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Solid-state transformation of erythromycin A dihydrate during drying monitored by near infrared spectroscopy

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Objective: Solid-state transformations have caused problems during manufacturing of many active pharmaceutical ingredients (APIs). One example for a drug that changes its solid state during processing is the antibiotic erythromycin. Erythromycin dihydrate incorporates two easily removable water molecules in its lattice channels. The lost of the two incorporated water molecules in erythromycin dihydrate results in the hygroscopic and isomorphic erythromycin dehydrate. The aim of the present study was to detect the conditions under which this transformation occurs.

Method: The pellets containing 50% (w/w) erythromycin dihydrate and 50% (w/w) microcrystalline cellulose were produced by extrusion-spheronisation. The pellets were dried with conventional oven tray drying at 30 °C and 60 °C, and with a microscale fluid bed device at 30 °C, 45 °C and 60 °C. First it was tested if near infrared (NIR) spectroscopy is able to detect dehydration of the hydrate form. Transformation to isomorphic dehydrate was observed at the moisture content of 1.4% (w/w) while at 1.8% (w/w) neither XRPD nor NIR were able to detect dehydration of the hydrate form. Transformation to erythromycin dehydrate is therefore strongly dependent on the moisture content of the pellet formulation.

Result: At a drying temperature of 30 °C no changes occurred for both drying techniques. For the drying process in the oven tray drier at 60 °C and the fluid bed drier at 45 °C transformation to erythromycin dehydrate was only detectable for one batch. For both batches dried in the fluid bed at 60 °C dehydration was detectable by in-line NIR and XRPD.

Conclusion: During fluid bed drying transformations to the isomorphic dehydrate form of erythromycin dihydrate are induced. While it is less obvious for the slower and less efficient oven tray drying process. Amount of water in the system affected strongly the solid-state stability: erythromycin dihydrate was observed at the moisture content of 1.4% (w/w) while at 1.8% (w/w) neither XRPD nor NIR were able to detect dehydration of the hydrate form. Transformation to erythromycin dehydrate is therefore strongly dependent on the moisture content of the pellet formulation.

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Effects of plasticization on mechanical properties of whey protein films

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Objective: Whey proteins are a common by-product of dairy industry and an ideal source of protein. The objective of the present study was to evaluate film formation and plasticization of aqueous whey proteins by using free isolated films. Special attention was paid to the effects of plasticizers on mechanical stress–strain properties of whey protein films.

Method: Free films were prepared by a casting/solvent evaporation method. For preparing free films, 10.0 g of the whey protein solution (10%, w/w) was poured into polytetrafluoroethylene (Teflon\textsuperscript{®}) molds. The films were dried for at least 48 h at a room temperature (21 ± 2 °C and 30–50% RH) before testing. The physical film properties such as appearance, moisture permeation and mechanical stress-strain properties were investigated. The mechanical and stress-strain properties of free films were determined using a Lloyd LRX materials testing machine.

Result: Smooth films with a moderate to high elongation were obtained with whey proteins plasticized with glycerol, mixtures of monosaccharides (fructose and glucose) or acacia honey. Inclusion of plasticizer resulted in a clear decrease in the mechanical strength and significant increase in elongation of the present films. A short pre-heating treatment of the proteins prior to film casting resulted in mechanically strong films. As regards with mechanical properties, the addition of glycerol at a concentration in the range of 60-80% of the protein concentrate weight seems to be beneficial for aqueous whey protein films. For effective plasticization, whey protein films required clearly higher amounts of plasticizer compared to that observed with the established cellulose ether films.

Conclusion: In conclusion, whey proteins are promising novel film forming material for pharmaceutical coating applications.

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Dissolution of nifedipine from tablets: Formulations registered in Estonia compared to those produced in Russia and Ukraine

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Eight formulations purchased from Estonian pharmacies (registered in Estonia, ATC code: C08CA05) and four formulations purchased from Russian pharmacies (produced in Russia and Ukraine) were studied. All preparations registered in Estonia were of prolonged release, two of them contained 10 mg, four 20 mg and two 40 mg of active substance. All preparations purchased from Russia and Ukraine contained active substance 10 mg and were considered of conventional release as there

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were never mentioned prolonged activity in accompanying patient information.

