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Effect of Superdisintegrating Agent and Osmogens on Metronidazole Loaded Colon Targeting Drug Delivery System

Jain CP[1] and Abhishek Kumar Jain[2]*

[1]Department of Pharmaceutical Sciences, M L Sukhadia University, Udaipur, Rajasthan, India
[2]Sagar Institute of Research and Technology-Pharmacy, Bhopal, Madhya Pradesh, India

Abstract

Site-specific drug delivery mainly colon-targeting delivery system is mostly used for the treatment of colonic diseases and provides local delivery of drug for the treatment of colonic diseases like inflammatory bowel disease (ulcerative colitis and crohn's disease) and colon cancer, where it is necessary to attain high drug concentration.

The Site-specific colon targeted system containing metronidazole using various natural biodegradable polymers i.e. guargum, xanthan gum, carragennan and pectin alone or in combination as a coating material. The polymeric films were characterized for their physical appearance, influence of disintegrating agents on the water uptake, hardness, and disintegration time and *in-vitro* release.

In vitro dissolution studies showed that metronidazole bearing tablets coated with polymeric blend containing guar gum, xanthan gum and carrageenan in ethanol: water 50:50 solvent released drug in simulated gastrointestinal conditions mainly at colonic environment. The release of drug was drastically reduced; regression coefficient value r^2 and T_{lag} time of the formulations were varied due to presence of disintegrating agents and osmogens. Results indicated that the nature of drug transport of coated formulations showed supercase-II type release. Statistical analysis of release data indicated that release pattern of metronidazole is significantly affected by the nature of polysaccharide used for coating and coating composition. The presence of superdisintegrant/osmotic agent inside core formed time-controlled drug delivery systems that could facilitate drug delivery into different segments of the gastro intestinal tract [GIT] depending upon the coat weight and the type of these agents. The result concluded that the formulations containing superdisintegrating agent (24 mg) showed a best drug delivery system for colon targeting.

Keywords: Metronidazole; Super disintegrating agents; Sodium lauryl sulphate; Sodium starch glycolate; Sodium carboxy methyl cellulose; Osmogen; Potassium Chloride; Sodium Chloride; Guargum; Xanthan gum; Carragennan; Pectin

Introduction

Inflammatory bowel disease is a set of chronic inflammatory conditions resulting from inappropriate and persistent activation of the mucosal immune system, driven by the presence of normal intra-luminal flora. Inflammatory bowel disease mainly refers to ulcerative colitis and crohn's disease [1]. Ulcerative colitis is characterized by a relapsing inflammatory condition involving the mucosa of variable lengths of the colon resulting in bleeding, urgency, diarrhea, and tenesmus. The endoscopic and radiographic appearance may demonstrate multiple diffuse erosions or ulcerations. Biopsy reveals distorted crypt abscesses and diminished goblet cells. When involvement is limited to the rectum, it is termed ulcerative proctitis. Crohn's disease may involve the gut from esophagus to anus; however, the small bowel or colon or both are the major areas of involvement. Inflammation is specific mucosal and transmural locations [2] and the distribution pattern of crohn's disease and ulcerative colitis is shown in Figure 1. If the colon is predominantly involved, the symptoms and presentation are quite similar to those of ulcerative colitis. Small bowel involvement may result in large-volume bloodless diarrhea or obstruction. Normal areas of gut may be found between areas of inflamed mucosa. Fistulas, strictures and abscess formation are fairly common in crohn's disease [3,4].

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost-effective manufacturing process [5]. Targeted-release dosage forms releases drug at or near the

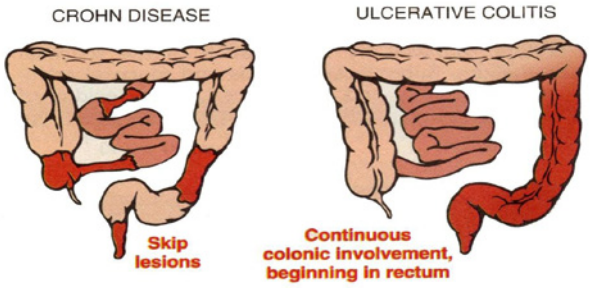

Figure 1: Comparison of the distribution pattern of crohn's disease and ulcerative colitis.

