

Probiotic-assisted colon-specific delivery of diclofenac sodium from guar gum matrix tablets: *In vitro* evaluation

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Purpose: The aim of present work was to investigate the *in vitro* release profile of diclofenac sodium from matrix tablets, which were prepared using guar gum with and without probiotics. Methods: Six matrix tablets formulations (F1-F6) of diclofenac sodium containing varying proportions of guar gum, 10-60% of tablet weight were prepared by wet granulation method and evaluated *in vitro* for their release profile. Four matrix tablets formulations (F7-F10) of diclofenac with guar gum (40%) were prepared incorporating varying concentration of commercial spores of *Lactobacillus* and *Bifidobacterium* species that are commonly found in colon microflora. Results: The tablets having same concentration of guar gum without probiotics (F4) showed a 54.47% cumulative release of diclofenac after 24 hr while that in presence of probiotics (F9) was 73.01%. These drug release studies were conducted without rat caecal content. In another set of experiments, the drug release studies were carried out in presence of rat caecal content. In such experiments, more than 95% drug was released from F4 and F9 formulations after 24 hr. Conclusion: The results showed that commercial probiotics are capable in digesting guar gum. These probiotics may be used to assist in colon delivery of drugs from formulations prepared with guar gum.

Key words: Colon, diclofenac, guar gum, matrix tablet, probiotics

INTRODUCTION

Site-specific drug delivery is preferred in order to reduce harmful adverse effects and enhance pharmacological response concerned with the drug. Colon is considered as a potential site to deliver therapeutic agents in clinical conditions such as colon cancer, irritable bowel syndrome, ulcerative colitis and Crohn's disease.^[1,2] Colon could be viewed as desirable site for oral delivery of protein and peptide drugs due to low diversity and intensity of digestive enzymes and near neutral pH. Long retention time of dosage form in colon offers suitability of prolong drug delivery in certain clinical conditions that have peak symptoms in the early morning that exhibit circadian rhythms like nocturnal asthma, rheumatoid arthritis, ulcer disease and ischemic heart diseases.^[3-5] Rectal route of drug delivery to the distal gut is inconvenient and patient noncompliant.^[6] Henceforth, oral route is a preferred route for colonic drug delivery.

Colon-specific drug delivery via oral route faces several challenges. The drug must neither be absorbed from upper GIT nor be degraded in small intestine lumen. To serve the purpose-desired dosage form prevents drug release in the upper GIT and deliver maximum drug content in the colon. Formation of prodrug, multicoating time-dependent delivery, coating with pH-sensitive polymers, pressure-dependent delivery and to system desired making use of biodegradable polymers are certain strategies currently being approached for colon-specific drug delivery.^[7-9]

Biodegradable polymer (viz polysaccharides)-based drug delivery approach seems quite promising. Polysaccharides arriving from small intestine are the main source of nourishment for microflora in the colon. The ability of colon microflora to degrade polysaccharides such as pectin, guar gum, chitosan,

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etc. forms the basis of formulation development for colon-specific drug delivery.^[10,11] The colonic microflora must be present in sufficient number to digest the carrier (like guar gum) to ensure the release of the drug at colon.^[12] However, intersubject variation of colonic microflora, sterilization of colonic microflora by antibiotics (commonly prescribed to treat colonic disease) and slow enzymatic degradation are some limitations of this approach for colon-specific drug delivery.^[13,14] The limitations can be resolved by incorporating bacteria in spore form (probiotics) in formulation to assure successful and efficient drug release selectively to colon. Probiotic supplements (*Bifidobacteria spp* and *Lactobacilli*) are known to improve resistance to gut infections by inhibiting the growth of harmful bacteria, to reduce cholesterol levels, improve the immune response and produce vitamins.^[15] Various probiotic-containing preparations like Sporlac (*Lactobacillus*) and Prowell (*Bifidobacterium*) are available in the market in spore form. Protective effect of probiotics (lactic acid producing bacteria) in colon carcinogenesis has also been demonstrated in clinical trials.^[16] Incorporation of probiotics would provide the health benefits on one hand, while ensure drug release at colon in any condition on the other.

