ColoPulse tablets in inflammatory bowel disease

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CHAPTER 8

General discussion and future perspectives

In previous research at our institute the ColoPulse concept was developed and a proof of concept study was performed in healthy volunteers. With this thesis we aimed to perform the next steps in the pharmaceutical and clinical development of ColoPulse dosage forms with a special focus on inflammatory bowel disease. We studied the *in vivo* release from ColoPulse tablets with an optimized study design, compared to the earlier mentioned proof of principle study, in healthy volunteers and in patients with Crohn's disease. The results obtained in this thesis have brought us a step forward into the direction of developing an oral dosage form of infliximab or another active protein/monoclonal antibody, that offers clinical advantages compared to the current parenteral treatment with infliximab in inflammatory bowel disease.

1. Formulation of ColoPulse tablets

In chapter 2 we obtained insight in several critical process parameters influencing release from a ColoPulse tablet using a quality by design approach. This systematic approach can be used to optimize pharmaceutical preparations and to improve the control over and the quality of the production process [1]. With the current composition, containing a hydroxypropylmethylcellulose (HPMC) interlayer between the tablet and the ColoPulse coating, substances with a neutral to weakly acidic or basic pH can be formulated in a ColoPulse tablet. For these substances we managed to create a platform technology so that it is now known which process parameters will result in a tablet with an adequate release profile. This will make future development of ColoPulse tablets more efficient. Studies confirming the physical and chemical stability of the active substance are still necessary however. From chapter 2 it also appeared that more research has to be done towards the formulation of active substances with acidic and basic pKa (pKa < 3 and > 11) into a ColoPulse tablet. Possible solutions as increasing the thickness of the HPMC interlayer, increasing the amount of filler material, lowering the drug load or titrate the core with acidic or basic substances remain to be investigated. This has to be done preferably in two separate studies, for acidic and basic substances, and using a quality by design approach. Combined, this will result in a complete profile of the formulation possibilities of a ColoPulse tablet.

2. Infliximab: formulation of ColoPulse tablets and kinetics

Monoclonal antibodies against tumor necrosis factor alpha (TNF alpha) such as infliximab are very effective in the treatment of inflammatory bowel diseases [2]. Infliximab was the first anti-TNF alpha antibody and is until now administered intravenously. Small-scale studies describe the successful local

administration of infliximab by injection in patients with Crohn's disease [3-5]. Several disadvantages related to parenteral therapy have been reported however. In chapter 3 we showed that infliximab could be successfully formulated in a ColoPulse tablet by incorporating this antibody into a sugar glass of the flexible oligosaccharide inulin. Tablets stored at 25ºC in a closed vial still displayed a mean biological activity of 83% 16 months after production compared to a fresh infliximab solution [6]. With this study we showed that the formulation and production of 5 mg ColoPulse infliximab is technically feasible, but some improvements remain necessary to be able to perform the next crucial step: a clinical study. A relatively simple improvement will be to reduce the storage temperature to 2-8ºC. By storage at a lower storage temperature, the difference with the glass transition temperature will be increased with approximately 20ºC which favors the stability of infliximab [7]. Lowering the storage temperature in combination with a reduction of the relative humidity in the container will possibly be even more effective, because water uptake during storage acts as a plasticizer. This lowers the glass transition temperature resulting in destabilization [8]. Furthermore, the stability indication profile has to be extended with methods of analysis to gain more knowledge about the mechanism of degradation of infliximab upon storage. Examples of these methods are LC-MS (intact mass and subunits), peptide mapping, FT-IR and glycosylation assays [9,10]. A different sugar glass formulation based on another sugar or a combination of sugars may also be an approach to prevent degradation, because size and molecular flexibility of sugars relate to their protein stabilizing ability [8].

Because oral therapy with ColoPulse infliximab tablets is still a scenario of the future and because these tablets are only intended for disease located in the ileo-colonic region, it remains necessary to work on strategies to optimize intravenous infliximab therapy. Therapeutic drug monitoring (TDM) of infliximab is being described in the literature for several years already and it is known that the development of anti-drug antibodies and low serum concentrations are associated with poor clinical outcomes [11]. On the other hand no stopping rules for anti-TNF-alpha therapy are available for patients with inflammatory bowel disease in remission. There is evidence that TDM can play a role in the decision making of dosing and stopping anti-TNF therapy, because remission with low infliximab trough levels at the time of discontinuation is predictive of sustained remission after terminating infliximab treatment [12]. However, TDM of infliximab is not already commonly applied everywhere in daily clinical practice. In Chapter 4 we have developed a pharmacokinetic model for infliximab in patients with inflammatory bowel disease to be able to use TDM in predicting serum trough levels and in performing dose optimization in

this population [13]. In patients without anti-infliximab antibodies trough level dosing based on longer intervals can reduce hospital visits and subsequently reduce costs. Simulations based on our model showed that dosing every 12 weeks instead of every 8 weeks still resulted in adequate serum trough levels in our population. Although the outcomes of our retrospective study are promising, unfortunately disease activity parameters as endoscopy of fecal calprotectin were not available for most patients. Therefore the results should be confirmed in a prospective study. Currently, the analysis of monoclonal antibodies is less common in hospital pharmacies compared to bioanalysis of the small drug molecules, but this is expected to change in the near future as more data and analytical methods will become available. This change will contribute to a more cost-effective use of this effective, though expensive, therapy.

