12.1. Summary

Several drug delivery techniques based on gastroretention and intended for oral route of administration have been reported. Among them gastroretentive pellets have attracted increasing interest among academic and industrial researchers for its applicability in both the fields.

Rifampicin has been reported to undergo rapid degradation in the presence of isoniazid under acid conditions, which means that there exists a strong possibility of the dose of rifampicin falling below the minimum required level, after administration of formulations containing the two drugs in combination. Thus, apart from the initial drug content in formulation, stability of rifampicin in stomach turns out to be an important factor in assuring therapeutic action of the drug.

So in the present study different gastroretentive drug delivery systems for rifampicin and delayed release systems for isoniazid were formulated and evaluated. Gastroretentive systems such as pellets, granules and beads were prepared for rifampicin and enteric coated delayed release systems were prepared for isoniazid. Based on the results obtained as discussed in the earlier chapters, results are summarized below.

12.1.1. Analytical method development

- Formulation development involved sensitive analytical method for the evaluation of drug in formulations and release media.
- Analytical methods such as UV and RP-HPLC methods were developed and validated as per the ICH guidelines to quantify rifampicin whereas for isoniazid UV method was developed and validated as per ICH guidelines.

12.1.2. Formulation development and evaluation

- Gastroretentive multiparticulate formulations such as pellets, granules and beads were prepared and evaluated for various physico-chemical parameters like friability, flow properties, surface morphology by SEM, assay, floating time and release of drug at 6 h.
- Gastroretentive pellets of rifampicin were prepared by extrusion-spheronization technique using rate controlling polymers like HPMC K100M, HPMC K4M, POLYOX WSR 301 and sodium bicarbonate (gas generating agent) in different quantities.

- Gastroretentive granules of rifampicin were prepared by wet granulation technique using the rate controlling polymers like HPMC K100M, HPMC K4M, POLYOX WSR 301 and sodium bicarbonate (gas generating agent) in different quantities.
- Gastroretentive beads were prepared by ionotropic gelation method using polymers HPMC K100M, POLYOX WSR 301 and sodium alginate, calcium chloride as cross linker and sodium bicarbonate as gas generating agent in different quantities
- Drug excipient compatibility study has shown no drug polymer interaction as confirmed by DSC and FTIR studies.
- These gastroretentive formulations were then optimized by design of experiments using design expert software v.9.0.3.1 where two level full factorial designs were used.
- All the final formulations showed good flow properties as confirmed by angle of repose, Carr's index and Hausner's ratio.
- Pellets containing 30 mg of HPMC K100M, 30mg of HPMC K4M, 60 mg of POLYOX WSR 301 and 120 mg of sodium carbonate were found to be superior to granules and beads with respect to evaluation parameters like release of drug at 6 h, floating time, usable yield, sphericity and size of the particle. So these optimized pellets were used for further studies.
- These optimized pellets showed zero order release with a release of 99.12% of rifampicin in 6 h. Further, the data when treated using Higuchi diffusion equation and Korsmeyer-Peppas equation to learn about the mechanism of drug released from the tablet, it was observed that the drug release is by diffusion process. The slope of the Korsmeyer-Peppas equation was 1.0356 indicating that the drug release is super case II transport.
- Immediate release pellets for isoniazid were formulated and evaluated for various physico-chemical parameters like friability, flow properties, surface morphology by SEM and assay.
- Delayed release (enteric coated) pellets for isoniazid were prepared by coating the immediate release pellets of isoniazid by eudragit L100 polymer by pan coating technique and they were evaluated for the release of the drug.
- The release of rifampicin from these optimized pellets was studied along with immediate release isoniazid pellets and it was observed that the release of rifampicin was reduced from 99.12% to 84.02% which clearly indicates that rifampicin interacts with isoniazid in stomach conditions.

- The release of rifampicin from these optimized pellets was also studied along with delayed release enteric coated isoniazid pellets and it was observed that the release of rifampicin was 98.72% which clearly states that by formulating rifampicin as gastroretentive formulations and isoniazid as delayed release formulations, the interaction between these two drugs can be minimized and the stability and release of rifampicin can be improved.
- These optimized pellets were tested ex vivo using rat stomach and intestinal for absorption study. It was observed that rifampicin gets absorbed to a greater extent under gastric conditions when compared to intestinal conditions.
- The optimized formulation (containing Barium sulphate) was tested in vivo in New Zealand white rabbits for gastroretention. It was observed that the formulation remained intact and floating in the rabbit stomach for 5 h.