***Corresponding author:** Abhishek Kumar Jain, Sagar Institute of Research and Technology-Pharmacy, Bhopal, Madhya Pradesh, India, E-mail: azawiabbas@yahoo.com

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intended physiologic site of action. Targeted-release dosage forms may have either immediate or extended-release characteristics.

The targeted drug delivery system is preferred in the following situations: [6]

- Pharmaceutical: drug instability, low solubility.
- Pharmacokinetic: short half life, large volume of distribution, poor absorption.
- Pharmacodynamics: low specificity, low therapeutic index

Colon specific drug delivery systems are designed to obtain targeted drug delivery to the large intestine (colon). They provide local delivery for the treatment of colonic diseases like inflammatory bowel disease (ulcerative colitis and crohn's disease) and colon cancer, where it is necessary to attain high concentration of the drug. These systems are also useful for delivery of therapeutic peptides and proteins, which are otherwise degraded and/or poorly, absorbed in the stomach and small intestine but may be better absorbed from the colon and mainly four strategies, are currently being pursued to achieve drug release specifically in the colon i.e. pH controlled drug delivery, Covalent linkage between drug and carrier (Prodrug), Time controlled drug delivery and Enzyme controlled drug delivery [7-11].

Materials and Methods

Metronidazole and Microcrystalline cellulose (Avicel PH 102) were obtained as gift sample from Plethico pharmaceutical pvt. Ltd, (Indore, India). Sodium starch glycollate and sodium carboxy methyl cellulose were obtained from plethico pharmaceutical pvt. Ltd, Indore, India. Other ingredients such as lubricant, glidant, and plasticizer used to prepare the tablet were of standard Pharmacopoeial grade and all chemical reagents used were of analytical grade.

Method

Solubility determination of metronidazole: The solubility of drug metronidazole was determined in various solvents (Water, 0.1 N Hcl, phosphate buffer pH 4.5, phosphate buffer 6.8 and phosphate buffer 7.4). Sodium thiosulphate was added to the medium, when phosphate buffer pH 6.8 and phosphate buffer pH 7.4 were used to prevent oxidation. The excess amount of drug metronidazole was added to 100 ml of medium and stirred continuously overnight at 37±0.5°C. The solubility value of drug metronidazole in different medium was determined spectrophotometrically in Table 1.

Preparation of core tablets: Core tablets containing 250 mg of metronidazole and Super Disintegrant (SD) / Osmogen (OM) were prepared with microcrystalline cellulose (Avicel PH 102) as filler by a wet granulation method using PVP K30 as a binder. The wet granulation mass was passed through a mesh # 10 and dried at 60°C for 1hr in a hot air oven. The dried granules were sized by passing through a sieve # 14. These granules were collected and mixed with 5% magnesium stearate and 5% talc. These lubricated granules were compressed into tablets on single-station tablet punch machine (Modern Engineering New Delhi, India) using 4 mm deep concave and 1.2 mm round, flat and plain punches (Table 2) [12,13].

Coating of Tablets: The coating solution containing Guar gum, Xanthan gum, Carragennan and Pectin in the ratio of 1:1:1:1 was prepared in a mixture of 20:80 ethanol: water mixture using trichloroethylene [TCE] (5% w/v) as plasticizer (Table 2). The dispersion medium stirred gently for a period of 10 min with magnetic stirrer. Dispersion was transferred to a filtering flask for removing of air bubbles using a vacuum pump after complete homogenization. The core tablets containing metronidazole were coated at different levels of coating by using spray pan-coater (Figure 2). Table 3 showed all details of the coating process parameters used for coating on formulations. Samples were removed every hour and mean coating weight gain by core tablets was calculated. The coating process may be repeated until the desired level coating weight was achieved [14-16].

