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FORMULATION AND EVALUATION OF COLON TARGETED DRUG DELIVERY OF SATRANIDAZOLE

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ABSTRACT

The colon is a site where both local and systemic delivery of drugs can take place. Treatment could be made more effective if it were possible for dugs to be targeted directly on the colon. Colon-specific systems could also be used in diseases that have diurnal rhythms. In the present study, attempt was made to target the drug to the colon, and intentionally giving release of the drug when it reaches to the colon. In DSC thermogram it shows there is no any possible interaction between drug and polymer.Different drug release patterns were obtained due to different polymers. The study was carried out at two different media 0.1 N HCl and phosphate buffer pH 7.4 This is due to change in gastric to intestinal pH media. For the first 2 hours the pH media was selected 0.1N HCl as gastric residence time is 2 hours then remaining study is carried out in phosphate buffer 7.4 pH media.The result of this study indicates that the Chitosan polymer dissolves above pH 6.5 so it shows burst release at pH 7.0 as compared to other polymers i.e. ethyl cellulose and HPMC. This is an important criteria in colonic drug delivery because most of the drug should be released in the colon itself and not in gastric or intestinal area. The Satranidazole-Chitosan tablet formulation after enteric coating by Eudragit S100 showed better result in physical characteristics and their in vitro drug release study.

KEYWORDS: Satranidazole, Chitosan, Eudragit S100, ethyl cellulose and HPMC etc.

1. INTRODUCTION

Colonic Drug Delivery

The goal for best therapy is to match the requirements of the patient while improving the efficiency and safety of the administered drugs. Various drug delivery approaches have always played a challenging and vital role in ensuring and predicting the delivery of promising and successful drugs to the target site of delivery in the human body. Oral drug delivery is the preferred route of delivery although it has become a widely accepted route of administration of therapeutic drugs; the gastrointestinal (GI) tract presents several difficult barriers to drug delivery. Recently significant interest has grown in targeting the delivery of drugs to the colon.

Colon specific drug delivery has gained increased importance not just for the delivery of drugs for the treatment of local diseases allied with the colon but also as potential site for the systemic delivery of therapeutic peptide and proteins. For a desired colon targeted drug delivery, a drug needs to be protected from degradation, release and/or absorption in the upper portion of the GI tract and then ensure abrupt or controlled release in the proximal colon. The other approaches used for colon delivery are formulation based approaches and drug modifications through covalent linkages with carrier or prodrug approach.[1]

1.1 Rationale For Colonic Drug Delivery[1]

Medical rationales for the development of orally administered colonic drug dosage forms include

1. The opportunity to lessen adverse effects in the treatment of colonic inflammation and colonic motility disorders by topical application of drugs active at the mucosal level.
2. Oral delivery of drugs to the colon is essential in the treatment of diseases of colon like ulcerative colitis, chron's disease, carcinomas and infections
3. In some cases the colon is capable of absorbing drugs efficiently.
4. Drug absorption enhancement works better in the colon than in the small intestine.
5. Protein drugs can be absorbed better from the large bowel due to hypothetic reduced proteolytic activity in this organ.
6. The unique metabolic activity of colon, which makes it an alternative organ for drug delivery system designer.

1.1.1 Advantages of Colonic Drug Delivery[1]

1. Local action, in case of disorders like ulcerative colitis, chron's disease, irritable bowel syndrome and carcinomas. Targeted drug delivery to the colon in these cases ensures direct treatment at the site with lower dosing and fewer systemic side effects.
2. In addition to local therapy colon can also be utilized as the portal entry of the drugs into systemic circulation for example molecules that are degraded/poorly absorbed in upper gut such as proteins and peptides may be better absorbed from the more benign environment of the colon.
3. The systemic absorption from colon can also be used as means of achieving chemotherapy for diseases that are sensitive to circadian rhythm such as asthma, angina and arthritis.
4. The drug can be supplied to the biophase by colon targeting only when it is required and maintenance of the drug in its intact form as close as possible to the target site.

1.1.2 Disadvantages of Colonic Drug Delivery[1]

1. The pH level in the small intestine and colon vary between and within individuals due to which drug may be released at undesired site due to pH variability so the pattern of drug release may differ from person to person which may cause ineffective therapy.
2. The pH level in the small intestine and that of cecum are same which reduces site specificity of formulation.
3. Poor site specificity is the major disadvantage of colonic delivery of drug.
4. Diet and diseases can affect colonic microflora which can negatively affect drug targeting to colon. Nature of food present in GIT can affect drug pharmacokinetics. In diseased conditions pH level of GIT differs from pH level of healthy volunteers which alters the targeted release of formulations which release the drug according to pH of desired site.
5. Enzymatic degradation may be excessively slow which can delay the enzymatic degradation of polymer thus alters the release profile of drug.
6. Substantial variation in gastric retention time may cause drug release to undesired site in case of time dependent colonic drug delivery system.

1.2 General Anatomy and Physiology of Colon

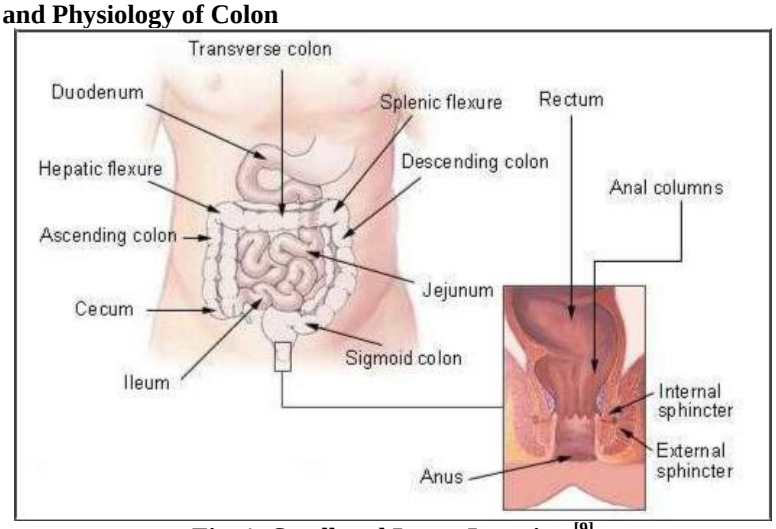

Fig. 1: Small and Large Intestine.[9]

The colon is a part of the intestine, but oftenly incorrectly used in the meaning of the entire large intestine altogether; it is really only the biggest part of the large intestine. The colon consisting of ascending colon, transverse colon, descending colon and sigmoid colon. The colon from cecum to the mid-transverse colon is also known as the right colon and remaining other is known as the left colon.

