Formulation and in-vitro evaluation of microbially triggered colon specific drug delivery using sesbania gum

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Abstract:
The aim of the present study is to develop colon targeted drug delivery systems for metronidazole using sesbania gum as a carrier. Matrix, enteric coated and compression coated tablets of metronidazole containing various proportions of sesbania gum were prepared. All the formulations were evaluated for the hardness, drug content uniformity, and were subjected to in vitro drug release studies. Matrix tablets and enteric coated tablets of metronidazole released 41–71% and 25–28% of the metronidazole, respectively, in the physiological environment of stomach and small intestine depending on the proportion of sesbania gum used in the formulation. Both the formulations failed to control the drug release within 5 hr. The compression coated formulations (CS2) released less than 5% of metronidazole in the physiological environment of stomach and small intestine. When the dissolution study was continued in simulated colonic fluids, the compression coated tablet with 150 mg of sesbania gum coat released another 76% of metronidazole after degradation by colonic bacteria at the end of 12 hr.

Key Words: sesbania gum, metronidazole, microbially triggered, compression coated

Introduction

Natural polysaccharides are now extensively used for the development of solid dosage forms for delivery of drug to the colon. A large number of polysaccharides have already been studied for their potential as colon-specific drug carrier systems, such as chitosan, pectin, chondroitin sulphate, cyclodextrin, dextrans, guar gum, inulin, amylose and locust bean gum[1].
Sesbania gum (SG) is derived from the endosperm of seeds of the plant sesbania grandiflora belonging to family Leguminosae (Papillionaceae)[2]. It contains high molecular weight hydrocolloidal polysaccharides composed of galactan and mannan units combined through glycosidic linkages [3,4,5]. Commercially galactomannans of guar gum (Cyamopsis tetragonolobus L. Taub, Man:Gal 2:1), locust bean gum (Ceratonia siliqua, Man:Gal 2:1) and tara (Caesalpinea spinosa, Man:Gal 3:1) are used

[6-10]. The good swelling characteristics of treated SG can be of value in formulation of sustained release tablets whereby the drug release from matrices can be controlled with the swelling of the polymer. Also, treated SG shows pH dependent swelling characteristics and has better swelling in pH-7.6 phosphate buffer and distilled water as compared to 0.1 N HCL. These differences in swelling can be effectively explored in the formulation of intestinal/colonic drug delivery systems.
Metronidazole is choice of drug for intestinal amoebiasis. This drug is to be delivered to the colon for their effective action against E. histolytica wherein the trophozoites reside in the lumen of the caecum and large intestine and adhere to the colonic mucus and
epithelial layers[11]. But the pharmacokinetic profile of metronidazole indicates that the drug is completely and promptly absorbed after oral administration reaching a concentration in plasma of about 10 µg/ml approximately 1 h after a single 500 mg dose[12]. The administration of this drug in conventional tablet dosage form provides minimal amount of metronidazole for local action in the colon, still resulting in the relief of amoebiasis, but with unwanted systemic effects.
Present study was carried out with following objectives
1) Preparation and in-vitro evaluation of matrix, enteric-coated and compression-coated tablets based on natural polysaccharide, SG as a carrier.
2) The susceptibility of SG to undergo degradation in colon was assessed by conducting in-vitro drug release studies in the presence of rat caecal contents in pH-6.8 phosphate buffered saline (PBS).

Experimental

Spectrophotometric method for estimation of metronidazole

The calibration curves for estimation of metronidazole were prepared in 0.1M HCl, Sorensen's Phosphate buffer pH-7.4, pH-6.8 PBS, and pH-6.8 PBS with 4% w/v rat cecal contents. The λ_{max} for metronidazole was found to be 279 nm in 0.1 M HCl and 319 in Sorensen's phosphate buffer pH-7.4, pH-6.8 PBS, and pH-6.8 PBS with 4% w/v rat cecal contents.