Characterization of coated CTDDS

All the tablet formulations under this study were assessed for their physical appearance, weight variation, friability, hardness [17,18]and

Disintegration test: The disintegration test was performed using disintegration test apparatus (9508/TEC-1) Indian Equipment Corp. following the method specified in Indian pharmacopoeia (1885) using 900 ml of 0.1 N hydrochloric acid (Table 4).

Bursting time: I: Bursting time of coated tablets: Bursting time

Media	Solubility (mg / ml)	Mean	% RSD	P Value
Water	4.525	4.579	0.15451	< 0.0001
0.1 N HCl	2.105	2.164	0.05412	< 0.0001
Phosphate buffer pH 4.5	0.0193	0.0197	0.00041	< 0.0001
Phosphate buffer pH 6.8	0.0256	0.02656	0.00087	< 0.0001
Phosphate buffer pH 7.4	0.0294	0.0303	0.00134	< 0.0001
RSD = Relative Standard Deviation				

Table 1: The solubility of metronidazole at different pH medium (n=3).

Ingredients	Amount (mg / tablet)				
	FM1	FM2	FM3	FM4	FM5
Microcrystalline cellulose (Avicel pH 102)	150	150	150	150	150
Di basic calcium Phosphate dihydrate (DBP)	150	150	150	150	150
Lactose anhydrous	124	124	124	124	124
Potato Starch	26	26	26	26	26
Sodium starch glycollate	24	-	-	-	-
Sodium carboxy methyl cellulose	-	24	-	-	-
Sodium lauryl sulphate	-	-	24	-	-
Sodium chloride	-	-	-	24	
Potassium chloride	-	-	-		24
Purified Talc	30	30	30	30	30
Magnesium stearate	30	30	30	30	30
Polyvinyl pyrrolidone K-30	10% w/v in iso propyl alcohol				
Total weight of core tablet	784	784	784	784	784
Coat Weight (% / Tablet) GG:XG:Carragennan:Pectin 1:1:1:1 (4 % w/v) in 50:50 Ethanol:Water mixture	10	10	10	10	10

Table 2: Composition of various super disintegrating agents and osmotic agents used for core tablets of metronidazole (250 mg).

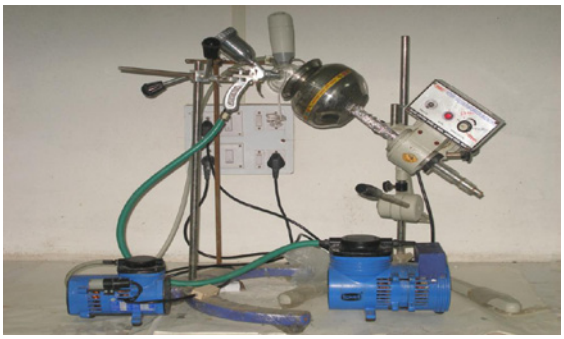

Figure 2: Spray coating pan fabricated in the laboratory.

Independent variables	Value
Atomizing pressure (bar)	1
X1, Inlet temperature (° C)	50
Bed temperature (° C)	25
X2, Pan speed (rpm)	50
Spray rate (gm / ml)	10
Drying in the equipment after coating (min)	15
Final drying in oven (for 1 hr)	60 °C

Table 3: Levels of coating parameters for coating of polysaccharide polymer on core tablets.

was determined as the time after which tablet was not able to withstand the internal pressure and the tablet opened up. The test was carried out in the dissolution media by keeping the tablets in phosphate buffer (pH 6.8) at 100 rpm at 37 ± 0.5°C. The test was carried out using 6 tablets from each formulation (Table 4).

