CHAPTER 5

Formulation Optimization of Enteric Coated Sustained Release Matrices of Metronidazole
5.1) INTRODUCTION

Drug delivery systems should be designed with an increasing and better understanding of the physicochemical and biological parameters of human behavior. The earlier chapters have focused on the development of immediate release CTDDS. These systems are designed for acute treatment of colonic disorders like CD. But most of the IBD have high chances of recurrence\(^1\text{-}\text{5}\) and thus the patient is subjected to chronic therapy after treatment with acute therapy\(^6\text{-}\text{8}\). For chronic treatment of the disease, a sustained release (SR) CTDDS would be an ideal choice. Researchers have demonstrated preparation of SR matrices for IBD\(^9,\text{10}\), but the formulation and process parameters affecting \textit{in-vitro} drug release profile of colon targeted SR matrices are not well discussed. The present research endeavor was directed towards the development of delayed (colon targeted) and SR dosage form of MTZ using different hydrophilic polymers.

SR-CTDDS have been developed and studied to restrict these systems to specific regions of the GIT (colon), as well as to improve the pharmacological activity and to reduce toxic effects\(^11\text{-}\text{14}\). Sustained release CTDDS will provide further significant advantages, including improved therapeutic effect and increased patient compliance by reducing dosing frequency\(^15,\text{16}\). A major constrain in oral sustained drug delivery is that; not all drug candidates are absorbed uniformly throughout the gastrointestinal tract (GIT).\(^17\) MTZ is absorbed uniformly through full GIT\(^18,\text{19}\). Thus, development of sustained release CTDDS of MTZ will serve as a chronic therapy for CD.

One method of fabricating SR formulations is by the incorporation of the drug in a matrix containing a hydrophilic, rate-controlling polymer\(^20,\text{21}\). Hydrophilic matrices containing swellable polymers are referred to as hydrogel matrices, swellable SR systems or hydrophilic matrix tablets. A number of polymers have been investigated to develop in situ gel forming systems, due to the ability of these hydrogels to release an entrapped drug in an aqueous medium and to regulate the release of such drug by control of swelling and cross-linking\(^22\text{-}\text{24}\).

Hydroxypropylmethylcellulose (HPMC) is the polymer most widely used as the gel-forming agent in the formulation of solid, liquid, semisolid and SR dosage forms. Within the literature, an extensive knowledge base spanning many decades has demonstrated that this polymer can perform reliably with a wide variety of therapeutic agents at both high and low drug loadings\(^25\), and many other factors such as polymer
GRAS status, the simplicity and low cost of dosage form manufacturing have contributed to the worldwide use of HPMC matrix dosage forms.

Another hydrophilic polymer which has been successfully used as an alternative to HPMC is Polyethylene oxide (PEO). PEOs have been explored by many researchers for its usage as rate controlling polymer for controlled drug delivery. PEOs provide an additional advantage of high hydrophilicity compared to HPMC, to provide a better SR profile.26-28

Along with HPMC and PEO, pectin was also explored for its usage as a hydrophilic polymer for preparation of SR matrices. Pectins provide an additional advantage of colon specific degradation along with SR property.29-31

The optimized sustained release matrices were then enteric coated with Eudragit® S100 to prevent the drug release in stomach and some part of small intestine. Thus, enteric coated sustained control release matrices led to the development of SR-CTDDS.

5.2) MATERIALS AND METHODS

MATERIALS

List materials and instruments are mentioned in Appendix I.

METHODS

Method of identification of MTZ, development of calibration curve of MTZ and drug-excipient compatibility study are discussed in chapter 3.

5.2.1) Preparation of MTZ matrix SR tablets

Addition of hydrophilic polymer to the matrix SR tablets affects the release rate of the drug from the dosage form.32

(d) Method of compression

HPMC and PEO containing lubricated blend was compressed into tablets using 10 station rotary tablet machine using 9 mm concave punch. Pectin containing lubricated blend were compressed into different tablet weights. Each tablet contained 200 mg of MTZ. The core tablets were tested for hardness, thickness, content uniformity, friability, and disintegration.

5.2.2) Preparation of enteric coating solution and enteric coated matrices
5.2.3) Evaluation for dried granules of MTZ
Refer chapter 3.

5.2.4) Evaluation of core matrices and enteric coated matrices
Refer chapter 3.