Modification of SG

The untreated sesbania gum was suspended in 9:1 acetone: chloroform mixture for 6 hr with intermittent stirring and supernatant which contain extraneous impurities (organic solvent soluble impurities) was removed. The precipitated gum was filtered, washed two times with organic solvent mixture and dried in a hot air oven at 45°C. The dried powder was passed through a 150 # sieve and used for further investigations.

Physicochemical properties of treated sesbania gum powder

Treated SG powder was studied for physicochemical properties like microscopic characteristics, loss on drying (moisture content), viscosity, specific gravity, density, ash value, solubility, microbial load, and pH etc. The results of physicochemical properties are shown in table 5.1.

Preparation of metronidazole matrix tablets using sesbania gum

Matrix tablets of metronidazole were prepared by wet granulation method using PVP-K30 solution (5%w/v in IPA) as the binder. The composition of different formulations used in the study containing 200 mg of metronidazole in each case is shown in the table 5.2. The powders were blended and granulated with PVP-K30 solution. These

granules were lubricated with mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed (12.4 mm diameter, flat punches) into tablets using multipunch tablet compression machine. (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India.).

Preparation of enteric-coated metronidazole matrix tablets

Preparation of coating solutions

The composition of the different coating solutions is shown in the Table 5.3. The coating solutions consisted of 10 %w/v polymer, 1 %w/v of castor oil and 0.5 %w/v talc. IPA- acetone (7:3) mixture was used as solvent. Required quantity of the polymers was dissolved in the IPA-acetone mixture by shaking. Then 1 %w/v of castor oil was added and finally talc was dispersed in the solution. Final volume was adjusted.

Method used for coating of the tablets[13]

In the present study, dip coating method was used to coat the tablets. The formulation SG4 was used as the core tablets. The weighed core tablets were dipped into coating solutions by holding with forcep and after dipping were placed on a glass plate (smeared with castor oil) for drying in air for 15 minutes at room temperature. The tablets were then dried at 60°C in an oven for 30 minutes. During drying, the tablets were rotated occasionally. The tablets were subjected to coat about 5%w/w of total weight of tablet.

Formulation code for the enteric-coated tablets was ES1, ES2, and ES3 according to application of different coating solution 1:0, 1:1, and 0:1 respectively.

Preparation of metronidazole compression coated tablets using sesbania gum

Preparation of metronidazole core tablets

The core tablets (average weight 250 mg) of metronidazole, for compression coating with SG, were prepared by wet granulation technique using PVP-K30 as binder. The composition of core tablets is given in table 5.4. Metronidazole, DCP and SSG were passed through the 100 mesh sieve and thoroughly mixed then granulated using PVP-K30 solution as the binder. The lubricated granules were compressed (9.6 mm diameter, flat punches) into tablets using multipunch tablet compression machine. (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, India.).

Preparation of metronidazole compression coated tablets

The core tablets of metronidazole were compression coated with different coat formulation. The compression coat formulations were prepared using varying concentration of SG (Table 5.5). Granules of the above material were prepared using PVP-K30 solution. The granules so obtained were dried at 40 °C for 2 hr in the oven. Dried granules were passed through 20-mesh sieve and were lubricated with mixture of talc and magnesium stearate (2:1). Metronidazole core tablets were compression coated with a different coating mixture. Initially, 40% of coat weight was placed in a 12.4 mm die cavity of a multipunch tablet compression machine followed by carefully centering the core tablet and addition of reminder of coat weight. The coating material was compressed around the core tablet with high compression force.

Evaluation parameters

Determination of swelling index of sesbania gum powder[14]

Swelling characteristics of the treated SG was studied in different medium (0.1 M HCl, pH-7.4 phosphate buffer and distilled water) as per method given in BP.

$$\textit{Swelling index} = \frac{\textit{Swollen height}}{\textit{Initial height}}$$

In-vitro drug release studies

Drug release studies were carried out using a USP XXIII dissolution rate test apparatus (Apparatus 1, 100 rpm, 37 °C) for 2 hr in 0.1 M HCl (900 ml) as the average gastric emptying time is about 2 hr. Then the dissolution medium was replaced with pH-7.4 Sorensen phosphate buffer (900 ml) and tested for drug release for 3 hr as the average small intestinal transit time is about 3 hr. After 5 hr, the dissolution medium was replaced with pH 6.8 PBS (900 ml) and tested for drug release up to 12 hr. At the end of the time period 10 ml of the samples were taken and analyzed for metronidazole content. A 10 ml volume of fresh and filtered dissolution medium was added to make the volume after each sample withdrawal.

