Lyophilized Orally Disintegrating Tablets Containing Taste Masked Naproxen Sodium Granules

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INTRODUCTION

Freeze-dried orally disintegrating tablets (ODTs) are promising dosage forms because of their beneficial characteristics regarding patient’s compliance and the possibility of buccal absorption of drug molecules. 1, 2 The most important key aspects for formulation of ODTs are a good taste and mouthfeel, fast disintegration and sufficient mechanical strength. Therefore formulations are often composed of a balanced mixture of a binder, filler and several additives. 3 Frequently used excipients are gelatin, mannitol, sweeteners and flavors. 4, 5 After preliminary studies a formulation consisting of sucrose and hydroxyethyl starch was found to be most promising for an adequate incorporation of taste masked granules. The objective of this study was to examine the influence of different total amounts of taste masked naproxen sodium granules on the morphology, fracture strength, disintegration time and residual moisture content.

MATERIALS & METHODS

Freeze-Drying: Taste masked naproxen sodium granules (Batch 13) were incorporated in a formulation consisting of 10 % (w/w) sucrose (Sigma-Aldrich, Germany), 5 % hydroxyethyl starch (Fresenius Kabi, Germany) and 0.01 % Tween 80 (Sigma-Aldrich, Germany). In each cavity of the PVC blisters 2 ml of the solution was filled and the granules were added subsequently. The used quantities per tablet were: 0 mg, 50 mg, 250 mg, 750 mg and 1250 mg. Thermocouples (TCs) were placed center bottom into an edge and a center cavity of each formulation. After the preparation the blisters were transferred into a -80 °C deep freezer. After complete solidification the blisters were loaded on the precooled shelves of the Lyostar® II (PTS Wyss, NV). Primary drying was conducted at -35 °C for the first 37.5 hrs and then the shelf inlet temperature was raised to -20 °C. The pressure throughout the freeze-drying process was 60 mTorr. Finally the shelf inlet temperature was ramped to 40 °C and maintained for additional 4.5 hrs for secondary drying.

X-Ray Powder Diffraction: The samples were weighed into a XRPD sample holder and compacted. A Philips model Expert MPD (Philips, Germany) with CuKα radiation at 40 kV / 40 mA was used for analysis. The scans were taken in the range of 2θ=0.5 ° to 40 ° with a step size of 0.02 °. The diffractograms were baseline corrected.

Fracture Strength: The fracture strength was determined using a PharmaTest PTB 5116 hardness tester (PharmaTest, Hainburg). Tablets were placed horizontally in the test chamber and the punch No. 2 compressed them until the breakage. The pressing force was increased during measurement with 5 N/sec. Disintegration Time: The method is described in the Ph. Eur. 6.0 as follows: 200 ml of water (15 – 25 °C) are filled into a beaker and the lyophilisate is placed on the surface of the water. The time needed for disintegration must be within 3 minutes. In total 6 tablets of each formulation were examined.

RESIDUAL MOISTURE: A Karl-Fischer Moisture Analyzer (Metrohm, Filderstadt) equipped with a 832 KF cell (Metrohm, Filderstadt) was used for analysis. The recorded moisture content was calculated using the Karl-Fischer equivalence of 20.68 mg H₂O/µl.

RESULTS & DISCUSSION

The temperature and pressure profiles during the freeze-drying process are shown in Figure 1. The measured temperatures of the center TCs were close to each other although they belonged to five different formulations. In comparison to that the values of the edge TCs differed over a broad temperature range. Except the formulation with 250 mg of taste masked granules, the edge cavities dried faster than their corresponding center cavities. But no consistent trends were observed how the incorporation of granules influenced the primary drying process. The visual inspection of the tablets revealed that the tablets with 750 mg and 1250 mg (Figure 2C and 2D) of taste masked granules were without defects whereas tablets with 250 mg (Figure 2C) showed a small crown formation. Reducing the mass of taste masked granules to 50 mg (Figure 2B) resulted into either cracked or intact tablets. Tablets without taste masked granules influenced the primary drying process. The visual inspection of the tablets revealed that the morphology to freeze-dried tablets (ODTs) are promising dosage forms because of their beneficial characteristics regarding patient’s compliance and the possibility of buccal absorption of drug molecules. 1, 2 The most important key aspects for formulation of ODTs are a good taste and mouthfeel, fast disintegration and sufficient mechanical strength. Therefore formulations are often composed of a balanced mixture of a binder, filler and several additives. 3 Frequently used excipients are gelatin, mannitol, sweeteners and flavors. 4, 5 After preliminary studies a formulation consisting of sucrose and hydroxyethyl starch was found to be most promising for an adequate incorporation of taste masked granules. The objective of this study was to examine the influence of different total amounts of taste masked naproxen sodium granules on the morphology, fracture strength, disintegration time and residual moisture content.

CONCLUSIONS

ODTs consisting of sucrose and hydroxyethyl starch with different amounts of taste masked naproxen sodium granules were successfully produced. The morphology and inner structure of the tablets is greatly dependent on the quantity of the incorporated particles. Generally, with increasing mass of taste masked naproxen sodium granules the tablet morphology and the fracture strength were improved. The incorporated particles cemented the porous structure of the lyophilized cake. XRPD measurements revealed that sucrose and HES were amorphous after freeze-drying and free naproxen.

REFERENCES