipients, prepared by direct compression. The preformulation compactibility testing is very important. The effects of the components in various compositions were therefore examined with an instrumented tablet machine and the results were compared with those of wettability studies. These results can be applied to evaluate the microstructure of the tablets.

Finally a complex, solid multiparticulate dosage form containing PAN and PEP was also developed for a possible pediatric use. Two intermediate products were prepared and filled into hard gelatine capsule. One of them is minitablets containing PAN with an enterosolvent coating. The other product is granules containing PEP.

MATERIALS AND METHODS

Materials

Materials for investigation of the applicability of proteins as excipients

The HSA was used as model protein. A solution containing 39.9 g/l of HSA (and also NaCl, KCl, Na_2HPO_4, KH_2PO_4, etc.) was used in this work. This liquid was lyophilized at –50 °C and 180-200 mTorr with a freeze-drying machine. The lyophilized products were dissolved in the original liquid (39.9 g/l) to produce liquids with contents of 5%, 10%, 12.5%, 15% and 20%.

In the case of investigation of film-forming effect of HSA, the carrier was powdered cellulose with an excellent flowability and superior stability (Arbocel A)

Different types of microcrystalline cellulose (MCC) (Vivapur 101, 103 and 105) and powdered cellulose (Arbocel P 290) were applied in powder mixtures for investigation of the granulation effects of HSA solution. In these investigations mannitol (MAN) (Ph.Eur. Hungaropharma Plc., Hungary) was used as filler.

Aqueous solutions of hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC) in the same concentration were used in order to compare with the original HSA solution.

Materials for evaluation of the applicability of proteins as active agents

PAN is a combination of digestive enzymes that is 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. 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 % and the average particle size (D50) was 134 μm.

PEP is synthesized in an inactive form by the stomach lining; hydrochloric acid, also produced by the gastric mucosa, is necessary to convert the inactive enzyme and to maintain the optimum acidity (pH=1–3) for the PEP function. The application of acids is therefore necessary. Porcine PEP (Meditop Ltd.) was used in this work. Tartaric acid (Ph. Eur.) and citric acid (Ph. Eur.) were applied as acidifying components.

Starch-hydrolysing activity of PAN based on the Ph. Eur. methode. Water-soluble starch, pH=6.8 phosphate buffer, 11.7 g/l sodium chloride solution, 1 M hydrochloric acid, 0.05 M iodine solution containing potassium iodide, 0.1 M sodium hydroxide solution and 20% sulphuric acid were applied Bovine haemoglobin, Folin-Ciocalteu reagent, trichloroacetic acid, hydrochloric acid (Ph. Eur.) and sodium hydroxide (Ph. Eur.) were used for PEP activity measurements.

Distilled water and 96% ethanol were applied for the study of the effects of wet conditions (can occur during granulation or coating). The excipents for making the tablets containing PAN were MCC and Mg st. A 20% aqueous dispersion of Acryl EZE (methacrylic acid-ethyl acrylate copolymer [1:1]) was used as enteric solvent coating liquid. Vivapur 101 was used for PEP granules.

Methods

Investigation of applicability of proteins as excipients

The modified layering technique was used. The samples were prepared with a fluid bed apparatus. The top-spray method was used. The concentration of the HSA solution was varied. The quantity of starting powder and the solid applied in the liquid were the same. Several other factors were also varied for the sample. First, powdered cellulose was treated with water to evaluate the effect of water on the aggregation.

The influence on different powder mixtures was studied. MAN (as a conventionally used filler such as in buccal preparations) and different types of cellulose were applied. The samples were prepared in a high-shear granulator. The powder mixture was prepared from 100 g of MAN and 100 g of cellulose. The type of cellulose and the composition of the granulating liquid were varied. The amount of water was the same for all the samples.

A Hitachi S2400 scanning electron microscope was used to determine the shape and the surface of the particles.

The sizes and the size distributions of the samples were evaluated. An analytical sieve was used for testing both types of intermediates. D50 was determined with sieving system software. In the case of samples prepared in the fluid bed apparatus, depending on the particle size, the products were divided into 3 groups (<200 μm, 200-315 μm and >315 μm).