Drug release study in the presence of 4 %w/v rat cecal media[16]

The drug release studies were carried out in USP XXIII dissolution rate test apparatus (apparatus 1, 100 rpm, 37°C) with slight modification. A beaker (capacity 150 ml) containing 100 ml of dissolution medium was immersed in the water contained in the 1000 ml vessel, which in turn, was the water bath of the apparatus. The swollen formulations after completing the dissolution study in 0.1 M HCl (2 hr) and pH-7.4 Sorensen's phosphate buffer (3 hr) were placed in the baskets of the apparatus and immersed in the dissolution medium containing rat caecal content medium. The experiment was carried out with continuous CO2 supply into the beakers to simulate anaerobic environment of the cecum. The drug release studies were carried out up to 12 hr and 1 ml samples were withdrawn at specified time intervals without a pre- filter and replaced with 1 ml of fresh PBS bubbled with CO_2. 1 ml of methanol was added in sample and was analyzed for metronidazole content as per above described method.

Statistical analysis[17]

The cumulative percent of metronidazole released from the compression coated tablets in the dissolution medium up to 12 hr with and without rat cecal contents was compared using USP dissolution specification, f_2 value, a similarity factor. A value less than 50 was considered significant value indicating dissimilarity in dissolution profiles.

This similarity factor is calculated by following formula,

$$f_2 = 50 \text{ x } \log \{[1+(1/n) \sum_{J=1}^{n} | R_j - T_j |^2]^{-0.5} \text{ x } 100 \}$$

When n is the number of dissolution time and R_j and T_j are the reference and test dissolution values at time t.

Result and discussion

Successful delivery of drugs specifically to the colon requires the protection of drug from being released in stomach and small intestine.

Swelling study of SG powder

Swelling characteristics of the treated SG was studied in different medium (0.1 M HCl, pH-7.4 phosphate buffer and distilled water). The swelling index of SG powder was 8.0, 27.5, and 30 in 0.1 M HCl, pH 7.4-phosphate buffer and distilled water respectively.

Treated SG shows pH dependent swelling characteristics and has better swelling in pH 7.6 phosphate buffer and distilled water as compared to 0.1 M HCL. These differences in swelling can be effectively explored in the formulation of intestinal/colonic drug delivery systems.

Characteristics of tablets

Matrix tablets of metronidazole were prepared by wet granulation method using PVP-K30 solution (5 %w/v in IPA) as the binder. All the formulations showed uniform thickness. The thickness of the tablets was in the range of 3.8 - 4.0 mm. The hardness of the tablets was found to be in the range of 6.3-6.6 kg. In the present study, the percentage friability of all the formulations was below 1% indicating that the friability is within the prescribed limits. In a weight variation test, the pharmacopoeial limit for the percentage deviation of all the tablet of more than 250 mg is ± 5%. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all the formulation passed the test for uniformity of weight as per official requirements. The matrix tablets were found to contain 98.6-101.4% of the labeled amount of metronidazole indicating uniformity of drug content. All the tablet formulations showed acceptable pharmacotechnical properties (Table 5.6).