Ascending Colon

The ascending colon, on the right side of the abdomen is about 12.5 cm long. It is the part of the colon from the cecum to the hepatic flexure. It is retroperitoneal in most humans. In grazing animals the cecum empties into the spiral colon

Transverse Colon

The transverse colon is the part of the colon from the hepatic flexure to the splenic flexure. The transverse colon hangs off the stomach, attached to it by a wide band of tissue called the greater omentum. On the posterior side, the transverse colon is connected to the posterior abdominal wall by a mesentery known as the transverse mesocolon. The transverse colon is encased in peritoneum, and is therefore mobile.

Descending Colon

The descending colon is the part of the colon from the splenic flexure to the beginning of the sigmoid colon. It is retroperitoneal in two-thirds of humans. In the other third, it has a (usually short) mesentery.

Sigmoid Colon

The sigmoid colon is the part of the large intestine after the descending colon and before the rectum. The name sigmoid itself indicates S-shaped. The walls of the sigmoid colon are muscular, and contract to increase the pressure inside the colon, causing the stool to move into the rectum.

The large intestine comes followed by the small intestine in the digestive tract and measures approximately 1.5 meters in length. Although there are differences in the large intestine between different organisms, the large intestine is mainly responsible for storing waste, reclaiming water, maintaining the water balance, and absorbing some vitamins, such as vitamin K. By the time the chyme has reached this tube, almost all nutrients and 90% of the water have been absorbed by the body. At this point some electrolytes like sodium, magnesium, and chloride are left as well as indigestible carbohydrates known as dietary fiber. As the chyme moves through the large intestine, most of the remaining water is removed, while the chyme is mixed with mucus and bacteria known as gut flora and becomes feces. The bacteria break down some of the fiber for their own nourishment and create acetate, propionate, and butyrate as waste products, which in turn are used by the cell lining of the colon for nourishment. This is an example of a symbiotic relationship and provides about one hundred Calories a day to the body. The large intestine produces no digestive enzymes — chemical digestion is completed in the small intestine before the chyme reaches the large intestine.

1.2.1. Colonic pH

The highest pH levels 7.5±0.5 are found terminal ileum, on entry into the colon; the pH is dropped to 6.4±0.6. The pH of mid colon was measured as 6.6±0.8 and in the descending colon; 7.0±0.7. Passing from the jejunum to the mid small bowel and the ileum, the pH rises slightly from approximately 6.6 – 7.5 and this falls to about 6.4 in the right colon. The mid and left colon has the pH values of about 6.6 – 7.7. Colonic pH is found to get reduced in diseased state. It was calculated that the mean pH in proximal colon is 4.7±0.7 in case of untreated ulcerative colitis; whereas in patients receiving treatment for ulcerative colitis it was found to be 5.4±0.4.

1.2.2. Transit and Residence Time

One of the major factors of absorption of a compound from the colon is the residence of the drug in any particular segment of the colon. The time taken for the food to pass through the colon accounts for residence time of the food in the gut. In normal subjects this is about 78 hrs, but may range from 18 to 144 hr. Thus compared to other regions of gastrointestinal tract, movement of materials through the colon is slow. The total time form transit tends to be highly variable and influenced by a number of factors such as diet, in particular dietary fiber content, motility, stress, disease and drugs.[9] The ingestion of food is known to stimulate colonic activity in what is termed the gastro colonic response. Dietary fiber supplementations may increase fecal weight, partly by retention of water and partly by increasing bacterial mass, and reduces colonic transit time. Diseases that affect colonic transit have important implications for drug delivery. Diarrhea results in increase in colonic motility and constipation in a decrease in colonic motility.

1.3 Absorption of Drug from Colon

The primary routes by which drugs are absorbed from the gastrointestinal tract are illustrated in fig.2.

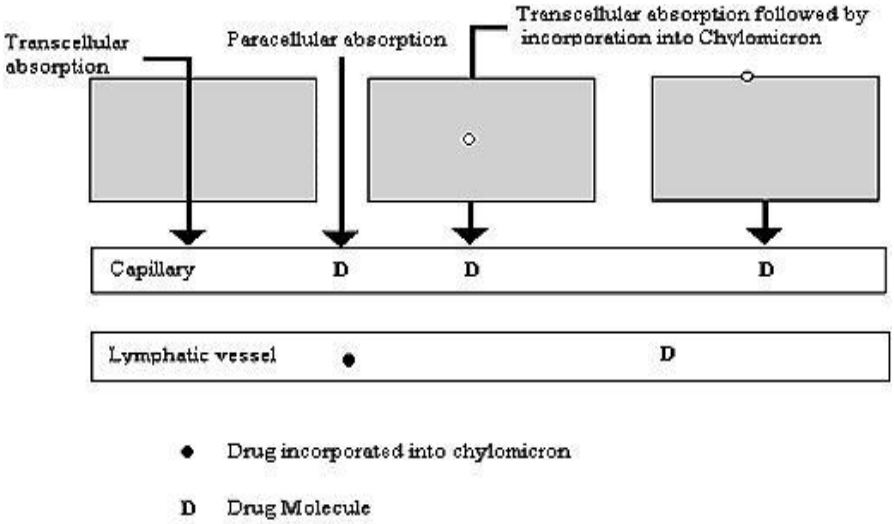

Fig. 2: Main Pathways of Intestinal Absorption.[1]

Drugs are absorbed passively through Paracellular and Transcellular routes. Transcellular absorption involves the transport of drugs through the tight junctions between the cells and this is the route most lipophilic drugs take, whereas hydrophilic drugs preferably absorb through paracellular route. Studies in rat have indicated that paracellular absorption is constant through the small intestine, but transcellular absorption appears to be

confined to the small intestine, with negligible colonic absorption by this route. The poor paracellular absorption of many drugs in the colon is due to fact that the epithelial cell junctions are very tight. The slow rate of transit in colon makes it possible for the drug to stay in contact with mucosa for a longer period than in small intestine which compensates the much lower surface areas.

