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Original Research Article

FORMULATION AND EVALUATION OF SATRANIDAZOLE TABLET FOR COLON DELIVERY

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Abstract:
Literature survey reveals that, amoebiasis is the second leading cause of death from parasitic disease worldwide. The causative protozoan parasite, Entamoeba histolytica, is a potent pathogen. Oral delivery of drugs in the colon is valuable in the treatment of diseases of colon like amoebiasis whereby high local concentration can be achieved while minimizing side effects. Satranidazole was selected as the drug of choice because it is most potent nitroimidazole derivative and clinically useful against common protozoa; it is twice as effective as other nitroimidazole against amoebiasis. Colon targeted tablet of satranidazole can maintain minimum inhibitory concentration (MIC_{90}) for desired duration in fewer doses and even with fewer side effects. The colon targeted matrix tablet of satranidazole which is composed of polysaccharides which are susceptible to enzymatic degradation i.e. Guar gum, Xanthan gum, Guar: Xanthan gum in combination at 2 ratios (1:1) and (2:1) and Pectin coated with enteric polymer Eudragit L, Eudragit S and Eudragit RS in ratio of 4:16:5 with less quantity of plasticizer PEG 400 showed excellent film properties and were able to release most of the drug into colon. 10% of coating was found to be optimum. Analytical methods were developed for the drug, and calibration curves were prepared in SGF, SIF, and SCF. Formulation SF7 was considered as optimum batch as it delivered 96 % of drug into colon. The in vivo studies showed that tablet does not disintegrate in stomach and small intestine and site of disintegration was found to be descending colon. The formulation SF7 can be employed as a promising colon specific drug delivery system of satranidazole.

Keywords- Satranidazole, Colon targeted tablets, Guar gum, Xanthan gum, Pectin, X-Ray Study

Introduction

Satranidazole was selected as the drug of choice because it is most potent nitroimidazole derivative and clinically useful against common protozoa; it is twice as effective as other nitroimidazole against giardiasis and amoebiasis. It is also significantly more active against anaerobes than other nitroimidazole. Duration of action of satranidazole is 12 hour. Conventional tablets available are in strength of 300 mg and are to be administered twice in a

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day. Satranidazole is available in the market in the form of film coated matrix tablet. In conventional matrix tablet (marketed) 100% of drug is released in stomach and from this released drug absorption takes place, thus drug that reaches to systemic circulation and available for action is very less than that is actually delivered by dosage form. This occurs because of some pharmacokinetic and pharmacodynamic parameters like extent of absorption, volume of distribution, and protein binding of drug. In order to overcome all these drawbacks of conventional tablet colon targeted tablet formulation of satranidazole is developed with the aim to deliver 100% drug to the targeted site i.e. diseased colon. Colon targeted tablet of satranidazole can maintain minimum inhibitory concentration (MIC_{90}) for desired duration in less dose and even with less side effects as given in less quantity is administered because the drug is targeted to colon where causative organism of amoebiasis, E. hystolytica is present.

Material and methods- Satranidazole was obtained as gift sample from Alkem Laboratories, Mumbai, Guar gum and Xanthan gum was purchased from M/s. Dabur Research Foundation, New Delhi, India, and was of USP/NF quality. MCC (Avicel ph 102) was obtained from Signet Corporation, Mumbai as gift sample and Eudragit L,

Eudragit S and Eudragit RS were obtained as gift sample from Degussa Rohm Pharma polymer. Other ingredients used were of US/NF quality.

Determination of solubility of drug-The study was carried out in glass vials of 10 ml capacity. Each vial charged with 5 ml of distilled water and different dissolution media and excess quantity of satranidazole. The vials were closed with rubber closures and kept for equilibrium at 25˚C±2˚C for a period of 24 hrs with continuous shaking; the solutions were then filtered and analyzed for the drug content spectrophotometrically at 318 nm.

Calibration curve of drug by UV absorption- In present studies Simulated gastric fluid, intestinal fluid, and colonic fluid without enzyme were used as a medium for drug release studies and hence estimation of satranidazole in these media was done by UV spectrophotometric method.

Analysis of satranidazole in simulated gastric, intestinal and colonic fluid- Estimation of small amount of satranidazole was necessary for studying the release properties and determining percent active ingredients (a.i.) in matrix tablet formulation. This was achieved by using an UV spectroscopic method. Different aliquots of satranidazole were prepared in Simulated gastric fluid, intestinal fluid, and colonic fluid and calibration curve were obtained. The stock solution of satranidazole containing (1000mcg/ml) in different dissolution media was prepared and 318 λ_{max} was selected on the basis of maximum absorption found in UV spectrophotometer (Shimadzu 1601).The dilutions were made to achieve final concentration in range of 2mcg/ml to 20mcg/ml. The absorbance of the resulting solution was measured against different dissolution media as blank.

