CHAPTER 2

REVIEW OF LITERATURE
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2. LITERATURE REVIEW

2.1) REVIEW OF WORK DONE ON COLON TARGETED DRUG DELIVERY SYSTEM (CTDDS)

2.1.1) Compression coating methodology

1) **Wu et al.** investigated the factors influencing *in-vitro* release characteristics of a model drug 5-fluorouracil from hydroxypropylmethylcellulose (HPMC) compression-coated tablets. Study revealed that release of drug from the formulations began after a time delay as a result of hydrogel swelling/retarding effect, followed by zero-order release. HPMC viscosity, lactose content, and overall coating weight of outer shell all had significant effect on release lag time ($T_{lag}$) and release rate ($k$). Increase in HPMC viscosity, lactose content, and coating weight all lead to increase in $T_{lag}$ and decrease in $k$. Hardness of the compression-coated tablets and pHs of the release media had little effect on drug release profile. It was concluded that The HPMC compression coated tablets achieve a release lag time that is applicable for colon-specific drug delivery of 5-fluorouracil.

2) **Ugurlu et al.** developed pectin–HPMC compression coated core tablets of 5-aminosalicylic acid (5-ASA) for colonic delivery. The main reason for selecting pectin was its biodegradation in the colon by colonic flora. On the other hand, high molecular weight HPMC increases the mechanical strength of the tablet wall around a drug core during its transportation in the gastrointestinal tract. Drug dissolution/system erosion/degradation studies were carried out in pH 1.2 and 6.8 buffers using a pectinolytic enzyme. At 20:80 ratio of HPMC:Pectin system protected the cores up to 6 h that corresponded to 25–35% erosion and after that under the influence of pectinase the system degraded faster and delivered 5-ASA to the colon.

3) **Ugurlu et al.** was the first researcher to prepare CTDDS using nisin as a model for a peptide drug. Nisin was tableted as the core, and then compression coated with pectin/HPMC mixture to form an enzymatically controlled delivery system. The concentration and the activity of nisin were quantified using Well Diffusion Agar Assay. Drug release studies were carried out in pH
3.3 buffer solution. It was found that pectin alone was not sufficient to protect the nisin containing core tablets since 40% drug released at the end of 6 h. Eighty percent pectin–20% HPMC appeared to be an optimum combination for directing drug to the colon.

4) Fell et al. prepared multiple unit CTDDS of indomethacin and paracetamol. Core tablets of 3 mm diameter were compression coated with either pectin USP or pectin in a 1:10 mixture with chitosan. Pectin:chitosan compression-coated tablets offer a greater degree of protection from premature drug release in the upper GI tract than pectin alone. The use of pectinolytic enzymes to simulate breakdown in the colon showed that the pectin:chitosan mixture was susceptible to enzymic breakdown and allowed drug release to occur.

5) Nunthanid et al. developed colonic drug delivery based on a combination of time-, pH-, and enzyme-controlled system. A combination of Spray-dried chitosan acetate (CSA) and hydroxypropyl methylcellulose (HPMC) was used as compression-coats for 5-aminosalicylic acid (5-ASA) tablets. Factors affecting in-vitro drug release, i.e. % weight ratio of coating polymers, enzyme activity, pH of media, and excipients in core tablets, were evaluated. The tablets compression-coated with HPMC:CSA at 60:40 and 50:50% weight ratio providing lag times about 5–6 h were able to pass through the stomach (stage I, 0.1 N HCl) and small intestine (stage II, pH 6.8, Tris–HCl). The delayed release was time- and pH-controlled owing to the swelling with gradual dissolving of CSA and HPMC in 0.1 N HCl and the less solubility of CSA at higher pH. After reaching the colon (stage III, pH 5.0, acetate buffer), the dissolution of CSA at low pH triggered the drug release over 90% within 14 h. Furthermore, the degradation of CSA by b-glucosidase in the colonic fluid enhanced the drug release.