Matrix tablets of metronidazole using sesbania gum

For the formulation of a delivery system for colon targeting, it is a prerequisite that the drug release should be minimal until the dosage form reaches the colon. The matrix tablets were subjected to in vitro drug release studies in 0.1 M HCl (2 hr), pH 7.4 Sorenson's phosphate buffer (3 hr) and pH 6.8 PBS up to 12 hr. The results of dissolution study were shown in Figure 5.1. In drug release studies, the percent of metronidazole release from matrix tablets of SG at the end of 5 hr and was found to be around 49 ± 6%. All the matrix tablets were failed to retard the drug release in physiological environment of stomach and small intestine. It can be attributed to formulation of a very loose gel upon introduction of the tablets in the dissolution media, leading to drug release from the outer layer of the tablets. At the end of dissolution studies, 75% ± 15% drug release from the matrix tablets. From the swelling study, it was showed that sesbania gum powder has swelling index 8.0 in 0.1 M HCl while 27.5 in pH-7.6 phosphate buffer. So, SG has better swelling in pH-7.6 phosphate buffer as compared to 0.1M HCL. But it is observed from the results that about 35 ± 15% of the drug was released from the formulations (SG1-SG5) in 0.1 M HCl. This may be because of the release of highly soluble (in 0.1 M HCl) metronidazole present on the surface of the matrix tablets. Hence, further studies on the in-vitro dissolution of the formulations in simulated colonic fluids (with rat caecal contents medium) were not carried out on formulations SG1-SG5 as they also released almost 50% of its drug in physiological environment of stomach and small

intestine.
It was found that only formulation SG4 (Metronidazole:SG - 1:1.25) give fewer drug release compare to other formulation at the end of 5hr, it was 41.69%. So formulation SG4 (Metronidazole:SG - 1:1.25) was selected for further studies. The results, thus, show that the matrix formulations containing different ratio of metronidazole and SG failed to control the drug release in the physiological environment of stomach and small intestine. Hence, it was planned to control the release of metronidazole by applying enteric-coating on the formulation SG4.

Enteric-coated metronidazole matrix tablets

The enteric-coated tablets were subjected to in vitro drug release studies in 0.1 M HCl (2 h), pH 7.4 Sorenson's phosphate buffer (3 h) and pH 6.8 PBS up to 12 h. The cumulative percent drug release of formulations ES1, ES2 and ES3 was shown in table 5.7. The formulations ES1, ES2 and ES3 give only 3 ± 1.5% of metronidazole released in the physiological environment of stomach (0.1 M HCl for 2 hr). The enteric polymers are insoluble at lower pH so the penetration of the dissolution medium in the matrix was not possible at lower pH and therefore very less amount of drug was released in 0.1 M HCl. After 2 hr, the dissolution study was conducted in pH-7.4 Sorensen's phosphate buffer up to 5 hr. At this pH, the formulations give faster drug release that was 27 ± 2%. It can be attributed that the enteric polymers get dissolved slowly and the leakage of the dissolution fluid was shown in the matrix and that's why higher amount of metronidazole release at this condition. The formulation ES3 (47.64%) released fewer drug as compare to formulation ES1 (54.52%) and ES2 (53.21%) at the end of 12 hr dissolution study. It was suggested that Eudragit S100 alone at higher concentration is able to retard the drug release in the physiological environment of stomach and small intestine.
Thus, the results were showed that the enteric-coated formulations of SG4 failed to control the drug release in the physiological environment of stomach and small intestine. Hence, it was planned to control the release of metronidazole by applying different amounts of sesbania gum as a release controlling layer by compression-coated tablets.

Compression coated metronidazole tablets

The matrix and enteric-coated tablets of metronidazole were failed to retard drug release in upper GIT, it was essential to minimize the release of metronidazole in the physiological environment of stomach and small intestine. So, metronidazole core tablet compression–coated using different amount of sesbania gum.
Fast-disintegrating metronidazole core tablets were characterized for different parameters. The core tablets of metronidazole were compression coated with a coat formulation containing different amount of sesbania gum. The cumulative amount of metronidazole release from tablets coated with coat formulations containing 100 mg SG (CS1) 150 mg SG (CS2), and 200 mg SG (CS3) was found to be 80.12%, 4.09% and 3.60% respectively after 5 h of the dissolution study in simulated gastric and intestinal fluids. From the dissolution studies, it was reveled that formulation CS1 give faster drug release in simulated gastric and intestinal fluids. This might be due to lower sesbania gum content and higher quantity of DCP in the coat formulation. So, SG as compression coat in less amount (100 mg) was not able to retard the drug release in simulated gastric and intestinal fluids. But, the formulation CS2 and CS3 was capable of protecting the drug from being released in the physiological environment of stomach and small intestine.