1.4. Approaches for Colonic Drug Delivery

Various approaches that can be used for the development of colon targeted drug delivery systems are summarized in table no.2.

Table No. 1: Approaches for the development of colon targeted drug delivery.[14]

Approach	Basic feature
I. Chemical Approaches	
1. Azo conjugates	The drug is conjugated via an azo bond
2. Cyclodextrin conjugates	The drug is conjugated with cyclodextrin
3. Glycosidic conjugates	The drug is conjugated with glycoside
4. Glucuronide conjugate	The drug is conjugated with glucuronate
5. Dextran conjugates	The drug is conjugated with dextran
6. Polypeptide conjugates	The drug is conjugated with polypeptide
7. Polymeric prodrugs	The drug is conjugated with polymer
II. Pharmaceutical Approaches	
1. Coating with polymer	
i. Coating with pH- sensitive polymer	Formulation coated with enteric polymers release drug when pH moves towards alkaline range
ii. Coating biodegradable polymer with	Drug is released following degradation of the polymer due to the action of colonic bacteria
2. Embedding in matrices	
i. Embedding in biodegradable polysaccharides	The embedded drug in polysaccharide matrices is released by swelling and biodegradable action of polysaccharides.
ii. Embedding in pH sensitive matrices	Degradation of pH sensitive polymer in the GIT releases the embedded drug
3. Timed released systems	
4. Redox-sensitive polymers	
5. Bioadhesive system	Drug coated with bioadhesive polymer that selectively provides adhesion to colonic mucosa.
6. Coating of microparticles	Drug is released through semipermeable membrane

2. MATERIALS AND INSTRUMENTS

List of materials used

Sr. No.	Name of Material	Grade	Supplier
1.	Satranidazole	Pharma grade	Alkem Laboratories, Mumbai
2.	Chitosan	LR	The Central Institute of Fisheries Technology (CIFT), Cochin
3.	HPMC	-	Merck Specialties Pvt. Limited, Mumbai- 400 072.
4.	Ethyl Cellulose	LR	RFCL Limited, A-3, Okhla Industrial Area, Phase-I, New Delhi- 110 020 (INDIA)
5.	Microcrystalline Cellulose (MCC)	AR	Burgoin
6.	Magnesium Sterate	LR	S d Fine Chemical, 315-317, T.V. Industrial Estate, 248, Worli Road, Mumbai -400 030
7.	PVP K30	LR	Sisco Research Laboratories Mumbai- 400 030
8.	Methanol	LR	Changshu Yangyan Chemical, China
9.	Sodium Hydroxide	LR	Ranbaxy Laboratories Limited
10.	Potassium Dihydrogen Phosphate	LR	Ranbaxy Laboratories Limited

3. RESULT AND DISCUSSION

Satranidazole Characterizations

The characterization of STZ was carried out by conducting various physicochemical tests including melting point determination, spectral analysis such as UV spectrum, IR Spectrum and DSC of pure Drug.

The Melting Point Determination

The melting point was found to be in the range of 184^{0}C – 188^{0}C which is in good agreement with the reported values. So it was confirmed that gift sample obtained was Satranidazole.

Spectroscopic Studies

Determination of λmax by UV Spectroscopy in Methanol

Stock Solution (100µg/ml) of STZ was prepared in methanol. This solution was approximately diluted with methanol to obtain a concentration of 40µg/ml. The solution was kept in fused silica cuvette 10 mm. The UV spectrum was recorded in the range of 200-400 nm on Simadzu 1601 double beam UV- visible Spectrophotometer at 1 cm, Slit width. The spectrum and wavelength of maximum absorption were recorded.

Preparation of Standard Curve in Methanol

10 mg of STZ was weighted accurately and transferred to 100 ml volumetric flask. This was dissolved in methanol and Volume made up to 100 ml. This solution was treated as the stock solution and contains 100µg/ml of STZ solution. From the stock solution 1.0, 2.0, 3.0, 4.0, 5.0 ml were withdrawn and diluted the each sample with distilled water to obtain the concentrations of 10, 20, 30, 40, 50 µg/ml. absorbance of these solutions was measured at 318 nm against blank solution i.e. distilled water. Same procedure was fallowed for the prepration of standard curve in 0.1NHCL and pH 7.4 Phosphate buffer. The coefficient of correlation and equation for the line are determined.

Table 2: Absorbance of STZ in Methanol.

Sr. No.	Conc. (g/mL)	Abs. at 318nm
1	10	0.74
2	20	1.073
3	30	1.334
4	40	1.891
5	50	2.094

Standard Curve in Methanol

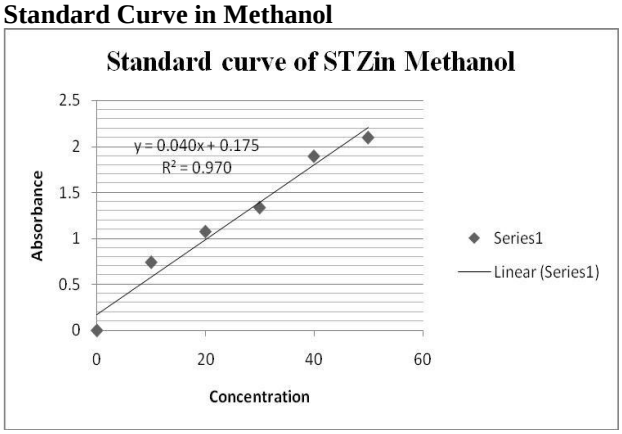

Figure 3: Standard Curve of STZ in Methanol.