All studied preparations were tested accordingly to United States 28th Pharmacopoeia nifedipine monograph “Nifedipine Extended-Release Tablets”, test 2. Although USP indicates to use a method recommended by manufacturer, this method was chosen due to the lack of manufacturers information as most suitable for our needs. Accordingly, apparatus 2 with sinkers rotating 50 rpm was used. The dissolution test was carried out in sodium lauryl sulphate and phosphate buffer containing medium at pH 6.8. The concentration of nifedipine was monitored for 12 h taking samples after every 15 min and measuring the UV absorption at wavelength of 338 nm. By this USP test not less than 80% of nifedipine had to be released and dissolved in 12 h.

All studied 10 mg and 20 mg tablets except Adalat Oros 20 mg released at least 80% of nifedipine in 12 h. Adalat Oros 20 mg (dosage form: osmotic pump) released 30% of nifedipine in 12 h. This was in accordance to the manufacturers information as it was supposed to release the active substance for 48 h. We also studied two 40 mg tablets from different manufacturers that released 50% of nifedipine in 12 h but after that dissolving and release of active substance continued at least for 12 h.

Our tests showed also that tablets manufactured in Russia and Ukraine released nifedipine similarly to those registered and available in Estonia and so they all passed this USP criterion of 80% released active substance in 12 h. The differences in dissolution of 20 mg tablets Adalat Oros and 40 mg tablets Nycopin and Cordipin were caused by the distinctive features of these dosage forms.

Accordingly to present study we can conclude that 10 mg nifedipine tablets produced in Russia and Ukraine had similar release characteristics to corresponding 10 mg tablets registered and available in Estonia.

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Fluid bed granulations in microscale fluid bed powder processor (MFP)

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Objective: Microscale fluid bed powder processor (MFP) has been developed for fast characterisation of materials. Miniaturised devices are advantageous especially in formulation development studies in the expensive drug development process. The purpose of this study was to clarify the key parameters of fluid bed granulation in micro scale using electrostatic atomisation for addition of granulation liquid.

Methods: The experiments were performed in MFP with a specially constructed nozzle which was connected to a high voltage supply. In electrostatic atomisation an electric field is applied at the granulation liquid surface and due to strong coulombic forces, the liquid surface disrupts to droplets. The model substance to granulate was lactose monohydrate and granulation liquid consisted of polyvinylpyrrolidone and water. After the granulation in MFP, the granules were transferred for drying to another fluid bed column due to adjustment accuracy of the air conditioning unit used. The variables in this study were the binder amount, the pumping speed and the atomisation voltage of the granulation liquid. Also the relative humidity of the process was controlled as one of the variables. The particle size of the granules was determined by sieve analysis. MODDE modeling software was used in the data analysis using median and average granule sizes as responses.

Results: The preliminary results indicate that pumping speed and binder content of the granulation liquid had the strongest positive effect on the granule size. The relative humidity had no effect on granule size and the effect of atomisation voltage remained unclear. In this study, only simple linear relationships could be generated between the variables due to the large variation in the analytical methods for small samples.

Conclusions: Electrostatic atomisation is a good technique for generating droplets in MFP. The granulation process in MFP is a delicate method and vulnerable to disturbances like cleaning of the device. Despite the challenges, it was shown to be possible to roughly predict the processability of pharmaceutical material in fluid bed device with MFP.

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Effect of diluents and disintegrants on the release of poorly soluble drugs from hard gelatine capsules

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The objective of present study was to determine the influence of the combinations containing diluents and disintegrants of different physicochemical properties to the release of poorly soluble drug.

Materials and methods: Release of model drug spironolactone (II class by BCS) was determined using rotating basket method (USP 24). The dissolution medium was pH 2 and pH 6.8. The volume of dissolution medium was 1000 ml, speed of rotation 75 rpm, the temperature of dissolution apparatus (Sotax AT 7) 37°C. Size 3 hard gelatine capsules were used. Amount of spironolactone (50 mg) was mixed with magnesium stearate (1% of total mass) and diluent, or mixture of diluent and disintegrant (10% of total mass). Lactose monohydrate and microcrystalline cellulose as diluents and croscarmellose sodium and crospovidone as disintegrants were used. Mixed powder was dispersed into capsule shells manually, using Feton apparatus. Verospiron 50 mg capsules (Richter Gedeon) were used as reference formulations.