To assess the integrity of the coats, drug release studies were carried out without the addition of rat cecal contents to pH-6.8 PBS. At the end of the 12 hr of the dissolution studies, all the tablets coated with coat formulations CS2 and CS3 were found intact and the percent drug release was 39.42 and 23.42 respectively. This indicates that until the coat was degraded, the coat will not permit the release of the bulk of the drug present in the core.

When the in vitro dissolution studies were carried out in the presence of rat cecal content medium, the percent drug release from metronidazole tablets coated with coat formulation CS1, CS2 and CS3 was found to be 99.83, 76.83 and 27.94 respectively. For formulation CS3, no significant difference was observed in the amount of metronidazole released at the end of 12 hr of the dissolution study with rat cecal content medium when compared to the dissolution study without rat cecal contents (Figure 5.5). The presence of higher amount of sesbania gum (200 mg, CS3) might not have allowed complete degradation of the coat during the time period of testing. The gel strength of the swollen coat of SG might be too high and prevented the drug release from the formulation Thus it is evident that unless the coat is degraded by colonic bacteria, drug release may not take place.

The percent drug release from metronidazole core tablets coated with coat formulation CS2 was found to increase from 8 hr onwards indicating the commencement of disruption of the hydrated SG coats. The percent of drug released from CS2 formulation is shown in table 5.8. The percent of drug released after 12 h of testing was 41.00 and 54.83 without and with rat cecal content respectively and the tablet coat was found to be degraded making way for the release of the drug. A significant difference was observed in the amount of metronidazole released at the end of 12 h of the dissolution study with rat cecal content medium when compared to the dissolution study without rat cecal contents. The results show that tight control of drug release from compression coated formulation CS2 might have facilitated the colonic bacterial action on SG and resulted in the degradation of the formulation thereby releasing the drug in the physiological environment of colon. The results of the study indicate that metronidazole tablets compression coated with SG (150 mg) would be potential formulations in delivering the drug to the colon.

Conclusion

The aim of present work was to develop microbially triggered colon-specific drug delivery systems based on polysaccharide, sesbania gum, were evaluated using in-vitro method. Treated SG, in the form of matrix and enteric-coated tablets failed to release the drug in the physiological environment of colon. In view of this result, fast disintegrating metronidazole core tablets were compression coated with coat formulation containing different quantity of sesbania gum and the ability of sesbania gum to release the drug in the colon is demonstrated by in vitro testing in the presence of rat caecal contents. The sesbania gum as 100 mg coat weight was found insufficient to protect metronidazole core till 5 hr dissolution study. The compression coated metronidazole tablets coated with SG in 150 mg provided best degradation in simulated colonic fluids. Also significant difference was observed in metronidazole release with and without rat cecal content. It appears that compression coated metronidazole tablets compression coated with SG (150 mg) is most likely to provide targeted delivery of metronidazole to the colon. Thus, the results clearly demonstrate that sesbania gum is a potential colon-specific drug delivery carrier.

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Table 5.1 Physicochemical properties of treated sesbania gum powder		
Sr.No.	**Properties**	**Characteristics**
1	**Average particle size (μm)**	17.12 μm
2	**Loss on drying (%)**	11.00%
3	**Ash value (%)**	1.5%
4	**Solubility in water**	Quickly soluble in hot water, 1 gm in 100 ml water produces viscous, pourable and opaque solution.
5	**pH**	7.16
6	**Density (gm/ml) 0.5%w/v solution**	1.059
7	**Specific gravity**	0.9442
8	**Microbial load**	Bacteria-2700 CFU/gm Fungi - 200 CFU/gm
9	**Volatile acidity**	9%
10	**Viscosity**	1900 cps (1%w/v)

Table 5.2 Composition of metronidazole matrix tablets containing SG					
Ingredients	**Quantity (mg) per each tablet**				
	SG1	**SG2**	**SG3**	**SG4**	**SG5**
Metronidazole	200	200	200	200	200
Sesbania gum	100	150	200	250	300
DCP (Anhydrous)	215	165	115	65	15
PVP-K30 (added as binder)	20	20	20	20	20
Talc	10	10	10	10	10
Magnesium Stearate	5	5	5	5	5
Total (mg)	550	550	550	550	550