Patients who regularly take anti-inflammatory drug NSAID, have a 40-50% reduction in mortality from colorectal cancer.^[17,18] Cyclooxygenase-2 (COX-2) is upregulated in colorectal and other cancers. It is suggested that prostaglandins may act as tumor promoters and that inhibition of COXs may be chemoprotective.^[19] Recently diclofenac has been identified as a possible potential agent has chemopreventive effect particularly in colorectal cancer.^[20,21] Morphine-sparing effect of diclofenac in cancer pain is reported.^[22] Like most of the NSAIDs, diclofenac is also associated with gastrointestinal problems. For such conditions, site-specific drug delivery of diclofenac to the colon is always desirable. Keeping the above in view, attempts were made to evaluate the *in vitro* drug delivery of diclofenac to the colon by incorporating the probiotics (*Lactobacillus* and *Bifidobacterium* spores) in guar gum matrix tablet.

MATERIALS AND METHODS

Diclofenac sodium (95–105% purity) was a gift sample from M/s. Torrent Laboratories, Ahmedabad, India. Guar gum was obtained from SD Fine Chemicals, Mumbai. Other materials used in the study such as lactose, talc, magnesium stearate were of analytical Grade. Sporlac®, Prowell®, Purchased from local medical store in Manduar. Double beam UV-visible Spectrophotometer (Thermospectronic, Merck, Mumbai), Brookfield viscometer (RVT/282889, Brookfield, USA) were used for analysis of samples.

In vitro digestion studies of guar gum by bacterial spores

In 200 ml guar gum (1% w/v) slurry one sachet of Sporlac (1 gm) and one capsule of Prowell (525 mg) was dispersed separately (test 1 and test 2, table 3) and incubated at 37°C in incubator. At different time interval the change in pH and

viscosity was measured using calibrated pH meter (Remi, Mumbai) and Brookfield viscometer, respectively.

Formulation of matrix tablets of diclofenac with guar gum

Matrix tablets of diclofenac sodium (75 mg) using analytical grade guar gum were prepared by wet granulation method. Lactose was used as diluent and the mixture of talc and magnesium stearate at 2:1 ratio was used as lubricant. Guar gum was sieved (sieve no. 60) separately and mixed with Diclofenac Sodium (sieve no. 100) and lactose (sieve no. 60). The composition of different formulations is shown in Table 1. The powders were blended and granulated with water. The wet mass obtained was then passed through sieve no. 14 and wet granules were dried at 50°C for 2 h. The dried granules were passed through a sieve no. 16 and were lubricated with a mixture of talc and magnesium stearate (2:1). The lubricated granules were compressed at compression force 5000-6000 kg using 12-mm-round concave-convex punch on eight-station rotary tablet machine (M/s Kambert Machinery Co. Pvt. Ltd., Ahmedabad, India).

Formulation of matrix tablet of diclofenac with guar gum containing probiotics

Matrix tablets of diclofenac sodium were prepared using guar gum (40% of tablet weight) by the wet granulation method using water as granulating agent.

Sporlac (containing *Lactobacillus sporogens*) and Prowell (containing *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Bifidobacterium infantis* spores) were used as probiotics. The method of preparation of tablets was same as described above with few modifications. Probiotics were added at two stages; half quantity was added before granulation and half quantity was added after granulation and the wet granules were dried at 40°C for 2 hr. Compositions of different formulations is shown in Table 1.