6) Sinha et al. developed colon-specific compression coated systems of 5-fluorouracil using xanthan gum, boswellia gum and hydroxypropyl methylcellulose (HPMC) as the coating materials. The coating of the core tablets was done using different coat weights and different ratios of boswellia gum and xanthan gum and different ratios of boswellia gum and HPMC. 1:3 ratio of boswellia:xanthan gum and 2:3 ratio of boswellia gu:HPMC gave the best release profile with the lowest coating weights. Drug release was directly
proportional to coat weight in all cases. The complete drug release was found in presence of 2% w/v rat caecal contents. Therefore, this study lays a basis for use of compression coating of 5-FU as a tool for delaying the release of the drug, which ensures better clinical management of the disease.

7) Zhang et al. prepared konjac glucomannan-hydroxypropyl methyl cellulose compression coated tablets for colonic delivery. No drug almost was released in simulated gastric and intestinal fluid, and released completely in stimulated colonic fluid. Drug release decreased with decreasing the ratio of konjac glucomannan-HPMC and increasing coat weight, compression force was not found to be a significant factor on drug release. The konjac glucomannan-HPMC compression coated tablets was a promising delivery system for drugs to be delivered to the colon.

8) Krishnaiah et al. developed colon-targeted drug delivery systems for ornidazole using guar gum as a carrier. The directly compressed core formulation containing ornidazole was compression-coated at various proportions of guar gum. The compression-coated formulations released less than 8% of ornidazole in the physiological environment of stomach and small intestine. As the amount of gum increases the drug release is decreases in simulated colonic fluid. The results of the study show that compression-coated ornidazole tablets with either 65% or 75% of guar gum coat are most likely to provide targeting of ornidazole for local action in the colon.

2.1.2) Compression coating followed by enteric coating methodology

9) Fukui et al. designed enteric coated timed-release press-coated tablets (ETP tablets) which were composed of three components; diltiazem hydrochloride containing core tablet (rapid release function), the press-coated hydroxypropylcellulose layer (timed-release function) and an enteric coating layer (acid resistance function). In-vivo study carried out in beagle dogs confirmed that the time at which diltiazem hydrochloride first appeared in the blood agreed well with the lag time estimated by the in-vitro dissolution tests.

10) Meiling et al. developed pH and time dependent colonic systems for tinidazole using HPMC K4M as a compression coat for providing time dependency and enteric type opadry for providing pH dependency. Drug
release from Colon targeted tablets began at about 3 h after the test started and was completed in 4–4.5 h, while drug release from normal tablets occurred immediately and completely within 5 min. The beginning time of drug release and release rate was greatly delayed with the increase of the viscosity grade of HPMC. The higher tablet hardness made the drug release begin at a later time than the lower one. The delayed time of the presscoating layer was controlled by its erosion rate, which followed the Hixson-Crowell equation.

2.1.3) Pulsincap® type approach

11) Mastiholimath et al. designed capsule device consisting of a non-disintegrating capsule body and a soluble cap. The microencapsulated drug formulation prepared by using Eudragit® L-100 and S-100 as coat and Theophylline (TPH) as core material, was filled within the capsule body and separated from the water-soluble cap by a hydrogel plug. The entire capsule was enteric coated to prevent variable gastric emptying. On reaching the small intestine, the capsule the enteric coat dissolved and the water-soluble hydrogel polymer plug inside the capsule swelled and released the microencapsulated drug from the capsule in the colon. Scitigraphic study confirmed the delivery of drug to the terminal ileum and colonic region.

2.1.4) Matrix and Enteric coated matrix systems

12) Mura et al. developed colonic matrices using pectin which were than coated Eudragit® S100. Due to the poor compactability properties of pectin, it was used in mixture with Emdex in order to make it possible to prepare tablets by direct compression. Theophylline was used as model drug. The effects of varying the type of pectin (low and high methoxylated, or amidated), the pectin:Emdex ratio and the level of the pH-dependent polymeric coating on drug release behavior were investigated. Methoxylated pectin was most promising candidate colonic delivery.