Table 5.3 Composition of coating solutions			
Ingredients	**1:0**	**1:1**	**0:1**
Eudragit S100	2.5	1.25	---
Eudragit L100	---	1.25	2.5
Castor oil	0.25	0.25	0.25
Talc	0.125	0.125	0.125
IPA-Acetone mixture(7:3) (up to)	25 ml	25ml	25ml

Table 5.4 Composition of fast-disintegrating core tablets of metronidazole	
Ingredients	**Quantity (mg)**
Metronidazole	200
DCP(Anhydrous)	22.5
Sodium starch glycolate	10
PVP-K30 (as binder)	10
Talc	5
Magnesium stearate	2.5

Table 5.5 Composition of sesbania gum coat formulation			
Ingredients	**Quantity (mg) present in the coat formulation**		
	CS1	**CS2**	**CS3**
Sesbania gum	100	150	200
DCP(Anhydrous)	115	65	15
PVP-K30 (as binder)	10	10	10
Talc	4	4	4
Magnesium stearate	2	2	2

Table 5.6 Characteristics of metronidazole matrix tablets containing sesbania gum in various proportion					
Tablets	Thickness (mm) n=10	Hardness (kg/cm^2) n=10	Friability (%) n=20	Weight variation (mg) n=20	Drug content (%) n=10
SG1	3.9 ± 0.1	6.5 ± 0.3	0.32 ± 0.03	448 ± 4.56	98.64 ± 0.43
SG2	3.9 ± 0.1	6.3 ± 0.2	0.49 ± 0.02	447 ± 3.94	101.31 ± 0.29
SG3	3.9 ± 0.1	6.6 ± 0.1	0.54 ± 0.03	551 ± 5.31	99.94 ± 0.46
SG4	3.9 ± 0.1	6.5 ± 0.2	0.39 ± 0.04	449 ± 6.84	99.83 ± 0.68
SG5	3.9 ± 0.1	6.3 ± 0.3	0.41 ± 0.06	552 ± 4.26	101.49 ± 0.72
n = No. of tablets					

Table 5.7 Characteristics of metronidazole compression coated tablets				
Tablets	Hardness (kg/cm^2) n=10	Friability (%) n=20	Weight variation (mg) n=20	Drug content (%) n=10
Core tablet	4.3 ± 0.6	0.69 ± 0.02	249 ± 3.74	101.27 ± 0.43
CS1	5.1± 0.4	0.57 ± 0.08	482 ± 2.84	101.27 ± 0.43
CS2	5.3 ± 0.5	0.61 ± 0.05	479 ± 4.75	101.27 ± 0.43
CS3	5.1 ± 0.7	0.49 ± 0.07	481 ± 5.93	101.27 ± 0.43
n = No. of tablets				

Figure 5.1 Drug release profile for formulation SG1-SG5 in different dissolution medium