3. *In vivo* studying of ColoPulse dosage forms

Based on the characteristics of an Eudragit-S coating, release from a ColoPulse dosage form occurs after pH 7.0 has been reached. This correlates *in vivo* with the ileo-colonic region and is supported by the results of two studies by Schellekens et al. [15,16]. In these studies release of ^{13}C-urea in the cecum and colon (urease-rich segment) from a ColoPulse capsule was compared to release of ^{13}C-urea from an uncoated capsule at a different day. When ^{13}C-urea is released in the colon this leads to fermentation of ^{13}C-urea by bacterial urease in $^{13}CO_2$ which is absorbed in the bloodstream and subsequently exhaled in breath. ^{13}C-urea from an uncoated capsule is released in the stomach or the small intestine (urease-poor segment), is directly absorbed in the blood stream and subsequently excreted into urine. It was shown that subtraction of the results from a coated and an uncoated capsule containing ^{13}C-urea with administration on two different days could estimate the release characteristics from a ColoPulse capsule and that release occurred in the ileo-colonic region.

The feasibility of using two different stable isotopes of urea to determine the release profile from a ColoPulse dosage form is presented in chapter 5. The study comprises the results of an optimized strategy characterized by simultaneous administration of ^{13}C-urea in a coated capsule and $^{15}N_2$-urea in an uncoated capsule [14]. This design was an improvement of the earlier published design in the proof-of-concept study by Schellekens et al. on the use of ^{13}C-urea [15]. By using two different stable isotopes of urea on a single day, day-to-day variation in urea kinetics is eliminated and the study power is increased. Compared with a conventional two-period study design, this approach reduces clinical study costs, because run through time and sample load are reduced by approximately 50%. Moreover, the sampling is completely non-invasive by replacing blood-samples for a single urine sample or only 24 h collection of

urine. Our new approach resulted in a non-invasive (only breath and urine are necessary) and one-day study design. This design was subsequently used in the clinical studies described in chapter 6 and 7.

In Chapter 6 a study confirming release from a ColoPulse tablet in the ileo-colonic region in healthy volunteers is described. In this study we used a new medical device, the IntelliCap system®. One of the functionalities of the IntelliCap system® is continuous measurement of the pH in the gastro-intestinal tract [17]. The obtained results supported our previous results based on urea-kinetics and confirmed that release from a ColoPulse tablet occurs in the ileo-colonic region and after pH 7.0 has been reached. Ideally this study using the Intellicap system® should also be performed in patients with inflammatory bowel disease to make the picture complete. Unfortunately this was impossible in the planned study period, but several small studies comparing pH in patients with inflammatory bowel disease and healthy volunteers have been published. They showed that there is little to no relevant difference in gastrointestinal pH between both groups. Generally, it was seen that the gastric pH is slightly elevated in the patient group compared to healthy volunteers and that patients with ulcerative colitis had slightly higher pH values in the terminal ileum, the caecum and the right colon compared to patients with Crohn's disease. There was no difference in patients with active disease and patients in remission [18,19]. In patients with ileocecal resections, cecal pH was somewhat higher and the time at pH above 7.0 was a little shorter compared to controls [20]. After release from the dosage form (local) bioavailability of drug substances depends also on transit times. A reduction in transit time will decrease the exposure of the target organ to the drug substance. On the other hand an increase in transit time, will also increase the possibility of local inactivation for substances sensitive to enzymatic or environmental degradation. In the literature it has been described that regional transit times are prolonged in severe ulcerative colitis [21] and prolonged to normal in patients with Crohn's disease [22]. Based on the information above it was concluded that the ColoPulse concept will probably function properly in inflammatory bowel diseases, not only in patients in remission but also in patients with active disease or (limited) ileocecal resections. Therefore no additional research on the ColoPulse concept is necessary. However, clinical studies to investigate bioavailability en effectiveness are necessary for each drug substance to be formulated in a ColoPulse dosage form.

4. Influence of food and disease on release from a ColoPulse tablet

One of the remaining issues to be addressed before a clinical study with ColoPulse tablets containing active substances can be performed in patients with Crohn's disease, was to investigate the performance of ColoPulse tablets in this patient group and to study the influence of food intake on release characteristics. In chapter 7 we present the results of a cross-over study in healthy volunteers and patients with Crohn's disease in remission [23]. Using a practical approach, we studied the influence of food and time of food intake on release from a ColoPulse tablet. Bioavailability was similar in healthy volunteers and in Crohn's patients. Food had no clinically relevant influence on release parameters in both groups.

This is the starting point for our future research. Now we have developed ColoPulse infliximab tablets and showed that the ColoPulse concept works in patients with Crohn's disease, we can move forward in preparing a clinical study to investigate whether or not our hypothesis that local delivery of infliximab is non-inferior to parenteral therapy will be true. Depending on the results, the research can potentially be expanded with more active substances and more sub-groups of patients with inflammatory bowel disease.

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