13) Saidan et al. developed and evaluated guar gum-based matrix tablets. Matrix tablets contained varying amounts of guar gum. Guar gum matrix tablets released only 5 to 12% of rofecoxib in the physiological environment
of stomach and small intestine. Amount of guar gum was inversely proportional to drug release profile

14) Demiroz et al.\textsuperscript{14} prepared colonic matrix tablets of mesalazine using guargum. Two different types of guar gum were used viz high and low viscosity. Tablets were prepared by the slugging method. The type and the amount of guar gum affected the \textit{in-vitro} release of drug from the matrix tablets. High viscosity guar gum, in the form of a matrix tablet was capable of protecting the drug from being released in the upper region of gastrointestinal (GI) system, i.e. stomach and small intestine. X-ray studies were also performed to prove the same.

15) Krishnaiah et al.\textsuperscript{15} determined the \textit{in-vivo} availability of guar gum-based colon-targeted tablets of tinidazole in comparison with immediate release tablets of tinidazole in human volunteers. Guar gum-based colon-targeted tinidazole tablets delivered drug to the colon as compared to immediate release tablets which released drug in the stomach and small intestine. Slow absorption of the drug from the less absorptive colon might result in the availability of the drug for local action in the colon. Thus for intestinal amoebiasis guar gum-based colon-targeted tablets of tinidazole may be useful.

16) Krishnaiah et al.\textsuperscript{16} prepared matrix tablets of mebendazole containing various proportion of guar gum by using starch paste as a binder. The \textit{in-vitro} evaluation of tablet s showed that matrix tablets containing 20\% or 30\% of guar gum are most likely to deliver the drug to the colon.\textgamma - scintigraphy studies of guar gum matrix tablets was done by using technetium – 99m DTPA as tracer and it was observed that some amount of tracer present on the surface of the tablets was released in stomach and small intestine and the bulk of the tracer present in the tablet mass was released in colon.

17) Ravi et al.\textsuperscript{17} developed colon targeted tablet formulation using naturally occurring and biodegradable polymers. Core tablets were prepared using chitosan and guar gum. Core tablet was coated subjected to dual coating, inulin was used as inner coat and shellac is used as enteric coat. In vitro studies revealed that the when chitosan was used as matrix material followed by coating of core tablets with inulin and shellac, drug release in stomach and small intestinal environment was controlled and maximum amount of drug
released in the colonic environment. The study revealed that natural polymers can be used for selective delivery to colon for the treatment of local as well as systemic disorders.

18) **Rodriguez et al.**\(^{18}\) developed sodium diclofenac formulation for colonic release. The delivery system consisted in a polymeric matrix tablet containing a drug central core purposely designed for obtaining a time-controlled release profile characterized by an initial phase of lag-time followed by a controlled release phase, according to zero order kinetics. Eudragit\(^{®}\) RS100 was used as inert polymeric matrix in the core tablets, mixed (50:50, w/w) with sodium chloride or Emdex\(^{®}\) as channeling agents. Formulations containing sodium chloride showed longer lag times than the corresponding with Emdex\(^{®}\) and were more effective in providing prolonged zero-order release periods. By varying the sodium chloride/Eudragit\(^{®}\) w/w ratio, it was possible to suitably modulate the length of both the lag time (for achieving colonic targeting) and zero-order release phases.

19) **Momin et al.**\(^{19}\) developed CTDDS for sennosides using guar gum as a carrier. Matrix tablets containing various proportions of guar gum were prepared. Matrix tablets containing 50% of guar gum were found to be suitable for targeting of sennosides for local action in colon. These tablets released 43% and 96% with and without rat cecal fluids. This suggests the susceptibility of matrix to colonic microflora. To prevent the initial drug release and to target drug to the colon, optimized batch containing 50% guar gum in matrix tablet was coated with 10% hydroxyl propyl methylcellulose phthalate.