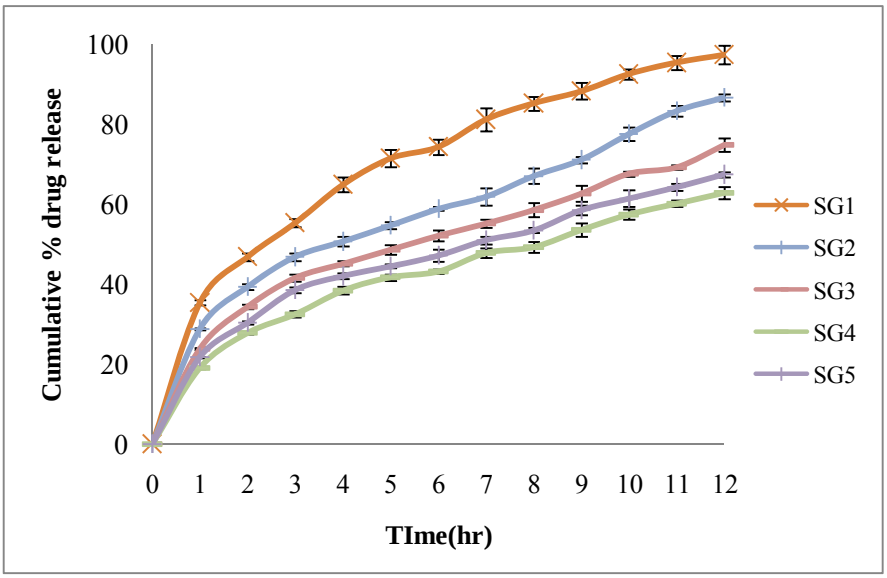


Figure 5.2 Drug release profile for formulation ES1-ES3 in different dissolution medium

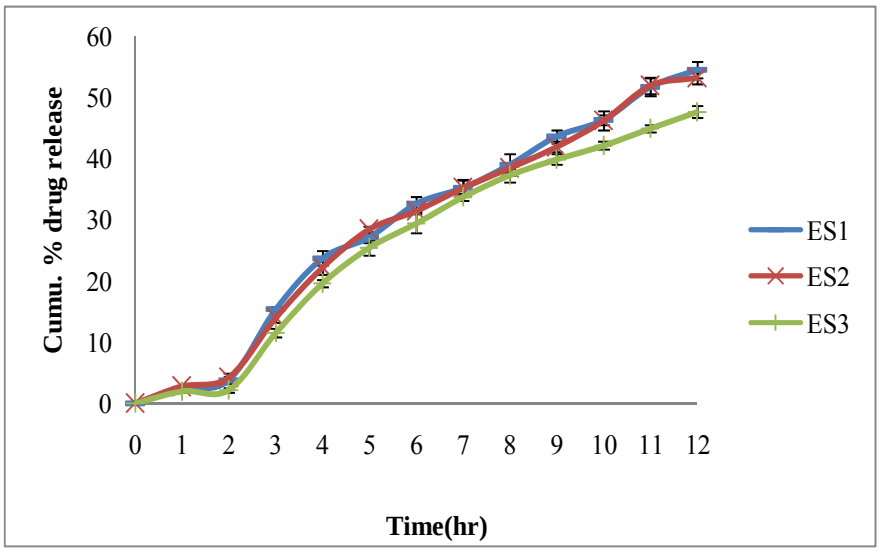


Figure 5.3: Drug release profile of formulation CS1 with and without rat cecal content medium

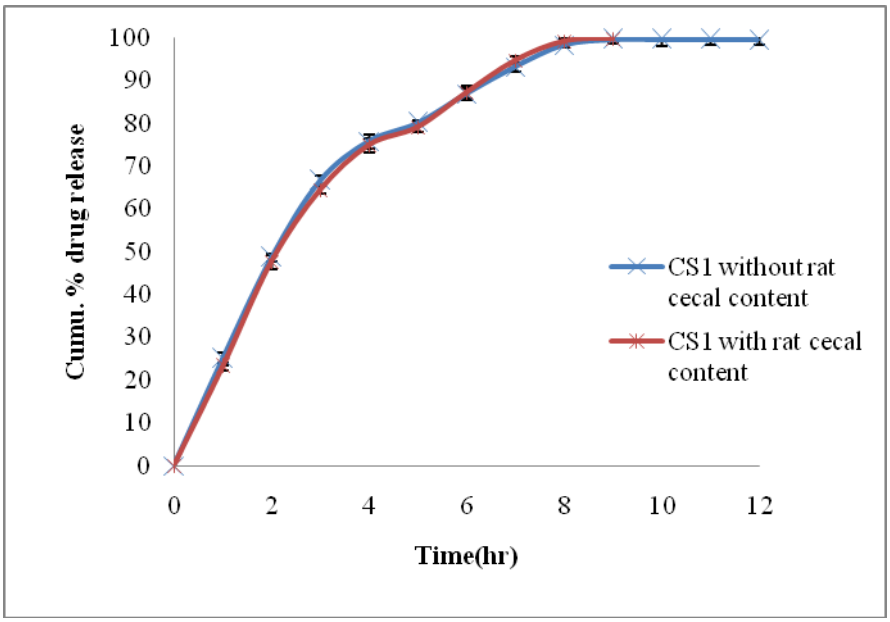


Figure 5.4: Drug release profile of formulation CS2 with and without rat cecal content medium