5.2.5) In-Vitro Drug Release Studies

a) Hydrophilic matrices

In-vitro drug release studies were carried out using USP XXIII dissolution test apparatus Type II, paddle apparatus (100 rpm/min, 37 ± 0.5°C). Core matrices were evaluated by exposing them to 900 ml pH 7.4 phosphate buffer solution (simulated intestinal fluid, SIF) wherein it was kept for 3 h and then SIF was replaced with 900 ml pH 6.8 phosphate buffer solution (simulated colonic fluid, SCF), and tested for release for the rest of the dissolution run. The drug release at different time intervals was analyzed by UV double beam spectrophotometer at 319.4 nm in SIF and 320.4 nm in SCF. Each test was performed in triplicate.

b) Enteric coated hydrophilic matrix tablets

In-vitro drug release studies were carried out using USP XXIII dissolution test apparatus Type II, paddle apparatus (100 rpm/min, 37 ± 0.5°C). Enteric coated core matrices were evaluated by exposing them to 900 ml 0.1 N HCl (simulated gastric fluid, SGF) for 2 h, which was then replaced with 900 ml pH 7.4 phosphate buffer solution (simulated intestinal fluid, SIF) wherein it was kept for 3 h and lastly SIF was replaced with 900 ml pH 6.8 phosphate buffer solution (simulated colonic fluid, SCF), and tested for release for the rest of the dissolution run. The drug release at different time intervals was analyzed by UV double beam spectrophotometer at 276.5 nm in SGF, 319.4 nm in SIF and 320.4 nm in SCF. Each test was performed in triplicate.

5.2.6) Stability Study

Optimized SR formulations of MTZ were packed in 75 cc HDPE bottles and stability study was carried out as per the procedure mentioned in chapter 3.

5.3) RESULTS AND DISCUSSION

5.3.1) Drug-excipient compatibility study
IR spectra and DSC curve of API was compared with the prototype blend.
From IR results it is concluded that API is compatible with other excipients of the
formulation and thus can be used for formulation of enteric coated colon targeted SR
matrices in the present study.

5.3.2) *In-vitro* drug release study of SR core matrices

The aim of the current investigation was to develop sustained release CTDDS. In
order to provide SR property, matrix formulation was developed using different drug
release rate limiting polymers.

Two different hydrophilic polymers HPMC and PEO were tried to prepare colon
targeted SR matrices, independent of activation by colonic bacteria. HPMC is mixed
alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups.
The hydration rate of HPMC increases with an increase in the hydroxypropyl content.
The solubility of HPMC depends on the nature of these substituents. The solubility of
HPMC and PEO is pH independent.\(^{21}\) HPMC as Methocel E15 and K4M and PEO as
polyox\(^{\circledR}\) 1105 were used because it forms a viscous gel on contact with aqueous
media,\(^{37-40}\) which may be useful in controlled delivery of water soluble drugs.

5.3.3) Granule analysis

Bulk density, tap density and flowability of the lubricated blend were measured as per
the method described in chapter 3. Granulometry was performed for optimized core
SR formulation.

The results of the flow property and sieve analysis indicate that lubricated granules
showed good compressibility and flow. The ratio of coarse is to fine granules was also
found good (>50% granules were coarse). Thus, there was no further need to alter the
formulation composition and granulation procedure.

5.3.4) Physical and chemical evaluation of optimized core SR formulation

Batch SR8 was the optimized core formulation used for preparation of enteric coated
colon targeted SR tablets. Thus, batch SR8 was subjected to physical and chemical
evaluation along with *in-vitro* drug release study.
5.3.5 Enteric coated sustained release CTDDS
Enteric coating was carried out on batch SR 8 using Eudragit® S100. Two different theoretical weight gains were tried at 4% and 6% w/w. Batch ESR2 coated at 6% coating level displayed only 10% drug release at the end of 5 h whereas batch ESR1 coated at 4% coating level showed 14% release at the end of 5 h Thus batch ESR2 was considered as best batch.

5.3.7 Stability Study
Physical appearance of all the stability Batches of ESR2 were similar to the fresh batches. $f_2$ value between initial and 3 month stability sample was 97.9, and that between initial and 6 month stability sample was 95.6. The $f_2$ value above 50 is indicative of statistical similarity of the two release profile. Thus, Batch ESR2 was considered as the best batch for delivering MTZ in SR form to the colon.

5.4) CONCLUSION
Results indicated that a change in the manufacturing process could yield significantly dissimilar dissolution profiles for the same formulation. Pectin cannot be used as matrix SR agent, since the presence of colon specific enzymes will degrade pectin in the colon and cause premature drug release. HPMC is not degraded by rat cecal content and thus the SR tablets prepared by it will not lead to premature drug release. Thus, HPMC based SR CTDDS are the most preferred choice for targeting drug in sustained form in the colon.

5.5) REFERENCES


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Ph.D. Thesis