20) **Fuentes et al.**\(^{20}\) prepared pH and time dependent colonic systems by direct compression of mixtures of hydroxyethylcellulose (HEC) with ethylcellulose (EC) or micro-crystalline cellulose (MCC) which were further coated with Eudragit\(^{®}\) S100. Theophylline was used as model drug. The duration of the lag-phase was dependent on enteric-coating level whereas the release rate mainly depended on the matrix composition. Formulations with higher HEC content showed a faster drug release. MCC-HEC combinations were more effective than EC-HEC ones.
2.1.5) Mix coated systems

21) Khan et al.\textsuperscript{21} coated mesalazine tablets with aqueous dispersions of Eudragit\textsuperscript{®} L100-55 and Eudragit\textsuperscript{®} S100 combination at various ratios. Disintegration data was obtained which was dependent on polymer combination, pH of disintegration media and coating level of tablets. This combination was used to manipulate release between pH range of 5.5 to 7.0. The combination can be used to direct drug to any part of GIT on basis of its variation in pH. Colonic delivery using such a combination was more successful than its individual use.

22) Takeshi et al.\textsuperscript{22} carried an \textit{in-vitro} testing program and a clinical trial in humans of coating materials designed to release a drug specifically to the colon in response to a change in pH between the small and large intestines. The system structured by film-coated tablets consisting of an inner acid-soluble layer (Eudragit\textsuperscript{®} E) and an outer enteric-coated layer (Eudragit\textsuperscript{®} S), effectively prevented drug release in the stomach and small intestine. Gamma scintigraphy studies suggested that this system might be useful for the delivery of drugs to the colon, especially the ascending colon.

2.1.6) Colon targeted multiparticulate systems

23) Akhgari et al.\textsuperscript{23} prepared single coat colonic systems of indomethacin pellets consisting of both pH and time dependent polymers in one coat. Eudragit\textsuperscript{®} RS provided time dependency whereas Eudragit\textsuperscript{®} L and Eudragit\textsuperscript{®} S provided pH dependency. The lag time prior to drug release was highly affected by coating level. The optimum formulation consisted of 20% Eudragit\textsuperscript{®} RS, 64% Eudragit\textsuperscript{®} S and 16% Eudragit\textsuperscript{®} L, and a coating level of 10%. This formulation was tested in continuous condition of dissolution, and also separately at pH 7.5. Thus this system can be used to prepare single coat colon targeted delivery.

24) Akhgari et al.\textsuperscript{24} evaluated different polymer combinations for providing colonic delivery. Different free films were prepared by casting and solvent evaporation method. Formulations containing inulin with Eudragit\textsuperscript{®} RS, Eudragit\textsuperscript{®} RL, Eudragit\textsuperscript{®} RS–Eudragit\textsuperscript{®} RL, Eudragit\textsuperscript{®} FS and Eudragit\textsuperscript{®} RS–Eudragit\textsuperscript{®} S with different ratios of inulin were prepared. After preparation, free films were evaluated by water vapor transmission test, swelling experiment and permeability to indomethacin and theophylline in different
media. Eudragit® RS and Eudragit® RL in combination with inulin made free films which had more swelling and permeation of drug in the colonic medium rather than the other media. It was shown that formulations containing sustained release polymethacrylates in combination with inulin have more potential as a coating system for specific colon delivery compared with pH-dependent polymers.

25) Cheng et al. developed Time- and pH-dependent colon-specific drug delivery systems (CDDS) for orally administered diclofenac sodium (DS) and 5-aminosalicylic acid (5-ASA). DS tablets and 5-ASA pellets were coated by ethylcellulose (EC) and methacrylic acid copolymers (Eudragit® L100 and S100), respectively. Release profile of time-dependent DS coated tablets was not influenced by pH of the dissolution medium, on the contrary release profile of pH dependent 5-ASA coated pellets was significantly governed by pH. The absorption kinetic studies of the DS coated tablets in dogs demonstrated that in-vivo lag time of absorption was in a good agreement with in-vitro lag time of release. It was concluded that, on using regular coating techniques also colon specific drug delivery can be obtained.

26) Lamprecht et al. aimed the development of an oral delivery system for 5-fluorouracil which allows the release of the anti-cancer drug locally in the colon in dependence of luminal pH. A pH-sensitive polymer Eudragit® P-4135F was used to prepare microspheres. In further attempts mixtures with Eudragit® RS100 were prepared to prolong drug release. Eudragit® P-4135F, pure or in mixture, was found to retain drug release at pH 6.8 lower than 35% within 6 h. At pH 7.4, nearly immediate release (within 30 min) was observed for pure P-4135F, while mixtures enabled to prolong the release slightly. this new formulation could serve as a good candidate for an application in oral treatment of colon cancer.