Table 1: Formulation of diclofenac sodium tablets* prepared with varying amount of guar gum and probiotics (sporlac and prowell)

Formulation	Quantity of ingredient present in a tablet (mg)			
	Guar gum	Lactose	Sporlac**	Prowell***
F1	50	360	-	-
F2	100	310	-	-
F3	150	260	-	-
F4	200	210	-	-
F5	250	160	-	-
F6	300	110	-	-
F7	200	130	40	40
F8	200	90	60	60
F9	200	70	70	70
F10	200	50	80	80

*Each tablet composition included diclofenac sodium 75 mg, magnesium stearate 5 mg and talc 10 mg in total tablet weight (500 mg). Distilled water was used to prepare granules for tablet compression. ** Each 10 mg of sporlac powder contains 0.1 billion spores of *Lactobacillus acidophilus*. ***Each 10 mg of prowell contains a total of 6.66 million spores of *Bifidobacterium bifidum*, *Bifidobacterium longum* and *Bifidobacterium infantis*

Granules of each composition after lubrication was compressed and tested for their hardness, drug content, and drug release characteristics with the required number of tablets for each test. The hardness of the matrix tablets was determined using a Monsanto hardness tester (M/s Campbell Electronics, Mumbai, India).

Determination of drug content

Ten tablets were finely powdered. Quantity of the powder equivalent to 100 mg of diclofenac sodium was accurately weighed and transferred to 100 ml volumetric flask containing 50 ml of 0.1 M NaOH. It was allowed to stand for 6 hr with intermittent sonication to ensure complete solubility of the drug. Then volume made up to 100 ml with 0.1 M NaOH and centrifuged at 500 rpm for 10 min. One milliliter of the supernatant liquid was suitably diluted, filtered and analyzed for diclofenac sodium content at 276 nm by double UV-visible spectrophotometer.^[23]

In vitro dissolution studies

In vitro dissolution studies for all matrix tablet formulations were performed by using USP dissolution test apparatus (Apparatus 1, Basket type, 37°C) at 100 rpm for 2 hr in 0.1 N HCl (900 ml). Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and tested for 3 hr as the average transit time of small intestine is 3 hr. After 5 hr, the dissolution medium was replaced with pH 6.8 phosphate buffer and tested for next 19 hr. At different time intervals a 10 ml of the sample was taken and analyzed for diclofenac sodium content at 276 nm by double beam UV-visible spectrophotometer. A 10 ml fresh dissolution medium was added to make the volume after each sample withdrawal.^[23]

In vitro dissolution studies on guar gum diclofenac matrix tablet in presence of 4%w/v rat caecal content

To assess the susceptibility of guar gum being acted upon by the colonic bacteria, drug release studies were carried out in the presence of rat caecal content as described by Krishanaiya.^[23] Appropriate approval from Institutional Animal Ethics Committee (Reg No. 918/ac/05/CPCSEA) was obtained (no. 113/MPh/09) and animal experimentation was performed accordingly. In order to induce enzymes specifically acting on guar gum in the caecum, male Albino rats weighing 150-200 g and maintained on normal diet were intubated with teflon tubing and 1 ml of 2% wt/vol dispersion of guar gum in water was administered directly into the stomach. The tubing was removed and this treatment was continued for 3 days in one set of rats and for 7 days in another set of rats. Thirty minutes before the commencement of drug release studies, four rats were killed by spinal traction. The abdomen were opened, the caecai were isolated, ligated at both ends, cut loose and immediately transferred into pH 6.8 PBS, previously bubbled with carbon dioxide gas (CO₂). The caecal bags were opened, their contents were individually weighed, pooled and then suspended in PBS to give a final caecal dilution of 4% wt/vol. As the caecum is naturally anerobic, all these

operations were carried out under CO₂. The drug release studies were carried out in USP dissolution 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 phosphate buffer (3 hr) were placed in the baskets of the apparatus and immersed in the dissolution medium containing rat caecal content medium. The drug release studies were carried out up to 24 hr and 1 ml samples were withdrawn at specified time intervals without a pre-filter and replaced with 1 ml of fresh Sorenson's phosphate buffer bubbled with CO₂. The volume was made upto 10 ml with Sorenson's phosphate buffer and centrifuged. The supernatant was filtered and filtrate was analyzed for diclofenac sodium content at 276 nm by double beam UV-Visible spectrophotometer.