***In-vitro* dissolution study:** *In-vitro* dissolution study was performed on the tablets to identify the effects of different coating levels on release profiles of the tablets. The spray coated dosage form of metronidazole was evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit. These studies were carried out using an IP dissolution rate test apparatus (apparatus type II, 50 rpm, 37±0.5°C). The tablets were tested for drug release for 2 h in 0.1 N Hcl (900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with pH 7.4 Sorenson's phosphate buffer (900 ml) and tested for drug release for 3 h as the average small intestinal transit time is about 3h. At the end of the time periods, two samples each of 1 ml were taken, suitably diluted and analysed for metronidazole content in 0.1 N HCl at 272 nm, in phosphate buffer pH 7.4 at 320 nm and in phosphate buffer pH 6.8 at 319 nm was determined using a double beam UV spectrophotometer (Shimadzu, UV-1800) [19].

Characterization of release profile: Release profile of natural biodegradable coated polymers containing superdisintegrating agent and osmogens tablets were characterized for release lag time (T_{lag}) and release rate k. Release data within the linear range were selected and fitted to a zero-order mathematical model:

$$Q = C + kt$$

Where Q is the release percentage at time t; k is the slope of the fitted linear equation and here represents release rate; and C is the intercept of the linear equation. T_{lag} is defined as the time of the start of ciprofloxacin release and calculated here from the fitted equation, setting Q=0:

$$T_{lag} = - C / k.$$

The linear equation is based on regression of at least three release data, and only correlation coefficient of over 0.99 is acceptable for T_{lag} and k calculation [20].

Results and Discussion

Disintegration test coated tablets

The disintegration time of coated tablets containing super disintegrating agents/osmogens was determined by disintegration test as prescribed under Indian pharmacopoeia standard for coated tablets. The coated tablets containing sodium starch glycolate as super disintegrant with highest level i.e. 24 mg (Formulation (FM) 1) showed the disintegration time is 3.24 h. The disintegration time of coated tablets with sodium carboxy methyl cellulose (Formulation 2) was found to be 3.50 h and coated tablets with sodium lauryl sulphate (Formulation 3) was 3.55 h. Table 4 showed that tablets with super disintegrating agents disintegrated at faster rate than tablets prepared with osmogens. This result pass disintegration test as prescribed under Indian pharmacopoeial standard for enteric coated tablet. Bursting times for each formulation with different coating formulations was also showed in Table 4. The formulation containing 24 mg sodium chloride (Formulation 4) was burst at 4.24 h before reached to colonic region. Bursting times for each formulation with different levels of coating are given in Table 4.

In-vitro dissolution test on SD tablets

The *in-vitro* dissolution time of coated tablets containing super disintegrating agents was determined. The coated tablets containing sodium starch glycolate at highest level i.e. 24 mg super disintegrating

Formulation code	Coating thickness (cm)		Average weight (mg)	Hardness (kg / cm^2)	Friability (%)	Disintegration Time (h)	Bursting time (hr)^n
	Diameter	Thickness					
FM1	0.218±0.001	0.198±0.003	866.03±8.78	6.24±0.32	0.89±0.11	3.24±0.012	5.05±0.18
FM2	0.228±0.002	0.198±0.002	866.33±6.28	6.31±0.37	0.86±0.10	3.50±0.013	5.18±0.08
FM3	0.237±0.001	0.210±0.003	866.14±6.69	6.24±0.29	0.87±0.15	3.55±0.012	5.25±0.15
FM4	0.219±0.001	0.205±0.002	865.23±9.20	6.26±0.31	0.84±0.16	4.05±0.011	4.24±0.13
FM5	0.229±0.001	0.199±0.003	864±7.211	6.31±0.36	0.83±0.10	4.44±0.012	4.45±0.10
n = 3							

Table 4: Physical characterization of metronidazole delivery system (FM1 to FM5).

agent with 10 % coating (FM1) released 5.32 % drug in the first 5th hr and drug release increased to 20.98 % in the 6th hr and to 92.34 % in 12th hr. The results of *in-vitro* drug release study of both formulations i.e. FM1 indicated that a desired release could be obtained with 24 mg of sodium starch glycolate. The FM1 tablets released nearly 20 % drug in 6th hr indicate rapid drug release. The *in-vitro* dissolution profiles of ciprofloxacin tablets containing 24 mg of SD (FM1, FM2 and FM3) are shown in Figure 3.