A powder testing apparatus was used to test the flow times of 100-ml samples. A teflon accessory 10 mm in diameter. In case of insufficient flowability a stirring at 25 rpm was utilized. Three parallel experiments were performed.

The concentration of HSA was determined with a UV spectrophotometer at 562 nm. The Micro BCA^{TM} Protein Assay was applied for the determination. The test fluid was phosphate buffer at pH=7.2. The concentrations of active agent in the 3 different groups were determined. Based on the composition the optimum calculated value was 13.04%.

Surface active property of the granulation fluid can influence the efficiency of the granulation. The surface tensions of the HSA, HPMC and HPC solutions and the water were measured with a ring method. A Brookfield LVDV-II viscosimeter with a CPE 42 spindle was used for the determination of the viscosity of the solutions at 25 °C.

Densities (bulk ($\rho 0$) and tapped ($\rho \infty$)) of both types of intermediates were determined with a STAV 2003 Stampfvolumeter. Carr's index was calculated from these results; three parallel tests were carried out:

$$\text{Carr`s index} = \frac{\rho_\infty - \rho_0}{\rho_\infty} \times 100$$

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The breaking hardness was tested for granules measuring between 710 and 800 μm. Twenty parallel measurements were performed.

Granulation is not only influenced by the features of the granulation liquid, but also by the wettability of the powder mixture. The Enslin number is a simple semiquantitative measure of the water uptake of a powder, and is equal to the amount of fluid absorbed by 1 g of the powder (ml/g). Each powder (0.5 g) was tested; 5 parallel experiments were performed. Statistica for Windows 8.1 AGA software was used for the statistical analysis. The two-sample T-test was applied for the comparison of two groups of results. The confidence interval was 95% ($p < 0.05$).

Evaluation of the applicability of proteins as active agents

These investigations were performed as preformulation steps. The main aim of this experiment was to evaluate the effect of some technological procedures on the properties of the proteins.

The starch-hydrolysing activity of PAN and PEP activity were measured according to Ph. Eur.

Both enzyme activity was investigated during the modelling of the circumstances of tabletting. Comprimates 12 mm in diameter were prepared with a hydraulic press at loads of 2, 4, 6, 8 or 10 t (19.62, 39.24, 58.86, 78.48 or 98.1 kN) from 100% PAN, 100% PEP, 50% PEP-50% tartaric acid and 50% PEP-50% citric acid powder mixtures. The surface of the comprimates was flat. The resulting tablets were pulverized in a mortar before the enzyme 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 enzyme activity during elevated temperature, the untreated enzymes was stored for 2 h under dry air conditions in a thermostat in which the heat was distributed homogeneously.

The 2^3 full factorial design was applied with 2 central points to evaluate the effects of the factors on the enzyme activity of PAN and PEP. The factors investigated were temperature, time and liquid content (Tables 3 and 4). The liquid was ethanol or distilled water for the investigation of the enzyme activity of PAN. During the evaluation of the

activity of PEP, the liquid was distilled water and the enzyme activity was studied in three different compositions: 100% PEP, 50% PEP-50% tartaric acid and 50% PEP-50% citric acid. Homogeneous mixtures were prepared in a mortar and the resulting wet masses were stored in hermetically closed containers for a given time. The content of liquid utilized during wet granulation is ~10-60%; hence, this range of liquid content was applied in these evaluations.

The following approach, involving the interactions of the factors, was used to determine the response surface and the relative effects of the factors (b):

$y=b_0+b_1x_1+b_2x_2+b_3x_3+b_{12}x_1x_2+b_{13}x_1x_3+b_{23}x_2x_3+b_{123}x_1x_2x_3$

Statistica for Windows 8.1 AGA sofware was employed for the calculations. During the mathematical evaluations, the confidence interval was 95%, i.e. the differences were significant if $p < 0.05$.

Distribution of the components during the direct compression is a very important parameter, since an uneven structure can induce additional problems (wettability, compactibility, dissolution etc.). The first group of powder mixtures contained only PAN and MCC in different ratios. The contents of PAN were 0, 10, 20, 30, 40, 50, 60, 80 and 100%. The second group of powder mixtures contained the same ratios of PAN and MCC, but also 1% Mg st. The flat comprimates 12 mm in diameter were prepared with a hydraulic press at 1 MPa.