RESULTS AND DISCUSSION

In vitro depolymerization studies on guar gum slurry in presence of commercial probiotics

L. acidophilus (Sporlac), *B. bifidum*, *B. longum*, *B. infantis* (prowell) are commonly prescribed as probiotics to balance disturbed intestinal microflora and related dysfunction of the gastrointestinal tract (GIT). *In vitro* digestion studies of guar gum slurry in presence of these bacterial species were performed to investigate the degradation effect of the bacteria on guar gum. In human intestine guar gum (a polysaccharide) is known to degrade by fermentation to short-chain fatty acids (SCFA) with evolution of CO₂.^[24,25] The viscosity of the guar gum polysacchrides is likely to be reduced by depolymerization process with reduction in surrounding pH due to generation of SCFA and CO₂. These two parameters were taken as indicator to investigate the depolymerization of guar gum *in vitro* in presence of the sporlac spores 1 g (test 1) and prowell 525 mg (test 2) and the results are shown in Table 2. Plain guar gum slurry (1% wt/vol) was kept as control to compare the changes in the viscosity. Initial pH and viscosity of test 1 was 6.98 and 2600 centipoises (cps), respectively while with test 2 it was 6.96 and 2600 cps. Up to 7 hr after incubation no change occurred in pH and viscosity of slurry. Decrease in viscosity and pH started after this point [Table 2] and at the end of 24 hr marked difference in pH and viscosity was observed in test 1 (pH 5.45, viscosity 600 cps) and test 2 (pH 5.22 and viscosity 860 cps). pH and viscosity of control (guar gum only) remained unchanged during the period of incubation. The bacterial species used was in the spore form and first 7 hr required to become in vegetative form. This might be the reason for unchanged pH and viscosity in first 7 hr. The results suggest that the commercial probiotics sporlac and prowell are capable to degrade guar gum. Henceforth, diclofenac guar gum tablets containing probiotics may also be expected to release the drug during *in vitro* dissolution

Table 2: Changes in viscosity and pH of guar gum slurry in distilled water (1%wt/vol) on incubation with spores (sporlac and prowell) at 37°±2° C (Values are mean ± SEM, n = 3)

Time (hrs)	Test-1 Guar Gum + Sporlac		Test-2 GG + Prowell		Control-1 GG* only	
	pH	Viscosity (cps)	pH	Viscosity (cps)	pH	Viscosity (cps)
0	6.98±0.005	2600±0.00	6.96±0.005	2600±0.00	6.99±0.00	2600±0.00
1	6.98±0.005	2600±0.00	6.96±0.00	2600±0.00	6.98±0.005	2600±0.00
2	6.97±0.01	2600±0.00	6.96±0.005	2600±0.00	6.98±0.00	2600±0.00
4	6.98±0.005	2600±0.00	6.96±0.00	2600±0.00	6.98±0.005	2600±0.00
6	6.97±0.005	2600±0.00	6.96±0.00	2600±0.00	6.98±0.005	2600±0.00
7	6.98±0.005	2600±0.00	6.96±0.00	2600±0.00	6.99±0.005	2600±0.00
8	6.88±0.005	2540±0.00	6.89±0.005	2500±0.00	6.99±0.00	2600±0.00
9	6.79±0.01	2460±0.00	6.54±0.005	2420±0.00	6.98±0.00	2600±0.00
10	6.68±0.0005	2400±0.00	6.22±0.00	2340±0.00	6.98±0.005	2600±0.00
12	6.32±0.016	2340±28.86	6.03±0.013	2220±11.54	6.98±0.00	2600±0.00
15	5.93±0.014	2180±28.86	5.77±0.005	2000±11.54	6.98±0.00	2600±0.00
18	5.55±0.012	1720±11.54	5.58±0.017	1740±11.54	6.98±0.005	2600±0.00
21	5.47±0.005	1300±5.77	5.37±0.01	1400±5.77	6.98±0.00	2600±0.00
24	5.45±0.015	600±5.77	5.22±0.00	860±5.77	6.98±0.00	2600±0.00

studies on digestion of guar gum by probiotics. With this objective, the tablets of guar gum in presence of probiotics were formulated. For comparison purpose plain guar gum tablets of diclofenac (without probiotic) were also formulated [Table 1].