Drug – Excipient interaction-The compatibility of drug and various excipients was studied using Fourier transform infrared spectroscopy (FTIR) techniques. FTIR was used as a tool to detect any physical and chemical interaction between drug and excipient. Drug (satranidazole) and various excipients were mixed thoroughly in a ratio of 1:1 as shown in table. Drug sample as well as drug and excipient, was stored at room temperature and at 50^0C in a closed vials. 10% weight / weight water was added in the samples which were kept at 50^0C to study effect of moisture. After three weeks samples were scanned with FTIR (IR 750 Nicolet) before and after 3 weeks of storage. The spectra of pure drug and drug with excipients were compared

to check any incompatibility and also physical change was monitored.

Preparation of tablets-Different formulation having the composition as shown in table 7 (SF1 TO SF9) were prepared. All ingredients were weighed, grinded in mortar pestle to reduce the size and passed through 100 mesh sieve. All ingredients were sieved through 100 mesh twice, mixed and blended manually in polyethylene bags so as to ensure proper mixing. The blended powder was granulated by adding sufficient quantity of 10% PVP K 30 in isopropyl alcoholas a binder to obtain a mass of proper wetness and the mass was passed through sieve no.12 to obtain granules and dried at 40˚C for 30 minutes. Dried granules were passed through 30 mesh sieve to obtain uniform sized granules and mixed with 1% of Magnesium stearate and 2% of in polyethylene bag. This blend was now ready for compression. The granule mix was compressed into tablets of the target weight 450 □□5 mg in a hand operated single punch tablet machine fitted with 11 mm biconcave punches. The compression pressure level was kept constant for all the batches by adjusting the pressure control knobs to the same setting.

Tablet formulas and the corresponding different percentages-

S.No	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9
1	Drug	22.22	22.22	22.22	22.22	22.22	22.22	22.22	22.22	22.22
2	Guar gum	20	30	40	-	-	-	-	-	-
3	Xanthan gum	-	-	-	20	30	-	-	-	-
4	Guar:Xanthan	-	-	-	-	-	20 (1:1)	20 (2:1)	-	-
5	Pectin	-	-	-	-	-	-	-	20	30
6	Ethylcellulose	-	-	-	-	-	-	-	5	5
7	MCC	44.78	34.78	24.78	44.78	34.78	44.78	44.78	39.78	29.78
8	PVP K30 in IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
9	Talc	2	2	2	2	2	2	2	2	2
10	Mg. stearate	1	1	1	1	1	1	1	1	1

Coating of tablets- Two coating solutions (SC1 & SC2) were prepared with composition as shown in table 8.PEG 400 was used as plasticizer. The solvent in which polymer disperses was taken in plastic beaker and stirred in a mechanical stirrer (Remi motors Ltd.). In the vortex of polymer the solvent in which polymer was soluble was added and stirred to obtain a clear solution. Finally the plasticizer was added and stirred for 20 to 30 minutes. The polymer taken was 5 % w/v of coating solution. The prepared concave tablets were loaded to a coating pan and heated for 20 min with the help of dryer. The tablets were

coated by spray coating using spray gun. The pan speed was kept at 15 rpm and temperature of hot air at temperature of 40˚C was blown over the tablets using dryer to dry the coated tablets. The tablets were coated till it attains predetermined weight. Finally coated tablets were dried at 40˚C for 30 minutes.

Composition of coating solution-

S. No.	Ingredients	SC1	SC2
1.	Eudragit L100	4 g	3g
2.	Eudragit S100	16 g	12g
3.	Eudragit RS100	5 g	10 g
4	PEG 400	2 g	2 g
5.	Acetone	350 ml	350 ml
6.	Isopropyl alcohol	150 ml	150 ml

Evaluation of coated tablets of satranidazole-All the batches (SF-1 to SF-9) were evaluated for following parameters- Hardness, Weight variation, Friability, Thickness, Swelling studies and Assay.

In vitro drug release-For targeted drug delivery systems in vitro dissolution studies are important for determining drug availability. Data generated by in vitro dissolution studies can be used by the formulator in the development stages of product and batch to batch uniformity can be ensured. The percentage release of satranidazole (100 mg) from the coated matrix tablet was determined using USP dissolution paddle type apparatus, (model TDT-08I. Electrolab) using 900 ml of specific fluids as dissolution medium. The stirring rate of paddle was 75 rpm and the temperature of medium was maintained at 37˚C±0.5˚C. During the release studies 10 ml samples of dissolution fluid was withdrawn at an interval of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 18, 20, 22, and 24 hr and were replaced with fresh dissolution medium subsequently. The samples were analyzed using double beam UV spectrophotometer (Shimadzu) at 318 nm The mean of 3 determinations were used to calculate the drug released from samples