Determination of λmax in Methanol

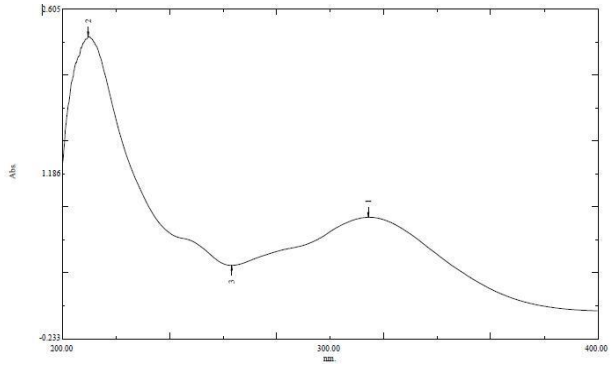

Figure 4: UV Spectrum of STZ in Methanol Preparation of Standard Curve in 0.1NHCL.

Table 3: Absorbance of STZ in 0.1NHCL.

Sr. No.	Conc. (g/mL)	Abs. at 318nm
1	10	0.555
2	20	0.805
3	30	1.326
4	40	1.701
5	50	2.314

Standard Curve in 0.1N HCL

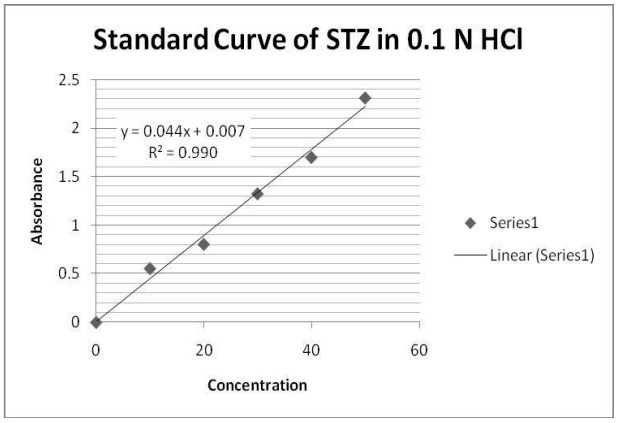

Figure 5: Standard Curve of STZ in 0.1N HCL.

Determination of λmax in 0.1NHCL

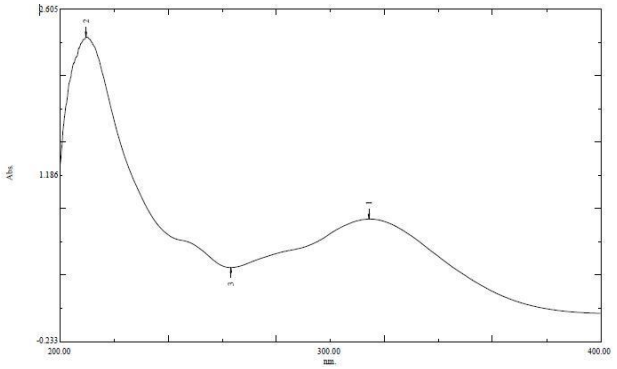

Figure 6: UV Spectrum of STZ in 0.1NHCL.

Preparation of Standard Curve in pH 7.4 Phosphate buffer

Table 4: Absorbance of STZ in pH 7.4 Phosphate buffer.

Sr. No.	Conc. (g/mL)	Abs. at 318nm
1	10	0.614
2	20	1.053
3	30	1.311
4	40	1.844
5	50	2.243

Standard Curve in pH 7.4 Phosphate buffer

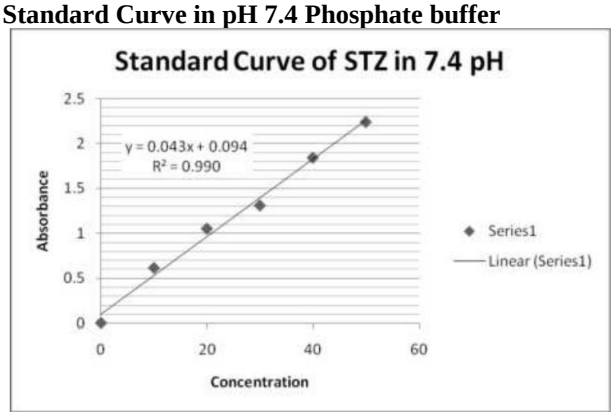

Figure 7: Standard curve of STZ in pH 7.4 phosphate buffer Determination of λmax in pH 7.4 phosphate buffer.

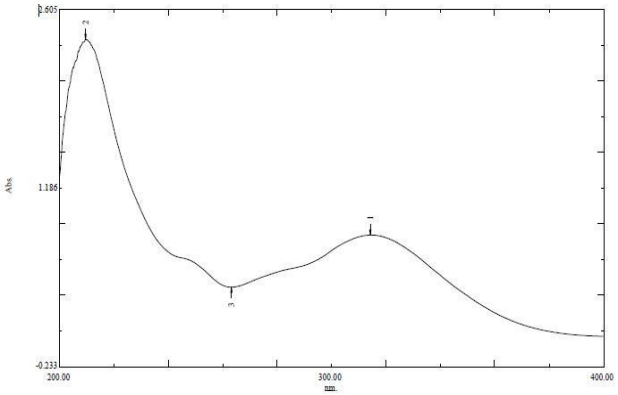

Figure 8: UV Spectrum of STZ pH 7.4 phosphate buffer.

Table 5: Wavelength of maximum absorption (λmax) in different solvents.