The hardness of all tablets was found between 5.5 and 6.5 kg/cm². All formulation satisfied the drug content of diclofenac sodium and found between 98±2%.

In vitro drug release studies

Diclofenac and guar gum matrix tablets were prepared with and without probiotics with different proportions of guar gum and dissolution studies were performed according to a method described elsewhere. Diclofenac matrix tablet formulation code F1, F2, F3, F4, F5 and F6 were prepared with 10, 20, 30, 40, 50 and 60% guar gum wt/wt while diclofenac matrix tablet with probiotics sporlac and prowell were formulated with 40% guar gum (F7-F10). Formulation code F7, F8, F9 and F10 contained varying proportions of probiotics [Table 1]. All tablets retained their shape during the course of dissolution. However, the tablets were swelled and showed different cumulative percent release of diclofenac sodium as shown in [Table 3]. Diclofenac matrix tablets when come in contact with water the guar gum present in it swells and form a gel layer around the tablet. The drug then diffuse out from it and rate of diffusion depends on the amount of guar gum present in the tablet. It was observed that the tablets having lower amount of guar gum (F1;10% and F2; 20%) released diclofenac faster as compared to the higher guar gum-containing tablets F3, F4, F5 and F6. The cumulative percent release with F1 tablets was 21.1% in first 5 hr while 87.01% at the end of 24 hour was observed while that of with F4 was 12.37% and 54.47%, respectively. Formulation F4 contained 40% guar gum while F1 contained 10% guar gum. The higher concentration of guar gum retarded the release of

Table 3: *In vitro* drug release profile of colon-targeted matrix tablet formulation of diclofenac sodium prepared with guar gum 10% (F1), 20% (F2), 30% (F3), 40% (F4), 50% (F5) and 60% (F6) of tablet weight (values are mean ± SEM, n=3)

Time (hrs)	Cumulative % drug release					
	Formulation code					
	F1	F2	F3	F4	F5	F6
2	5.06 ±0.013	4.12 ±0.018	2.88 ±0.036	2.73 ±0.013	2.37 ±0.029	1.86 ±0.024
5	21.12 ±0.167	19.26 ±0.113	16.22 ±0.154	12.37 ±0.131	11.75 ±0.143	8.85 ±0.264
7	33.53 ±0.378	30.90 ±0.336	22.96 ±0.113	18.85 ±0.269	16.77 ±0.486	13.55 ±0.693
9	45.74 ±0.551	41.03 ±0.283	29.07 ±0.358	27.50 ±0.417	23.78 ±0.947	20.55 ±0.274
12	60.48 ±0.214	54.83 ±0.568	36.99 ±0.693	34.22 ±0.847	33.25 ±0.592	29.95 ±0.726
15	68.41 ±0.335	61.37 ±0.459	43.58 ±0.582	41.69 ±0.938	39.75 ±0.158	36.80 ±0.386
18	74.63 ±0.227	68.01 ±0.335	50.43 ±0.837	47.43 ±0.164	45.11 ±0.385	41.11 ±0.596
21	83.50 ±0.869	77.01 ±0.569	56.18 ±0.313	52.72 ±0.529	51.43 ±0.693	48.11 ±0.749
24	87.01 ±0.358	79.96 ±0.417	58.94 ±0.639	54.47 ±0.374	53.53 ±0.621	50.28 ±0.527

the diclofenac sodium in first 5 hr up to 12.37% as compared to 21.1% from F1. Further increase in guar gum amount (F5 and F6) did not make remarkable difference in diclofenac release than from F4. The ideal colon-targeted oral drug delivery system is expected to release the minimal amount of drug in upper GIT i.e. stomach and small intestine while should release maximum amount of drug in colon. The first 5-hr drug release is considered analog to *in vivo* drug release in upper GIT. F4 tablets showed only 12.37% drug release in

first 5 hr and are expected to release maximum drug to the colon provided the bacteria responsible to digest guar gum are present in sufficient number.