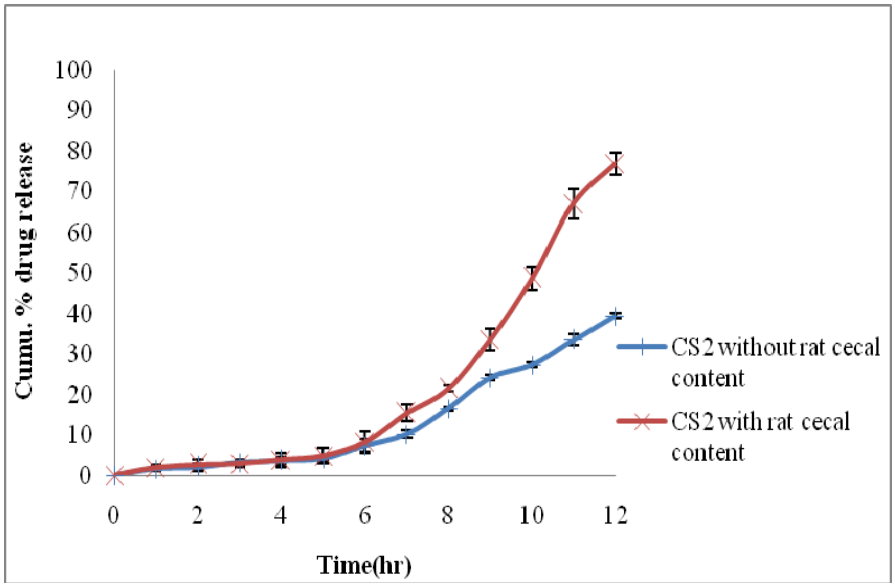
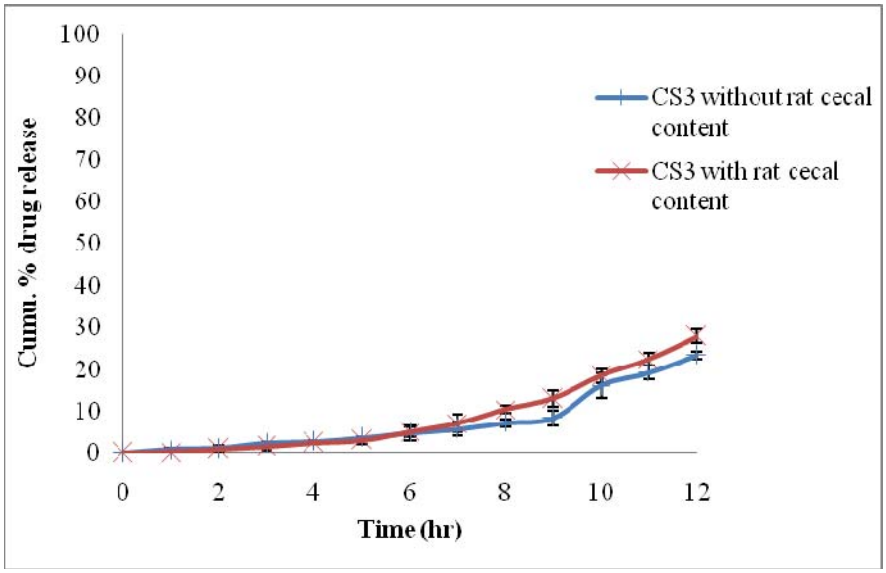


Figure 5.5: Drug release profile of formulation CS3 with and without rat cecal content medium


100
90
80
70
60
50
40
30
20
10
0
Cumu. % drug release
0
2
4
6
8
10
12
Time (hr)
CS3 without rat cecal content
CS3 with rat cecal content