Sr. No	Solvent	λmax
1	Water	318.5 nm
2	0.1 N HCL	318.5 nm
3	pH 7.4 Phosphate Buffer	318.5 nm

Solvent	Coefficient of correlation (R^2)	Equation of line (Y=mx+C)
Water	0.970	0.038X-0.009
0.1 N HCL	0.9904	0.035X-0.046
pH 7.4 Phosphate Buffer	0.9902	0.029X+0.038

FT- IR Spectrum Interpretation

IR Spectrum of Pure Drug

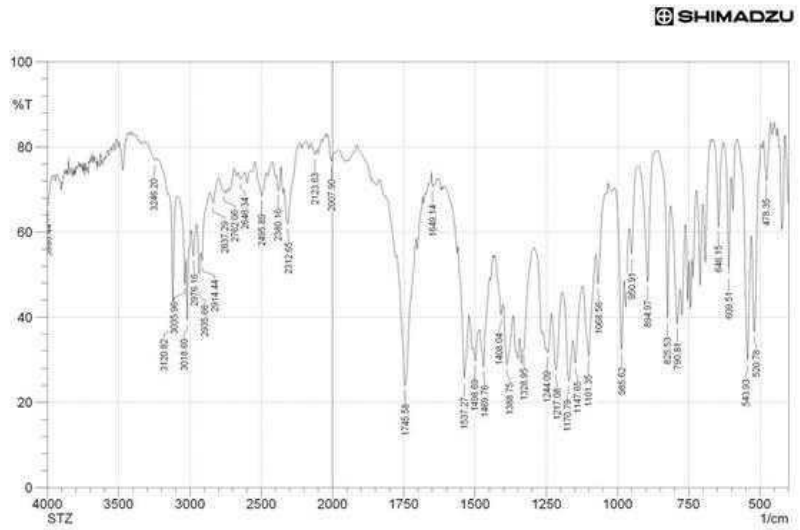

Figure 9: IR Spectrum of Pure Drug.

The IR spectra pure drug, showed all principle peaks of Satranidazole at

- 1742 cm-1(C=O stretch),
- 3019 cm 1(Aromatic-CH stretch),
- 1351 cm-1 (-NO2 stretch),
- 754 cm-1 (NO2 aromatic).

This FTIR spectra resembles with the standard FTIR spectra that of Satranidazole[23] so it is confirms that the gift sample is Satranidazole.

Drug - Excipients Compatibility Studies

Compatibility studies of pure drug Satranidazole with polymers and other excipients were carried out prior to the preparation of tablets. I.R spectra of pure drug Satranidazole and that of with polymers and other ingredients were obtained. All the characteristic peaks of Satranidazole were present in spectra thus indicating compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug.

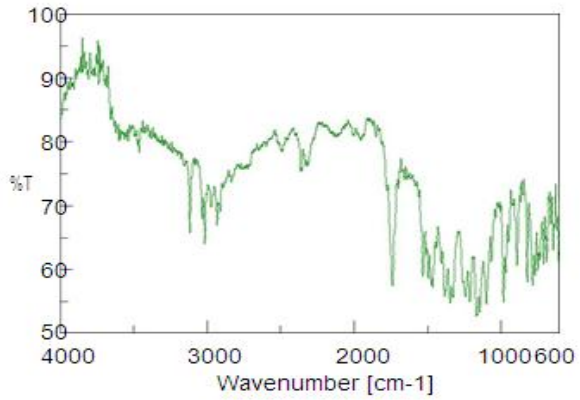

Fig. 10: FTIR of Drug +Ethyl Cellulose.

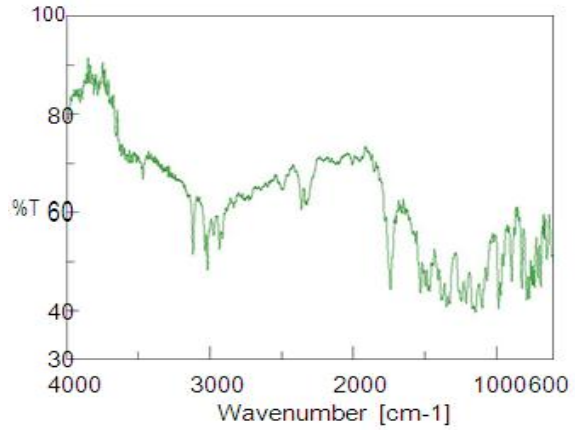

Fig. 11: FTIR of Drug +Chitosan.

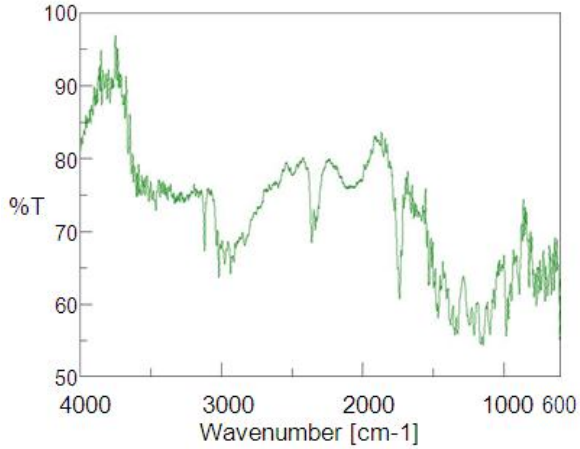

Fig. 12: FTIR of Drug +HPMC.

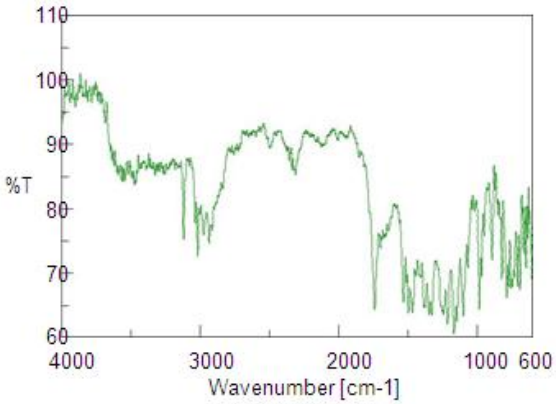

Fig. 13: FTIR of Drug +PVP K30 IR Spectrum of Drug and all Excipients.