2.1.7) Colon targeted Osmotic tablets

27) Chaudhary et al. developed colon targeted microporous bilayer osmotic tablet bearing dicyclomine hydrochloride and diclofenac potassium. The tablets were coated with microporous semipermeable membrane and enteric polymer using conventional pan-coating process. The developed microporous bilayer osmotic pump tablet (OPT) did not require laser drilling to form the
drug delivery orifice. *In-vitro* dissolution results indicated that system showed acid-resistant, timed release and was able to deliver drug at an approximate zero order up to 24 h.

2.1.8) *In-vivo* studies for colon targeted drug delivery systems

28) Fan et al. evaluated the permeability and swelling characteristics of isolated films prepared by mixing of pectin with ethylcellulose in presence of rat cecal contents. Furthermore, the IVIVC investigations of pectin/ethylcellulose-film coated pellets in dogs were also performed to check the activation of drug delivery by microflora. 5-FU was used as a model drug. The results of this study revealed that pectin/ethylcellulose films were susceptible to enzymes present in the colon. Pharmacokinetics in dogs indicated that the pectin/ethylcellulose film-coated pellets could provide sufficient time delay, which may be related with more effective delivery of drugs to the colon.

29) Basit et al. compared two colonic drug delivery concepts; a bacterially-triggered approach (amylose/ethylcellulose coating) with a pH-responsive system (Eudragit® S coating) in order to establish which physiological factor is the more reliable trigger. Theophylline was chosen as the model drug. Combining drug plasma profiling and scintigraphic analysis of transit *in-vivo* in healthy human subjects allowed comparisons of the site specificity and reproducibility of the two concepts. *In-vivo* Eudragit® S coated theophylline pellets showed premature release in the small intestine with a shorter Tmax and a higher Cmax. The amylose/ethylcellulose coating prevented any drug release from the pellets until they reached colon, where sustained theophylline release was seen. Thus, bacterially-triggered system behaved more reproducibly and reliably, and provided superior colonic targeting.

30) Shen et al. developed diclofenac sodium (DS) loaded Eudragit® L 100-55 nanofibers. XRD and DSC analysis of fibers confirm electron microscopic evidence that DS is evenly distributed in the nanofibers in an amorphous state. *In-vitro* dissolution tests verified that all the drug-loaded Eudragit® L 100-55 nanofibers had pH-dependent drug release profiles, with limited, less than 3%, release at pH 1.0, but a sustained and complete release at pH 6.8.
2.2) REVIEW OF WORK DONE ON METRONIDAZOLE CTDDS

1) **Kumar et al.**\(^{31}\) designed microbially activated osmotic delivery systems (MAODS) for colon-targeted delivery of MTZ. MAODS consisted of an osmotic core (containing drug, osmotic agent and wicking agent), an inner semipermeable membrane (SPM) layer composed of the mixture of cellulose acetate and guar gum as a pore former, and an outer enteric-coating layer. During its transit through the GIT, MAODS remains intact in the stomach due to the enteric-coating layer, but this layer dissolved in the small intestine, where pH is above 6, and fluid is imbibed into the core due to osmotic pressure gradient across SPM. The continuous imbibition of core forms a saturated solution of drug within the device. When MAODS reaches the colon, guar gum (pore former) in the semipermeable membrane is specifically degraded by microflora of the colon and thereby results in an *in situ* formation of a delivery pores. The saturated solution of drug is delivered from these delivery pores at a relatively constant release rate for up to 12 h in the colon.

2) **Krishnaiah et.al.**\(^{32}\) developed colon targeted delivery for metronidazole using guar gum as a carrier. Matrix, multilayer and compression coated tablets of metronidazole were prepared using various proportions of guar gum. Matrix and multilayer tablets failed to deliver drug to the colon as they released 43-52% and 25-44% of metronidazole respectively in the simulated gastric and intestinal fluids. Compression coated tablets prepared using 275-350 mg guar gum as compression coat released less than 1% of drug in simulated gastric and intestinal fluids. The presence of rat caecal contents in dissolution medium affected drug release from its formulation. The tablets did not show any change in physical appearance, drug content or dissolution pattern on storage for 6 months at 40 °C/75% RH.