The diclofenac release was studied next from the tablets containing probiotics and 40% guar gum. Results are shown in Table 4 and Figure 1. Cumulative percentage of drug release from F7 was 11.06% in first 5 hr while that was 63.96% at 24 hr. F7 tablets contained sporlac and prowell and the spores are expected to be become vegetative after 7 hr as revealed by guar gum depolymerization study and capable of degrading to guar gum, consequently the higher drug release at colon. The addition of sporlac and prowell did not affected the release of diclofenac in first 5 hr while enhanced the cumulative percent release at 24 hr. The situation mimics the condition as if colon microflora is present as happens *in vivo* at colon. As the amount of sporlac and prowell increased in formulation the cumulative drug release at 24 hr also increased. F9 tablets showed a cumulative percentage release of 73.01% of diclofenac after 24 hr. F10 (sporlac 0.8 billion spores and prowell 12 million spores) showed maximum release of diclofenac in 24 hr (75.53%) as compared to 54.47% from F4 tablets. However, there was not significant change in diclofenac release on increasing the amount of sporlac and prowell in F10 (75.53%) as compared to F9 (73.01%). The presence of the bacterial spores (probiotics) caused at least more than 70% of drug release after 24 hr. This indicates that the guar gum was degraded by sporlac and prowell that released more amount of drug as compared to the formulation without probiotic (F4). The incorporation of

probiotics guar gum matrix tablet ensured at least 70% drug release at colon while protecting the diclofenac release in upper GIT.

The *in vitro* release studies of diclofenac from selected formulation F4 and F9 were conducted in absence and in presence of rat caecal content. The observations are shown in Figures 1, 2 and 3. Formulation code F4 showed 95.26 and 54.47 cumulative percent release of diclofenac in presence and in absence of caecal content, respectively. Formulation F9 containing probiotic (lactobacillus and bifidobacterium spores) showed 98.13 and 73.01% diclofenac release in presence and absence of rat caecal content, respectively. There was about 20% more release of diclofenac in F9 (containing probiotic) as compared to F4 (without probiotic) in absence of rat caecal content. The situation mimics the conditions of GIT without bacterial flora as happens in antibiotic therapy. Formulation F9 is expected to show better drug release in colon as compared to F4 in absence of colonic microflora and ensures major portion of drug in formulation to be released at the colon. Both formulations F4 and F9 showed almost similar amount of drug released (95 and 98%) in presence of colonic flora (rat caecal content).

Table 4: Result of *in vitro* drug release study of colon-targeted diclofenac-guar gum matrix tablet containing probiotics (values are mean ± SEM, n=3). F4 tablets are without probiotics while F7, F8, F9 and F10 were prepared with varying proportions of probiotics.

Time (hrs)	Cumulative % drug release				
	Formulation code				
	F4	F7	F8	F9	F10
2	2.13 ±0.013	2.37 ±0.018	2.24 ±0.036	2.19 ±0.068	2.31 ±0.029
5	11.68 ±0.131	11.06 ±0.113	12.56 ±0.154	11.15 ±0.096	12.45 ±0.143
7	17.46 ±0.269	20.46 ±0.336	21.86 ±0.113	22.66 ±0.164	23.37 ±0.486
9	25.92 ±0.417	29.83 ±0.283	31.07 ±0.358	32.09 ±0.538	32.78 ±0.947
12	31.59 ±0.847	38.13 ±0.568	41.99 ±0.693	44.71 ±0.286	46.25 ±0.592
15	40.06 ±0.938	48.27 ±0.459	54.58 ±0.582	57.95 ±0.497	59.75 ±0.158
18	46.37 ±0.164	55.11 ±0.335	61.43 ±0.837	65.13 ±0.692	67.11 ±0.385
21	51.69 ±0.529	60.01 ±0.569	65.18 ±0.313	69.87 ±0.837	71.43 ±0.693
24	53.95 ±0.374	63.96 ±0.417	68.94 ±0.639	73.01 ±0.739	75.53 ±0.621