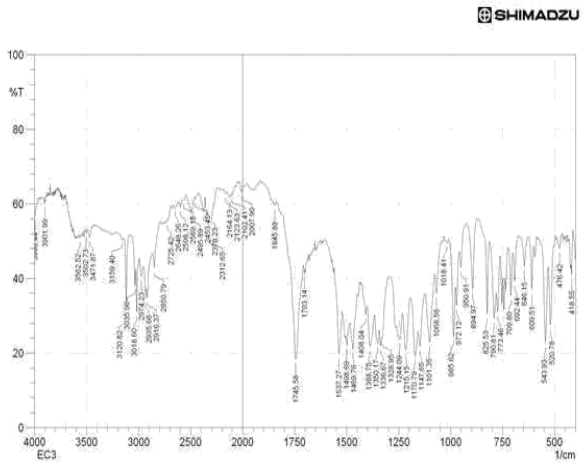

Figure 14: IR Spectrum of STZ-Excipients.

This FTIR Spectra of STZ and all excipients show all the principle peaks of Satranidazole i.e.

Wave. No (cm^{-1})	Characteristic Bands
1742	C=O Stretching
3019	Aromatic-CH stretch
1351	-NO2 stretch
754	NO2 aromatic

There is no shifting of bands of Satranidazole so it shows that there was no significant change in the chemical integrity of the drug. Hence all these excipients show compatibility with Satranidazole.

DSC of Satranidazole Drug and Polymer Mixture

DSC thermogram of Satranidazole and physical mixture of drug and polymers are shown in Figure no. 15. DSC of pure Satranidazole exhibits a sharp endothermic peak at 189.3 ºC corresponding to its melting point.

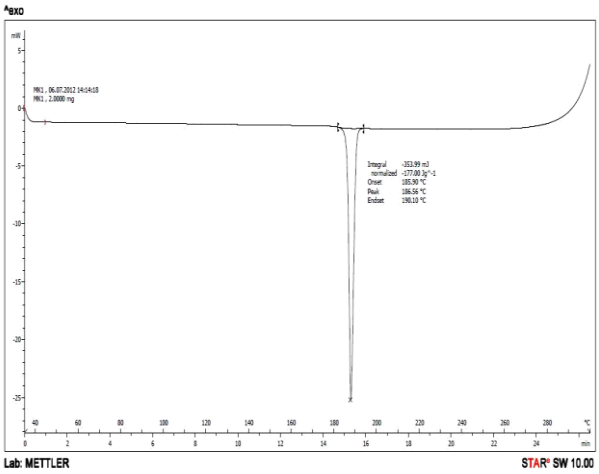

Figure 15: DSC of Satranidazole Drug.

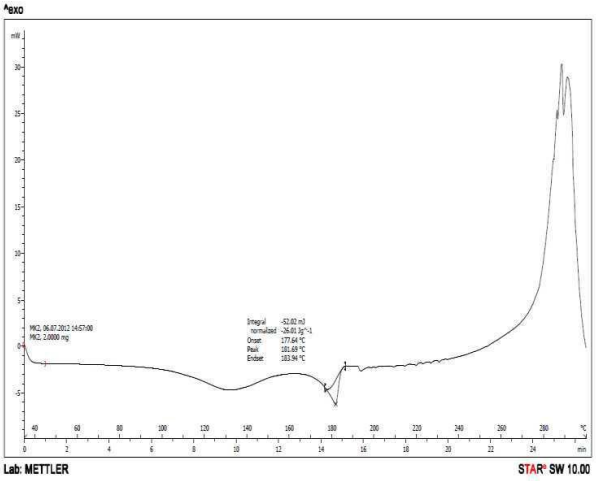

Figure 16: DSC of Mixture of Satranidazole and all Polymers.

In DSC thermogram of Drug and Polymer mixture, there is slightly shifting of endothermic peaks characteristic of melting point at 182^0C which gives there is no possible interaction between drug and polymer.

Evaluation of powder characteristic of tablets

The powders prepared for compression of tablets were evaluated for their flow properties. The powder characteristic indicates good flowability with an angle of repose value ranging from 25-30 i.e. (<30). The angle of repose of all formulations was found to be the range of 23.92±0.31 to 28.99±0.57. The bulk density of all the formulation showed acceptable range. The bulk density of these powders was found to be in the range of 0.424±0.08 to 0.621±0.04gm/cm3for all formulations. The measured tapped density was in the range of 0.483±0.07 to 0.770±0.05gm/cm3 for all formulations. Carr's index of powder was found the range of 09.73±0.03 to 20.00±0.02 for all formulations. These values indicate that the prepared powder exhibited good flow properties. The result mentioned in the table no: 18.

Table 6: Comparative study of various powder characteristics for formulation.

Batch Code	Angle of repose (θ)	Bulk Density (gm/cm^3)	Tapped Density (g/cc)	Carr's index (IC)
F1	25.71±0.21	0.532±0.02	0.670±0.06	15.00±0.02
F2	26.57±0.08	0.424±0.08	0.490±0.01	14.00±0.14
F3	27.38±0.12	0.588±0.03	0.661±0.03	12.18±0.02
F4	24.04±0.340	0.568±0.02	0.641±0.02	11.60±0.12
F5	25.10±0.750	0.621±0.04	0.770±0.05	20.00±0.02
F6	28.99±0.57	0.530±0.02	0.625±0.07	15.32±0.03
F7	23.92±0.31	0.592±0.04	0.671±0.04	11.77±0.06
F8	26.32±0.09	0.436±0.09	0.483±0.07	09.73±0.03
F9	27.22±0.10	0.601±0.07	0.691±0.09	13.91±0.03
Broad Range	26.12±0.31 to 28.99±0.57	0.424±0.08 to 0.621±0.04	0.483±0.07 to 0.770±0.05	09.73±0.03 to 20.00±0.02

(*n=3)

Characterization of colon tablets

The weights of the tablets of all formulations were low standard deviation values, representing uniformity of weight. The difference in weight was within the range of 5% complying with Pharmacopoeial specification (Indian Pharmacopoeia). The weight variation deviation of different formulations was found to be 3.384 to 4.584. The hardness for different formulations was found to be between 4.8±0.22 to 6.4±0.35 kg/cm2. It was indicate satisfactory mechanical strength. The diameter and thickness of all the formulations were found in the range of 10.01±0.03 to 10.17±0.04 and 3.28±0.03 to 3.44±0.08 mm respectively. The friability of all formulation was found to be between 0.45±0.02 to 0.66±0.07%. The tablets compressed were stable and having good physical characteristics. The percentage drug content for different tablets formulation varied from 96.24±0.04 to 99.13±0.05 was found to be within limits which indicate uniform drug distribution in all formulations.