In vivo study-X-ray imaging was used to monitor the tablets throughout the gastrointestinal system. Human volunteers, with an age of 25 year and 80 kg body weight, participated in in vivo studies. Volunteer was non-alcoholics, non-smoker and had not taken any drugs. The purpose of the study had been fully explained. Subject orally ingested barium sulphate containing guar: xanthan matrix tablets with 200 ml of water, after an overnight fast. Abdominal radiographs were taken at fixed time intervals, and the tablets were visualized using X-ray imaging to establish whether they had reached the colon or not. Volunteers were served with food after 2 h (breakfast) and 4 h (lunch) after the administration of the tablet. In the present study, X-ray imaging was used on the tablets, in order to monitor the Guar: xanthan matrix tablets throughout the gastrointestinal system and to test them in vivo. The data were analysed to provide information regarding the time and site of disintegration of the prepared tablet.

Results and discussion-

In solubility studies the drug was found to be more soluble in SGF (0.612 mg/ml) in comparision to SIF and SCF (0.493 and 0.517 mg/ml respectively). This much of solubility is sufficient to dissolve approximately 400 mg of drug in 900 ml of dissolution media in each case. UV spectra of satranidazole (50µg/ml) solution in DM water shows peak at wavelength 318 nm. This wavelength was considered as λ_{max} and all the observations by UV spectrophotometer to calculate the amount of drug were taken at this wavelength. Calibrartion curve of satranidazole in Simulated Gastric Fluid, Simulated Intestinsal Fluid and Simulated Colonic Fluid shows straight line in range of 2 to 20 µg/ml with respective R^2 value of 0.9964, 0.9984, and 0.9966 which follows Beer-Lambert law. After three weeks of drug interaction study, from the FTIR spectra of drug plus excipients, it was concluded that there was no interaction between any excipient and drug.

Evaluation of uncoated tablet

Formulation	Friability (%± SD)	Weight variation (mg)	Average Weight (mg)	Drug content (mg)
SF1	0.6±0.023	***0.2±0.06***	***450-455***	101.123
SF2	0.6±0.012	***0.4±0.10***	450-455	100.654
SF3	0.7±0.056	0.3±0.24	450-455	101.354
SF4	0.7±0.034	0.2±0.07	450-455	100.712
SF5	0.7±0.021	0.6±0.05	450-455	102.245
SF6	0.6±0.041	0.2±0.08	450-455	100.219
SF7	0.8±0.052	0.4±0.01	450-455	101.356
SF8	0.7±0.039	0.5±0.06	450-455	100.458
SF9	0.7 ±0.027	0.6±0.03	450-455	101.243

S.No.	Time (hr)	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9

Evaluation of coated tablets-

S. No.	Parameters	Value obtained
1.	Hardness (Kg/cm^2)	12.0-14.0
2.	Thickness (mm)	4.25-4.35
3.	Percentage weight gain on tablets after coating	9-10 %
4.	Appearance of coating	Smooth, transparent without any coating defects

Swelling studies of Batch SF1 to SF9-

Time (hr.)	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9
2	0.39	0.33	0.39	0.41	0.42	0.34	0.29	0.36	0.41
5	5.89	6.15	6.05	8.05	8.23	6.93	6.14	6.71	6.52
10	23.03	23.11	25.19	35.31	37.53	32.44	28.02	35.42	36.27
16	44.11	44.26	45.21	71.09	75.31	54.17	50.21	60.09	61.34
24	45.59	46.31	48.54	74.35	78.24	56.25	51.32	64.25	64.85

Swelling study shows that xanthan gum had greater swelling index comparative to other polysaccharides. Studies carried out on swellable matrices have shown that as the concentration of the swellable polymer is increased in the formulation, the gel thickness increases upon swelling. This increases the diffusion path length, which in turn decreases the drug release from the tablet.

***In Vitro* Drug Release-** The dissolution studies were performed for all the batches and the release profile of drug was calculated. Maximum percent of drug release was attained in colon in all the batches, After 24 hr. from administration of dose was calculated. Guar gum, xanthan gum, guar xanthan combination and pectin were used as enzyme dependent polymer to reduce the drug release in stomach and small intestine and release the maximum amount of drug into colon. In all batches control drug release was observed up to small intestine. Batch with guar and xanthan gum in combination in a ratio with (2:1) was found to be most optimum as it releases 80.21% after 24 hour. Presence of xanthan gum in presence of guar gum would allow formation of a thicker viscous gel layer (as compared to while using guar gum alone) on being exposed to the fluids of the GIT. This viscous layer retards seeping of the fluids. Formulation SF7 containing 20% guar xanthan combination (2:1) of was able to control 96% of drug of drug release in colon