3) **Chourasia et.al.**\(^{33}\) combined pH dependent and biodegradable approach for colon-targeted delivery of metronidazole. The multiparticulate system was prepared by coating cross-linked chitosan microspheres with Eudragit® L-100 and S-100 as pH-sensitive polymers. *In-vitro* drug-release studies were performed in conditions simulating stomach-to-colon transit in presence and absence of rat caecal contents. No release was observed at acidic pH; however, when it reached the pH where Eudragit® starts solubilizing there was
continuous release of drug from the formulation. Due to the susceptibility of chitosan matrix to colonic enzymes release of drug was found to be higher in the presence of rat caecal contents.

4) **Singh et.al.** developed and characterized capsular extrusion system for enteric delivery of metronidazole loaded liposomes. The system is similar to miniosmotic pump except that the release/extrusion in this system is brought about by the swelling of a swellable polymer which raises the vestibule and extrudes out the contents through a deliver orifice. Drug reservoir of the system contained freeze dried liposomes which become hydrated prior to extrusion. Extruded liposomes were uniform in size with 45-68% entrapment efficiency. Liposomal metronidazole had significantly higher *in-vitro* antiamoebic and antibacterial activity as compared to the unformulated drug.

5) **Nasra et al.** evaluated potential of matrix, multilayer and compression coated tablets of metronidazole as colon targeted drug delivery system. *In-vitro* release studies indicated that matrix and multilayer tablets failed to control the drug release in the physiological environment of stomach and small intestine. On the other hand, compression coated formulations were able to protect the tablet cores from premature drug release. Compression coat consisted of pectin or mixture of pectin and chitosan.

6) **Mundargi et al.** evaluated effect of polysaccharides such as GG, xanthan gum, pectin, carrageenan, beta-cyclodextrin (CD) or methacrylic acid-g-guar (MAA-g-GG) gum for their colon targeting property. The dissolution data demonstrate that the rate of drug release is dependent upon the nature and concentration of polysaccharide/polymer used in the formulations. Uncoated tablets containing xanthan gum or mixture of xanthan gum with graft copolymer showed 30-40% drug release during the initial 4-5 h. After enteric coating, the release was drastically reduced to 18-24%. The other polysaccharides were unable to protect drug release under similar conditions.

**2.3) REVIEW OF WORK DONE ON METRONIDAZOLE FOR OTHER THAN CTDDS**

1) **Yang et al.** investigated the potential of poly(ethylene glycol-co-lactide) (PELA tri-block with a segmental sequence of PLA-PEG-PLA) electrospun membranes as drug-delivery vehicles using metronidazole as a model drug.
PELA biodegradable electrospun membranes were proposed for the therapy of post-surgical adhesions and infection.

2) **Herculano et al.** developed a dermatological delivery system comprising a topically acceptable, inert support impregnated with a metronidazole (MET) solution was developed. Natural Rubber Latex (NRL), used as inert support material can be used successfully in controlled release drug delivery due to their excellent matrix forming properties. MET was incorporated into the NRL, by mixing it in solution for *in-vitro* protein delivery experiments. The solutions of latex and MET were polymerized at different temperatures, from −100 to 40 °C, in order to control the membrane morphology. Results demonstrated that the best drug-delivery system was the membrane polymerized at −100 °C, which does release 77.1% of its MET content for up to 310 h.

3) **Kuge et al.** postulated the use of metronidazole in management of advanced and recurrent breast cancer. Oral use of metronidazole may cause adverse reactions, therefore a metronidazole gel was formulated. The clinical study was carried out in five female patients. The topical use of metronidazole in a gel form improved the quality of life for patients with malodorous ulcerated tumors and facilitates intensive treatment of the underlying disease.