Table 7: Physico-Chemical Characterization of Satranidazole Tablets.

Batch Code	Weight variation		Hardness (kg/cm2)	Diameter (mm)	Thickness (mm)	Friability (%)	Drug Content (%)
	Average weight (mg)	Highest (%) deviation					
F1	498	4.115	5.7±0.24	10.12±0.05	3.28±0.03	0.57±0.02	98.02±0.02
F2	502	3.942	4.8±0.22	10.01±0.03	3.42±0.05	0.63±0.05	97.42±0.03
F3	501	3.586	6.2±0.16	10.10±0.08	3.29±0.02	0.46±0.04	99.13±0.05
F4	500	3.816	5.9±0.26	10.17±0.04	3.33±0.04	0.53±0.03	97.32±0.03
F5	503	4.105	6.4±0.35	10.07±0.02	3.31±0.01	0.64±0.06	96.32±0.04

F6	502	3.584	5.6±0.12	10.15±0.03	3.39±0.09	0.45±0.02	97.51±0.04
F7	499	3.384	5.7±0.29	10.11±0.04	3.44±0.08	0.54±0.03	98.66±0.03
F8	501	4.223	5,2±0.24	10.09±0.03	3.27±0.10	0.66±0.07	97.30±0.04
F9	500	4.623	5.4±0.21	10.03±0.05	3.35±0.12	0.79±0.01	96.24±0.04

(*n=3)

Table 8: Physico-Chemical Characterization of Satranidazole Tablets after Coating.

Batch code	Weight variation Average weight (mg)	Thickness (mm)
F1	512	4.28±0.03
F2	514	4.42±0.05
F3	510	4.29±0.02
F4	509	4.33±0.04
F5	515	4.31±0.01
F6	511	4.39±0.09
F7	509	4.44±0.08
F8	512	4.27±0.10
F9	512	4.35±0.12

In vitro dissolution studies for colon targeted satranidazole tablets

The *in vitro* dissolution studies were carried out by using USP apparatus type II at 100 rpm. The dissolution medium was 900ml 0.1M HCl maintained at 37± 0.5^0C for first two hours then the dissolution media was replaced by 7.4 phosphate buffer media. Aliquots of dissolution medium were withdrawn at predetermined intervals and content of Satranidazole was determined at 318.5nm spectrophotometrically.[39]

Table 9: Dissolution data of formulation containing Satranidazole-Ethyl Cellulose.

Time (hrs)	Cumulative % drug release		
	f1	**f2**	**f3**
0	0.00	0.00	0.00
1	1.82	1.63	1.43
2	2.28	2.11	1.95
3	7.54	7.87	8.21
4	17.70	20.59	23.48
5	18.63	24.86	31.09
6	24.08	31.77	39.46
7	26.65	36.84	47.03
8	31.08	43.14	55.20
9	33.00	46.39	59.77
10	34.71	50.66	66.61
11	38.63	57.12	75.60
12	43.01	59.58	76.14
13	47.26	62.71	78.16
14	59.44	69.25	79.07

(*n=3)

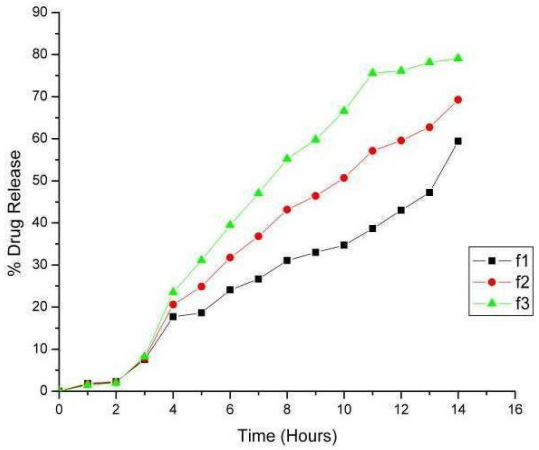

Figure 17: Dissolution Profile of formulation containing Satranidazole-Ethyl Cellulose.

In the all batch formulation it is observed that in simulated gastric fluid, the enteric coating is able to maintain its integrity in the stomach and the drug release was not more than 2 % in the first phase of dissolution studies. The release was varied in the next dissolution run that is in the simulated colonic fluid.

The f1 formulation shows 59.44% drug release only in 14 hrs whereas formulation f2 Shows 69.25% drug release at the end of 14 hrs. The f3 formulation at highest concentration of polymer shows 79.07% drug release at the end of 14hrs and it is better drug release as associated to other concentration of polymer drug ratio. Then the drug release is good enough in case of formulation F3.

Table 10: Dissolution data of formulation containing Satranidazole-Chitosan.

Time (hrs)	Cumulative % drug release		
	f4	**f5**	**f6**
0	0.00	0.00	0.00
1	1.21	1.11	1.30
2	2.31	1.95	1.53
3	11.87	14.21	17.61
4	15.34	23.72	25.58
5	21.45	31.99	29.34
6	22.31	37.99	38.81
7	28.96	42.37	42.53
8	33.98	43.95	44.92
9	41.39	48.71	51.61
10	44.15	51.78	52.76
11	50.69	51.97	54.14
12	52.43	55.86	60.18
13	56.40	61.76	75.79
14	60.82	76.71	85.59

(*n=3)

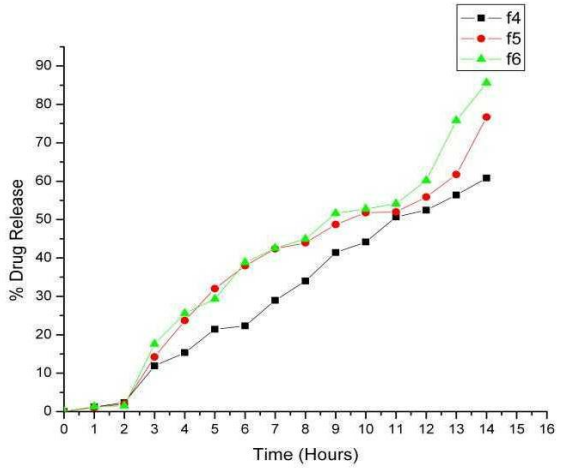

Figure 18: Dissolution Profile of formulation containing Satranidazole-Chitosan.

