CHAPTER 8

CONCLUSIONS

The aim of this research work was to design and evaluate gastroretentive controlled release delivery systems for the candidate drugs, celecoxib and acyclovir. Single unit and multiple unit based formulations were prepared for both the drugs employing matrix embedding, microencapsulation and ionic cross-linking using different types of polymers.

To support the whole work, new UV spectrophotometric methods, for estimation of celecoxib (in 0.1 N HCl with 1.0 % w/v SLS) and acyclovir (in 0.1 N HCl), were developed and validated separately. They were validated as per ICH guidelines-2005, USP-2000 and statistical methods. The developed methods were found to be simple, sensitive, accurate, precise, repeatable and rugged. The methods were successfully used for the preformulation studies and evaluation of developed products.

0.1 N HCl with 1.0 % w/v SLS and 0.1 N HCl were used as dissolution media for celecoxib and acyclovir respectively. Drugs were found to be highly stable with most of the excipients used for this study.

In case of single unit matrix based systems, designed formulations were found to possess good appearance, uniform drug content, very low weight variation, low friability and optimal hardness. The hardness, type & amount of floating agent in the matrix, relative proportion of base and acid, type & proportion of single polymer and combination of polymers had significant impact on both the floating behavior as well as release profile of the formulations of both drugs. In general, acyclovir tablets floated very fast but showed faster release as compared to celecoxib tablets. Tablets with lesser hardness floated fast, but showed higher surface erosion/ fragmentation and decreased control of release. Sodium alginate, alone or in combination, gave best results with respect to floating and release behaviour. First hour release was found to be high in most of the formulations, suggesting no requirement of additional loading dose to these products. In vitro release profile obtained for the manufactured formulations could be directly linked to their fragmentation and disintegration behaviour.

Designed microencapsulated formulations of both drugs were also found to possess excellent physicochemical properties and all the products floated immediately and continued to float beyond 24 h in case of celecoxib and till the end of release in case of acyclovir. Microencapsulated products of celecoxib were found to have slower rate of drug release due to poor solubility of the drug. On the other hand, acyclovir microcapsules released the drug at a faster rate and drug release extended from 6 to 24 h or beyond. In general, increase in the proportion of hydrophilic polymer in the coating mixture (at fixed core to coat ratio) and increase in core to coat ratio increased the rate of release. Most of the microcapsules of celecoxib followed quasi-Fickian release, while microcapsules of acyclovir followed variety of release mechanisms.

In case of designed calcium alginate bead formulations of both the drugs, good appearance, uniform size, uniform drug content, high entrapment efficiency were observed, but these systems were not as buoyant as microencapsulated formulations, with only a fraction floating in all the cases. Freeze dried products showed good floating characteristics as well as better release compared to vacuum dried products. Products containing sodium bicarbonate showed better release, but lacked floating property. Decreasing the amount of calcium alginate increased the rate of release in both celecoxib and acyclovir. All celecoxib calcium alginate beads extended the release beyond 24 h, while acyclovir beads extended the release between 6 to 24 h or beyond. In case of celecoxib, most of the beads followed anamolous release, while in case of acyclovir beads followed variety of release mechanisms.

A selected batch of matrix based placebo tablet formulation was retained in the stomach of human volunteer for more than 5 h 20 min under fasted state. Contrast enhanced ultrasonography (CEU), in which the gas entrapped matrix based formulation itself acted as a self-marker, was employed for visualization. Similarly, in vivo gastroretentivity studies of microencapsulated product of celecoxib [Cele(31)-EC:PVP(1:3)21] in rat model showed that the microencapsulated product was retained in the stomach of Wistar rats beyond 6 h under fasted condition. These studies indicate even a better and prolonged residence is expected in the stomach in the fed state in case of both tablet and microencapsulated formulations.

Employed methods produced stable and reproducible products indicating usefulness of the methods. Products were found to be stable on storage at ambient conditions with insignificant change in formulation characters and drug content.

Hardness was found to control the porosity (the penetration of dissolution media into this matrix base), surface erosion and fragmentation pattern. Therefore, failure to maintain hardness within the range will affect the in vitro and in vivo performance of the product. A drawback with celecoxib based multiple unit formulations was that none of the product could release complete amount of the drug in 24 h, indicating that some intervention need to be done to ensure entire release.

Also, the developed products of these drugs need to be studied for their pharmacokinetic profiles on animal/ human models to actually quantify the increase in bioavailability and nature of extended absorption of drug. Further studies can be carried out using other techniques and some other combinations of hydrophilic/ hydrophobic polymers to ensure lesser impact of hardness on release and floating behaviour of single unit dosage forms of both the drugs and complete release of drug, in case of multiple unit based delivery of celecoxib.