4) **Hillier et al.** assessed the efficacy of 0.75% metronidazole vaginal gel for the treatment of bacterial vaginosis in a double-blind, placebo-controlled crossover trial. Treatment with intravaginal metronidazole gel resulted in a clinical cure in 87% (placebo-controlled trial) to 91% (crossover trial) of women with bacterial vaginosis. The recurrence rate of 15% at 1 month after treatment was similar to that reported with oral metronidazole.

5) **Maddin et al.** compared the efficacy and safety of topical azelaic acid 20% cream and topical metronidazole 0.75% cream in the treatment of patients with papulopustular rosacea. The study concluded that Azelaic acid 20% cream provides an effective and safe alternative to metronidazole 0.75% cream with the added benefit of increased patient satisfaction.

### 2.4) REVIEW OF WORK DONE ON SATRANIDAZOLE CTDDS

1) **Jain et al.** developed multiparticulate system, hydrogel beads, combining the pH-sensitive property of enteric polymers as well as the biodegradability of
chitosan in the colon for targeting delivery of satranidazole (SNZ) for the treatment of amoebiasis. Chitosan hydrogel beads were prepared by the cross-linking method followed by enteric coating with Eudragit® S100. The amount of the drug released after 24 h from the formulation was found to be 97.67% in the presence of extracellular enzymes as compared with 64.71% and 96.52% release of drug after 3 and 6 days of enzyme induction, respectively, in the presence of 4% cecal content. Degradation of the chitosan hydrogel beads in the presence of extracellular enzymes as compared with rat cecal and colonic enzymes indicates the potential of this multiparticulate system to serve as a carrier to deliver macromolecules specifically to the colon and can be offered as a substitute in-vitro system for performing degradation studies. Studies demonstrated that orally administered chitosan hydrogel beads can be used effectively for the delivery of drug to the colon.

2) Chandra et al. developed controlled and colon targeted drug delivery system of satranidazole for the treatment of chronic amoebiasis by using Eudragit® L 100 as a pH-sensitive polymer. The release profile of satranidazole from Eudragit® microspheres was pH dependent. In acidic medium, the release rate was much slower; however, the drug was released quickly at pH 7.4. It is concluded from the present investigation that Eudragit® microspheres are promising controlled release carriers for colon-targeted delivery of satranidazole.

3) Tiwari et al. developed satranidazole loaded calcium-pectinate microbeads by ionotropic gelation method. The in-vitro drug release studies exhibited low drug release at gastric pH, however continuous release of drug was observed from the formulation at colonic pH. Further, the release of drug from formulation was found to be higher in the presence of rat cecal contents, indicating the effect of colonic enzymes on the calcium pectinate microbeads.

2.5) REVIEW OF WORK DONE ON SATRANIDAZOLE FOR OTHER THAN CTDDS

1) Muzaffar et al. studied efficacy, side effects, and tolerance of metronidazole and satranidazole in 49 patients of amebic liver abscess. Twenty-five patients received metronidazole (800 mg TID) and 24 received satranidazole (300 mg TID with placebo at mealtime). Patients recorded side effects and tolerability
through a peram. The time taken for resolution of fever and pain and the fall in abscess size was not significant. However, tolerance of satranidazole as reported by the patients was significantly better than metronidazole (P < .005). The incidence of adverse effects was significantly lower in the group given satranidazole (P < .005). The incidence of nausea and metallic taste was significantly lower in the patients given satranidazole (P < .005). Thus, despite having a similar efficacy, satranidazole showed a far lower incidence of side effects and had a significantly better tolerance than Metronidazole.

2) Derle et al.\textsuperscript{46} prepared Satranidazole β-Cyclodextrin inclusion complexes by kneading method to reduce crystallinity of the drug. On inclusion into the hydrophobic cavity of the β-Cyclodextrin solubility of satranidazole increased.

3) Saboktakin et al.\textsuperscript{47} designed a new extended release gastroretentive multiparticulate delivery system by incorporation of the hydrogel beads made of chitosan. Satranidazole as a model drug was entrapped in nano-gels and \textit{in-vitro} release profiles were established separately in both enzyme-free SGF and SIF. The drug release was found to be faster in SIF. The drug-release profiles indicated that the drug release depends on their degree of swelling and cross-linking.

2.6) REFERENCES


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