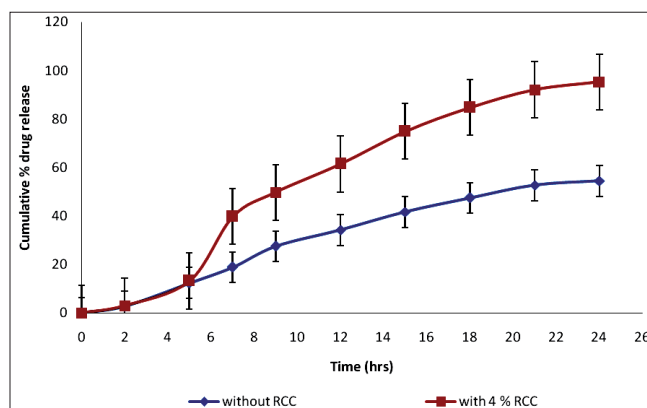


Figure 1: Cumulative percent of diclofenac sodium released from colon-targeted matrix tablet containing 40% of guar gum (F4) of total tablet weight without and with 4% wt/vol rat caecal content

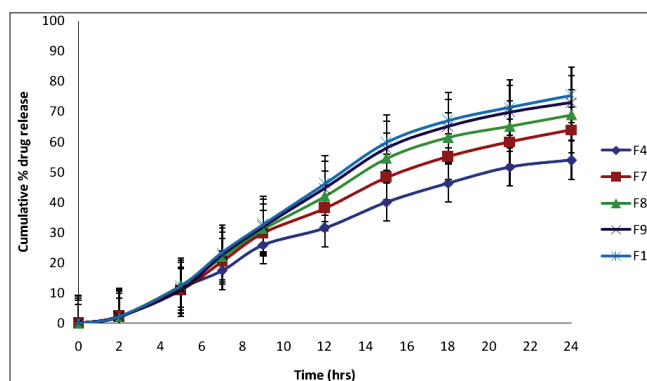


Figure 2: Cumulative percentage of diclofenac sodium released from colon-targeted matrix tablet containing probiotics in absence of rat caecal content

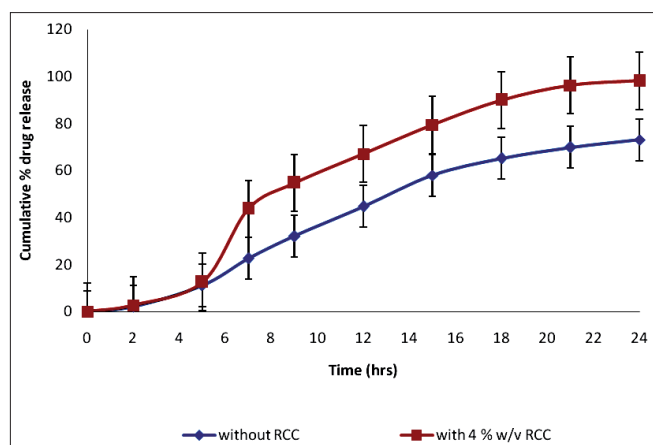


Figure 3: Cumulative percentage of diclofenac sodium released from colon-targeted matrix tablet containing probiotics (F9) without and with 4% w/v RCC

CONCLUSIONS

On the basis of above study it may be concluded that the formulation containing probiotics ensures the major portion of drug (more than 70%) to be released at colon even in absence of colonic microflora. However, *in vivo* studies are needed to confirm the results obtained in *in vitro* studies. In present research work *in vitro* characterization of probiotic-assisted colon delivery of diclofenac was studied. The guar gum matrix tablet formulation developed with probiotic holds tremendous potential to deliver a variety of drugs in colon diseases (viz anticancer drugs) specifically at colon and ensures maximum drug concentration at colon even in case of disturbed GIT microflora on one hand while reduce the dose and frequency of the drug and consequently lowers drug-associated side effects on other.

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