In the Satranidazole-Chitosan formulation the chitosan shows good burst release of drug when comes in contact with the colonic fluid as it is soluble in pH above 6.5 i.e. in alkaline pH. The f4 formulation shows 60.82% drug release in 14 hrs. The f5 give 76.11% drug release at the end of 14 hrs and it is good burst release as compare to f4. The highest concentration f6 gives the drug release 85.59% at the end of 14 hours and it is good enough burst release compare to above two formulations.

Table 11: Dissolution data of formulation containing STZ-HPMC.

Time (hrs)	Cumulative % drug release		
	f7	f8	f9
0	0.00	0.00	0.00
1	0.82	0.95	1.08
2	1.27	1.37	1.47
3	18.72	10.69	2.65
4	35.36	26.67	17.99
5	54.36	42.86	31.36
6	69.22	54.83	40.43
7	74.53	64.25	53.97
8	78.99	67.31	55.64
9	90.09	78.44	66.80
10	98.22	90.27	76.58
11		99.12	86.75
12			99.49

(*n=3)

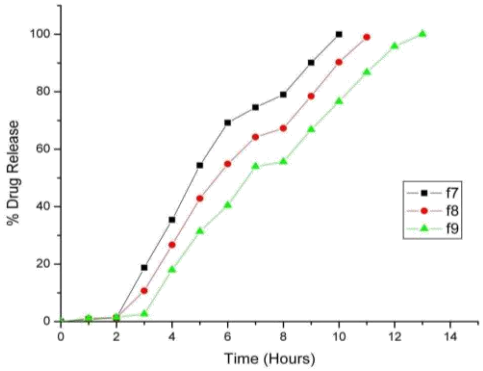

Figure 19: Dissolution Profile of formulation containing STZ-HPMC.

In the Satranidazole-HPMC matrix formulation the drug release found in first 2 hours is as expected i.e. below 2%. In the f7 formulation at the end of just 10 hrs it shows the 98.22% drug release and in f8 it gives the 99.12% at 11 hrs. The highest concentration formulation f9 shows the drug release 99.49% in 12 hrs.

Table 12: Dissolution data of formulation containing F3, F6, F7.

Time (hrs)	Cumulative % drug release		
	F3	F6	F7
0	0.00	0.00	0.00
1	1.43	1.30	0.82
2	1.95	1.53	1.27
3	8.21	17.61	18.72
4	23.48	25.58	35.36
5	31.09	29.34	54.36
6	39.46	38.81	69.22
7	47.03	42.53	74.53
8	55.20	44.92	78.99
9	59.77	51.61	90.09
10	66.61	52.76	103.95
11	75.60	54.14	
12	76.14	60.18	
13	78.16	75.79	
14	79.07	85.59	

(*n=3)

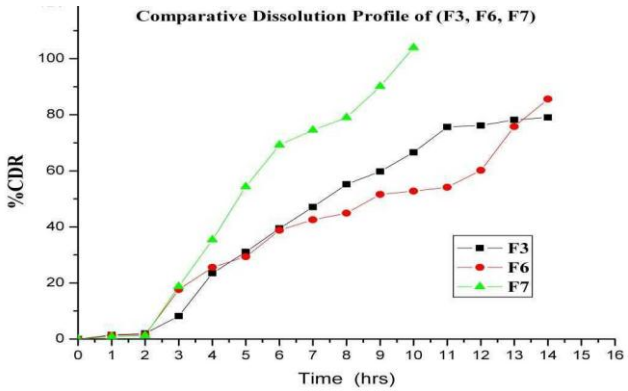

Figure 18: Comparative Dissolution Profile of formulation F3, F6, F7.

In case of formulations F3, F6, F7 the burst release takes place in f6 when in it reaches in the colon after 6-7 hours. The f7 batch also shows the good result but the burst release takes place in small intestine and drug reaches at the colon will be small quantity and same in the case of ethyl cellulose i.e. f3. The f3 shows 79.09 % drug release at the end of 14 hours f6 shows 85.59% drug release at the end of 14 hours and that of f7 gives103.95 % drug release in 10 hours.

CONCLUSION

In the present study, Colon Targeting tablets were prepared by different drug to polymer ratio using direct compression method. The powder Characteristics of various formulations are found within a limit. After the powder characteristics the tablets prepared by direct compression using 12 station rotatory tablet compression machine then the tablet was coated by enteric coating and further evaluated.

In the FT-IR study all characteristic peaks due to pure Satranidazole were appeared in matrix tablet spectra, without any markable change in their position after successful compression, indicated no chemical interaction and stability of drug during compression process. In DSC thermogram it shows there is no any possible interaction between drug and polymer.

Different drug release patterns were obtained due to different polymers. The study was carried out at two different media 0.1 N HCl and phosphate buffer pH 7.4 This is due to change in gastric to intestinal pH media. For the first 2 hours the pH media was selected 0.1N HCl as gastric residence time is 2 hours then remaining study is carried out in phosphate buffer 7.4 pH media.

The result of this study indicates that the Chitosan polymer dissolves above pH 6.5 so it shows burst release at pH 7.0 as compared to other polymers i.e. ethyl cellulose and HPMC. This is an important criteria in colonic drug delivery because most of the drug should be released in the colon itself and not in gastric or intestinal area. The Satranidazole- Chitosan tablet formulation after enteric coating by Eudragit S100 showed better result in physical characteristics and their in vitro drug release study.

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