Results showed that the rapid release period depend on nature and concentration of various super disintegrating agent given in Table 4 and the rapid release was observed between 5–6th hr interval and more than 90 % drug released within 6-12th hr. The lag time for drug release from the formulation was 1.60 to 2.53th hr. The result also showed that sodium starch glycolate was found to be best disintegrant for immediate release of drug (Figure 3).

In-vitro dissolution test on osmogen tablets

The *in-vitro* dissolution test of coated tablets containing osmogen 24 mg (Formulation 5), the cumulative percent drug release was found to be 22.35 % in the first 5th hr and showed burst effect and a total of 99.99 % in 12th hr. These results may be attributed to the fact that a type of osmogen, increase osmotic pressure inside coated tablets, thus showed bursting effect.

Tablets containing 24 mg of sodium chloride as osmogen (FM4) showed cumulative percent drug release was 28.35 % in the first 5th hr and a total of 99.99 % drug released in 12th hr. The dissolution profiles of metronidazole tablets containing sodium chloride (FM4) are shown in Table 4. The result showed that the release from sodium chloride containing tablets was significantly similar but faster as compared with potassium chloride containing tablets at approximately the same coating level. The release of drug from the tablets containing osmogens is due to development of hydraulic pressure when dissolution medium imbibe the osmogens, it exerts hydraulic pressure on the film and ruptures the coating. The r^2 value and T_{lag} time of the formulations are shows in Table 5. The formulation containing sodium starch glycolate as superdisintegrating agents was found to be best drug delivery for colon targeting.

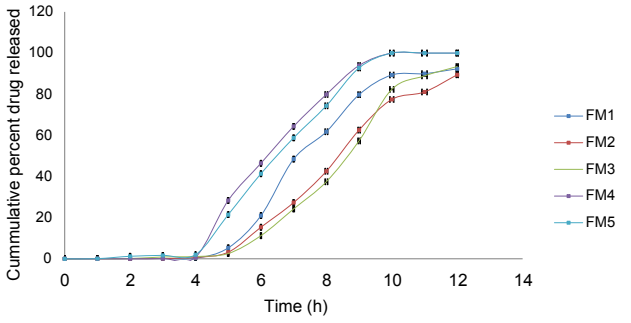

Figure 3: *In vitro* dissolution profile of FM1 to FM5.

Factor	Formulation code	Amount of SD / OM	Time span	r^2	T_{lag} (hr)	k
SSG	FC5A	24 mg	4.12-12	0.890	2.12	20.6
Sod. CMC	FC5C	24 mg	3.54-12	0.876	2.37	20.2
SLS	FC5E	24 mg	3.37-12	0.847	2.49	21.9
Sodium chloride	FC5G	24 mg	3.21-12	0.919	1.60	17.8
Potassium chloride	FC5I	24 mg	2.34-12	0.922	1.73	18.6

Table 5: Zero-order kinetics data for metronidazole coated tablets.

Conclusion

The effect of super disintegrating agents and osmogens on selected core tablet was determined by disintegration test as prescribed in Indian pharmacopoeia for uncoated tablets. The result showed that sodium starch glycolate (24 %) was best disintegrating agent. The result of *in-vitro* drug release study of osmogens containing tablets showed that the release from sodium chloride containing tablets was significantly similar but faster as compared with potassium chloride containing tablets at approximately the same coating level. The presence of superdisintegrant/osmotic agent inside core formed time-controlled drug delivery systems that could facilitate drug delivery into different segments of the GIT depending upon the coat weight and the type of these agents. According all the results conclude that the formulation containing superdisintegrating agents showed a best drug delivery system for colon targeting.

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