5 SUMMARY

The objective of the study was to develop extended release pellet formulations with pH-independent drug release for the weakly basic drug SAG / ZK. The drug substance has a short biological half-life of approx. 2.3 hours. The expected daily dose is in the range of 1.8 g drug substance per day. Additionally, a strong pH-dependent solubility was observed because of the weakly basic nature of the drug substance. Pellets with a drug load of 60 % (% w/w based on the core weight) were prepared by extrusion / spheronization. Two methods were used to overcome the problem of pH-dependent drug release. Firstly, organic acids were added to the core formulation in order to lower the micro-environmental pH inside the pellet core and therefore to increase the solubility of the drug substance in media with higher pH-values. Secondly, layers of an insoluble extended release polymer and an enteric polymer were applied onto pellet cores in order to reach a pH-independent drug release by adjusting the polymer permeability contrary to the drug solubility.

pH-modifier within the pellet core

Organic acids were added to the core formulation in order to lower the micro-environmental pH inside the pellet core and therefore to keep the solubility of the drug substance independent from the pH of the aqueous medium. Uncoated pellets with a 15 % (% w/w based on the core weight) fumaric acid content showed pH-independent drug release. As expected no extended release patterns were reached. Afterwards, the pellets were coated with an aqueous polyvinyl acetate dispersion (Kollicoat® SR 30 D) in order to reach extended release profiles. Only after incorporation of the water-soluble pore former polyvinyl pyrrolidone into the extended release film coat the desired in vitro dissolution profiles were reached. Coated pellet formulations with fumaric acid as pH-modifier showed pH-independent drug release. However, the drug release from coated pellets with a 15 % (% w/w based on the core weight) tartaric acid content stayed dependent on the pH of the medium. The drug release patterns of fumaric acid formulations were found to be mainly influenced by the pH-adjusting properties of the organic acid. In contrast, the increasing porosity of the core pellets mainly influenced the dissolution behavior of tartaric acid containing formulations. X-ray diffraction studies showed no differences between the graphically combined diffractograms of the individual components and the pellet formulation. This indicates that

extrusion / spheronization does not lead to recrystallisation or the formation of new salts of the active ingredient and the organic acid, which might have led to a different solubility of the drug substance.

Layers of insoluble and enteric polymers

In the second part of the work, layers of insoluble and enteric polymers were applied onto pellet cores in order to influence the permeability of the polymer contrary to the solubility of the drug substance.

Pellets coated with a first layer of an enteric polymer (Kollicoat® MAE 30 DP) and a second layer of an insoluble polymer (Kollicoat® SR 30 D) showed a pH-dependent drug release. However, pH-independent drug release was observed from pellets coated with a first layer of the insoluble polymer and a second layer of the enteric polymer. The resulting dissolution level was to low for an oral extended release application.

An increase in drug release was reached by the addition of different osmotically active excipients to the core formulation. The rank order of drug release profiles of double-layered pellet formulations: sodium chloride > potassium chloride > sucrose > mannitol was in a good agreement to the osmolality of the saturated excipient solutions. Pellet formulations with a 15 % (% w/w based on the core weight) content of ionic excipients as sodium chloride and potassium chloride and the nonionic excipient sucrose showed pH-independent drug release. The drug release from double-layered pellet formulations with an addition of osmotically active ingredients was shown to be osmotically driven.

Final dosage form

Double-layered pellets were compressed to fast disintegrating multiple unit tablets. Even tablets with a tablet hardness of 180 N disintegrated within 30 seconds to the pellet subunits. Tablets containing a 25 % and 50 % pellet content showed pH-independent drug release. Compression of pellets into tablets resulted in increasing in vitro release profiles. On the other hand filling of pellets into hard gelatine capsules had no effect on the in vitro release.