1	1	0.027	0.031	0.029	0.022	0.09	0.021	0.012	0.021	0.017
2	2	0.031	0.049	0.042	0.037	0.12	0.031	0.018	0.034	0.025
3	3	1.39	1.32	1.27	1.31	1.28	1.22	1.09	1.4	1.49
4	4	2.48	2.41	1.93	2.05	2.04	1.34	1.25	2.14	2.05
5	5	3.71	3.21	2.85	3.22	3.25	3.05	2.93	6.59	6.12
6	6	4.12	3.97	3.21	5.75	5.73	3.53	3.41	8.42	8.24
7	8	8.2	7.78	6.64	8.99	9.84	7.12	6.58	24.21	22.35
8	10	12.43	11.32	10.09	14.06	14.74	10.89	13.25	32.63	30.63
9	12	20.26	18.24	14.03	21.02	21.62	19.64	19.02	59.37	48.12
10	14	32.45	31.21	21.24	29.53	29.82	28.25	29.23	83.25	64.37
11	16	56.21	54.04	38.53	39.68	38.43	45.61	54.59	102.23	79.25
12	20	77.48	70.35	49.85	58.25	51.83	68.73	72.26		100.21
13	24	85.68	78.51	61.32	72.24	62.21	77.25	80.21		

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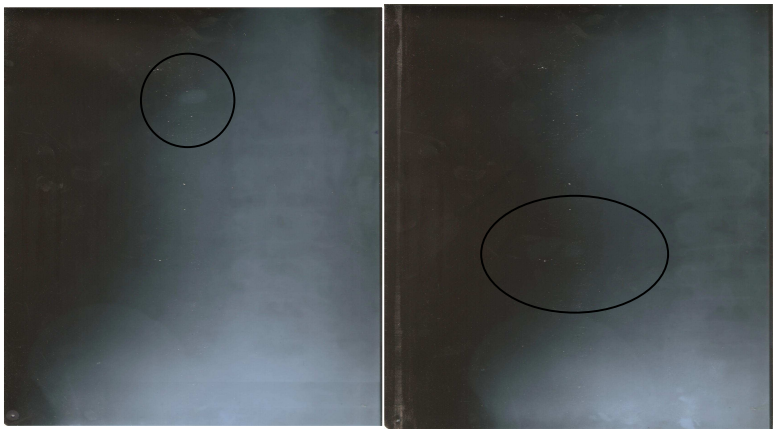
***In vivo* study-**The recorded time for onset of disintegration and the time for complete tablet disintegration were taken as the mid-time between the times recorded for the two images about the transition. After 1 hr. the tablet was found to be in stomach intact and after 3 hrs it was found some where in the region of transverse colon and after 8 hrs the tablet was found in descending colon region and it starts disintegrating, after 12 hours few traces of tablet were seen in the region of descending colon and sigmoid colon and after 16 hours no traces was visible in the X ray. In volunteers, tablet integrity was maintained whilst the preparation resided within the stomach and the small intestine indicating that the matrix of xanthan gum and guar gum is capable of protecting the core from being released. In the volunteers, the initial signs of disintegration were observed while the tablet had arrived into the colon. The time of disintegration of the tablet may be from 6.0 h. The anatomical location of disintegration was found to be descending colon to the hepatic flexure.



Summary and conclusion-

Colon targeted tablet of satranidazole can maintain minimum inhibitory concentration (MIC 90) for desired duration in less dose administered. The colon targeted matrix tablet of satranidazole which is composed of polysaccharides which are susceptible to enzymatic degradation i.e. Guar gum, Xanthan gum, Guar : Xanthan gum in combination at 2 ratios (1:1) and (2:1) and Pectin coated with enteric polymer Eudragit L, Eudragit S and Eudragit RS.As the requirement of formulation to bypass the release in stomach and small intestine Eudragit L, Eudragit S and Eudragit RS was suitable polymer in combination. Tablets coated with Eudragit L, Eudragit S and Eudragit RS in ratio of 4:16:5 with less quantity of plasticizer PEG 400 showed excellent film properties and were able to release most of the drug into colon. 10% of coating was found to be optimum. Formulation SF7 was considered as optimum batch as it delivered 96 % of drug into colon.On the basis of above findings it can be inferred that enteric coated Guar: Xanthan gum in combination at ratio (2:1) based matrix tablet can be developed to deliver the drug in the colon. The formulation SF7 can be employed as a promising colon specific drug delivery system of satranidazole. The in vivo studies showed that tablet does not disintegrate in stomach and small intestine and site of disintegration was found to be descending colon. But gamma scintigraphic studies are, however, needed before reaching to a final conclusion

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