Due to the acid sensitity of PAN, these potential tablets must be coated with intestinosolvent coating. The spreading of 12 µl of Acryl Eze dispersion on the tablet surface was studied via its contact angle. Ten parallel experiments were performed.

The test fluids were distilled water and diiodomethane Circle fitting was applied to determine the contact angle formed on comprimates prepared from different samples.

Formulation of solid dosage form containing proteins

In the first step, the preformulation study was carried out. The flowing time, the moisture content, the average particle size and the compressibility were measured, and the Carr index and the Hausner factor were calculated. Based on the previous results the powder mixture contained 50% PAN, 49% Avicel 101 and 1% Mg st., and was homogenized in the Turbula mixture. Tablets 3 mm in diameter were prepared with a Korsch EK0 eccentric tablet machine. The temperature was 28 °C and the relative humidity was 48%. The average mass of the tablet was 18 mg. The minitablets were coated with Acryl EZE dispersion with the

Wurster method. The coating liquid was contained 20% Acryl EZE, 0.2% simeticon emulsion, 0.2% indigo carmine and distilled water.

The average mass, diameter and height, the breaking force, the friability, the disintegration time in distilled water and the enzyme activity of the minitablet without coating were investigated. After the coating, the average mass, diameter and height, and the disintegration time in artificial gastric fluid (pH=1.2) and in phosphate buffer (pH=6.8) were investigated. A dissolution tester with a paddle was used for the PAN content measurement and the dissolution study. In the first step, the coating in artificial gastric fluid (pH=1.2) was checked after the dissolution of PAN was measured in phosphate buffer (pH=6.8). Samples of 5 ml were withdrawn at 5, 10, 15, 20, 30, 45, 60, 80, 100 and 120 min. At was measured spectrophotometrically at λ_{max} = 258 nm. Six parallel tests of dissolution were performed.

The powder mixture containing 50% PEP and 50% MCC 101 was homogenized in a Turbula mixer for 10 min. The granules were prepared in a high-shear granulator with a glass bowl of 1000 ml. The granulation liquid was distilled water.

The average particle size analysis was carried out with an analytical sieve. D50 was determined with sieving system software.

A dissolution tester with a paddle was used for the PEP content measurement and the dissolution study. The dissolution medium consisted of 900 ml of artifical gastric fluid (pH 1.2) kept at 37.0 ± 0.5 °C. Samples of 5 ml were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min. At was measured spectrophotometrically at λ_{max} = 274 nm. Six parallel tests of dissolution were performed.

In the first step the 75 % PEP granules and 25 % tartaric acid were homogenized in the Turbula mixture for 10 min. The coated minitablet containing PAN (320 mg) and the PEP granules and tartaric acid mixture (120 mg) were filled into hydroxypropyl methylcellulose (HPMC) capsules.

RESULTS AND DISCUSSION

Investigation of the applicability of proteins as excipients

Investigation of film-forming effect of HAS solution

It can be seen from the SEM pictures that the surface of the original Arbocel A 300 was irregular (Fig. 1). The sticking of the treated particles is clearly visible, with the irregular surface of the cellulose with binder layers of HSA forming bridges between the particles (Fig. 2). A covering layer (‘‘film-like’’) of HSA was detected at higher magnification.

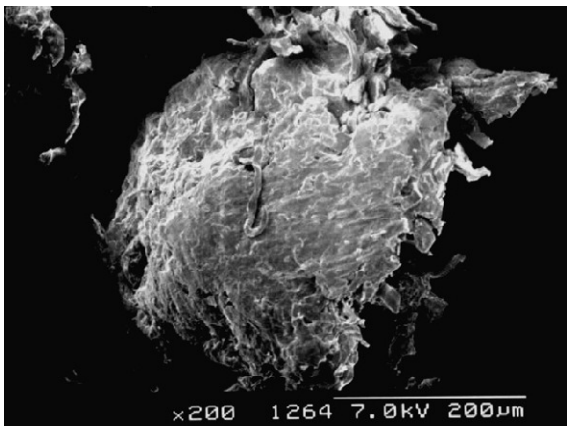

Fig. 1. Arbocel A 300 (SEM 200)

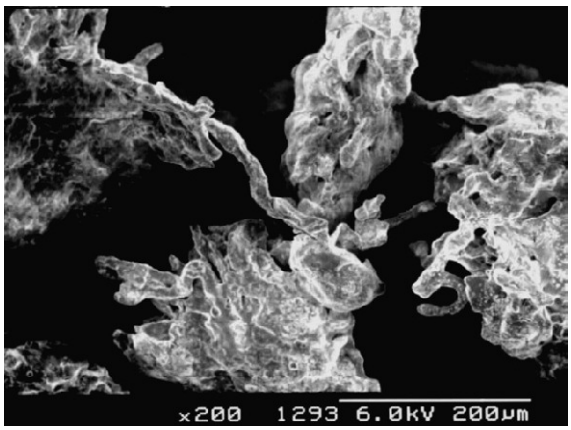

Fig. 2. S4 particle <315 µm (SEM 200)

The main aim was to prepare intermediates for the preparation of tablets with different concentrations of HSA. It can be concluded that the yield of the fluidization technique was very good, independently of the concentration of the applied liquid. The process caused an increase in the particle size. The HSA was responsible for the increase, because water did not cause aggregation. The least increase was detected for the samples prepared with liquid containing 15% HSA (about 2 times higher than for the second best).

Not only the size, but also the shape of the particles changed, leading to a change in flowability. The concentration of HSA in the fraction containing smaller particles was higher because of the abrasion of the particles and the spray-drying of the HSA.

Finally, it may be stated that this modified layering of powder cellulose with a fluid bed technique can be applied for the production of an intermediate from HSA for the preparation of solid dosage forms. Previously, the appropriate concentration of this protein solution must be optimized, as HSA can act as a binder. Our results indicated that the best value can be reached with liquid containing between 12.5% (the most homogeneous distribution of HSA) and 15% HSA (the best flowability).

Investigation of granulation effect of HAS solution

It can be concluded that the HSA solution had a very good granulating effect when the system contained the studied MCCs. Powdered cellulose in this composition was not appropriate for granulation with HSA solution. As compared with the conventionally used binder in the same concentration, the granules formed with HSA displayed a larger particle size, a significantly better compressibility, a higher breaking hardness and a favourable deformation process. The explanation of the advantageous properties is the good adhesive properties of the protein. This was connected with the structure of the particles and their water uptake. According to our results, the best compressibility (highest bulk density), and the best mechanical behaviour were detected for materials containing MCC 105 and granulated with HSA solution.

It may be stated that the inclusion of HSA in the granulating fluid can be very useful, the granulating effect is considerable and the amounts of additives can be decreased.

Evaluation of the applicability of proteins as active agents

Investigation of enzyme activity

It can be concluded that the enzyme activity of PAN and PEP was not changed because of direct compression. High temperature did not induce a decrease in this parameter for the relatively dry active component. Modelling of the wet conditions which can occur during granulation and coating led to significant modifications. Ethanol caused more relevant changes than water for PAN, thus this component must be avoided during the formulation. In both cases, the most important factor was temperature. The PEP activity was altered significantly with application of acids. The citric acid caused a more relevant decrease.

This information is helpful as concerns the design of the preparation of multiparticulate dosage forms containing PAN and PEP. Wet granulation can be applied for the processing of PAN if the temperature is < 40 °C, only a low amount of water is applied, and the process time is short. A better way is to produce minitablets by direct compression, since degradation of the active agent can then be avoided. Wet conditions must also be considered during the coating. This step is obligatory in this case and ethanol cannot be used as liquid. Aqueous systems must be applied at low temperature, but quick drying is also advisable, since overwetting of the surface can occur.

PEP can be processed with wet granulation without the application of acids or with tartaric acid at low temperature and within a short time. The PEP activity decreased significantly with increasing temperature in case of citric acid. The processing of PEP with citric acid is not recommended with wet granulation. This study emphasizes the importance of special aspects in the process of solid dosage forms containing enzymes.

Investigation of properties of surface

It can be stated, that the extent of spreading of the coating liquid to form an enteric soluble film on the tablets decreased with increasing amount of PAN. However, the change in this parameter was not proportional to the concentration of this component. The deviation from linearity was highest for the mixture containing 50% P. A deviation was also detected in the presence of 1% Mg st., but its extent was then lower. The enrichment of the PAN on the surface of tablets prepared from binary mixtures was supported by the spreading coefficient between the components. The spreading coefficient of Mg st. revealed that both components were covered by this lubricant. The deviation from the predicted wettability was therefore decreased when this excipient was applied.

The plasticity was not affected in a similar way as the wettability, for it is a bulk property. The alteration in the friction exhibited a similar tendency to the spreading of the coating liquid on tablets containing powder mixtures.

The determination of surface free energy can be a useful tool for prediction of the microstructure of the surface of tablets.

Formulation of solid dosage form containing protein

The multiparticulate solid dosage form containing PEP and PAN was prepared with filling of minitablets and granules into the same capsule. The previous results relating to the enzyme activity were taken into consideration in the selection of the applicable pharmaceutical technology process. The activity of the enzymes was not decreased significantly and therefore these pharmaceutical technological processes are appropriate for the preparation of solid dosage forms containing PAN and PEP. Further optimization of the other factors was not performed in this study, but these should be taken into consideration during the formulation.

SUMMARY

The main aim of this work was to examine the applicability of the proteins during the processing into solid dosage forms.

Major conclusions for protein used as a pharmaceutical excipient:

- HSA solution can be applied in modified layering technique, since yield of the fluidization technique was very good, independently of the concentration of the applied HSA solution.
- The process caused an increase in the particle size. The HSA was responsible for the increase, because water did not cause aggregation.
- HSA solution had a very good granulating effect in the tested system. As compared with the conventionally used binder at the same concentration, the granules formed had a larger particle size, significantly better compressibility and higher breaking hardness.
- The advantageous properties are not reflected by a changed surface tension. The explanation for this was the good adhesive properties of protein.
- It may be stated that the application of HSA in the granulating fluid can be very useful, because pretreatment of this component is not necessary and the granulating effect is also considerable.

Major conclusion for protein used as active agent:

- Direct compression can be applied for the processing of PAN, since neither the pressure nor the temperature induced any appreciable modification of its function.
- Granulation with an aqueous system can be applied under well controlled circumstances (low moisture content, short process).
- In a conventionally used direct compression composition the enrichment of PAN on the surface of the tablet must be taken into consideration int he course of processing. It can be critical due to the wettability and water sensitivity of the API.
- To achieve the appropriate activity PEP must be applied in combination with acid. The combinations with citric and tartaric acid were appropriate for direct compression at low compression force.
- At low temperature, small amount of water and short process time, the activity PEP did not alter significantly for the sample with tartaric acid, and the wet granulation can therefore be used under these circumstances
- The processing of pepsin with citric acid is not recommended with wet granulation.

Based on these preformulation tests, the production of intermediate products with suitable properties was feasible, the predicted importance of the factors were proven.

Practical usefulness

The importance of proteins in therapy is constantly increasing, thus formulation must support this tendency. The use of alternative administration routes for these active agents is also a reasonable demand of the patients. One option can be the use of the methods generally used for the solid dosage forms of small molecules. These methods were evaluated in this work and the following practically useful conclusions can be drawn.

- Some proteins have special properties to enhance the formulation. Main advantage of these properties, that the number of excipients and/or preliminary formulation steps can be reduced. This is very important because the proteins are very sensitive materials so the number of additives must minimised.

- The modified layering technique in the fluid bed apparatus and the high shear granulation can be appropriate for the preparation of intermediate products of solid dosage forms containing proteins. Direct compression can also be applied for some proteins.

- The individual steps of these technologies must be understood and the critical control points must be appropriately controlled. PAT is currently becoming more and more important in the pharmaceutical industry during the manufacturing of medicines. In this study, some examples are demonstrated that can be critical control points in the course of the production of solid dosage forms containing proteins.

Considering these aspects is more important for sensitive drugs. The final conclusions of this study underline of this statement, and these results also show that the conventionally used equipments and methods (with some small modifications) can be applied for the formulation of solid dosage forms from certain proteins. The further evaluation of these aspects can promote the development of dosage forms for future therapies with proteins.

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