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Research Article

FORMULATION AND EVALUATION OF COLON SPECIFIC DRUG DELIVERY SYSTEM FOR ANTI-NEOPLASTIC DRUG

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ABSTRACT

In controlled drug delivery systems, the drug level in the blood follows the profile, remains constant, between the desired maximum and minimum, for an extended period of time. There are three primary mechanisms by which active agents can be released from a delivery system which includes diffusion, degradation, and swelling. The present investigation is aimed at using these inexpensive, naturally occurring and abundantly available polysaccharides for colon delivery of 5-fluorouracil. An attempt was made to formulate a dosage form which consisted of biodegradable polysaccharides as the main constituent, showed minimal release of 5-fluorouracil in the tracts of the upper GIT and rapid release in the tracts of the colon. 5-Fluorouracil is a pyrimidine analogue and is the drug of choice for colon cancer, it inhibits RNA function and processing and synthesis of thymidylate. It is administered parenterally since absorption after ingestion is unpredictable and incomplete. Targeting of 5-fluorouracil to the colon in cases of colon cancer would not only reduce the systemic toxicity of the drug but would also show the desired action in a lesser dose. Nine batches of 5-fluorouracil matrix tablets were prepared by wet granulation method with different drug-polymer ratios (1:0.5, 1:1, and 1:1.5) by using guar gum, pectin and combination guar gum and pectin gum. The prepared formulations were given enteric coating using Eudragit L-100, S-100 and combination of both Eudragit L-100 and S-100 (1:2). The tablets were evaluated with different physicochemical evaluations. The results indicate the good physicochemical characteristics for matrix tablets.

Keywords: Matrix, CDDS, Colon Cancer, Guar gum and Pectin, Eudragit.

INTRODUCTION[1-8]

The goal of many of the original controlled-release systems was to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets or injections, the drug level in the blood follows the profile, in which the level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent a toxic level, and a minimum value, below which the drug is no longer effective.

There are three primary mechanisms by which active agents can be released from a delivery" system which includes diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can

occur on a macroscopic scale as through pores in the polymer matrix or on a molecular level, by passing between polymer chains.

Drug delivery selectively to the colon through the oral route has been the subject of new research initiatives. Drug release is delayed until it enters the colon. These types of systems are used as follows: Drugs used for local effect in colon for inflammatory bowel diseases (e.g. ulcerative colitis) and crohn's disease. Colon cancer for effect and safe therapy. E.g. 5-amino salicylic acid, 5-fluorouracil etc.

a) Macromolecules such as peptide and protenic drugs for systemic effects because colonic environment is less hostile (with less diversity and intensity of enzyme activities) to those drugs. E.g. Calcitonin, insulin, contraceptive peptides etc.
b) Drugs which are poorly absorbed orally, as colon has longer residence time and is highly responsive to agents that enhance the absorption of poorly absorbable drugs.
c) Some orally administered drugs, which exhibit poor uptake in upper G.I. tract or show enzymatic degradation, can be investigated for better bioavailability through colon.
   E.g., Metaprolol, Nifedipine, Theophylline Diclofenac, Ibuprofen etc.

This system needs wide study before its regular implementation in drug delivery.

Several approaches have been made in the last decade to achieve improved colon specific delivery. In considering the physiological conditions of G.I tract various systems have been developed. They are

1. pH dependent systems
2. Time dependent systems
3. Micro flora activated systems

5-fluorouracil is a pyrimidine analogue, which has been used in the treatment of cancer for more than two decades.[9-11]

Fluorouracil is a pyrimidine analogue, which acts as an antimetabolite to uracil. It is converted to active nucleotide metabolite 5-fluoro-2 deoxy uridylate (FdUMp) within the target cell it self by a series of enzymatic reactions.

Initially, 5 monophosphate nucleotide (FUMP) is formed by oratate phosphoribosyl transferase in the presence of 5-phosphoribosyl-1- pyrophosphate (PRPP), or by the action of uridine phosphorylase and then uridine kinase. The FUMP is further metabolized to diphosphate (FUDP) and then to triphosphate (FUTP), which can be incorporated in to RNA thus producing a fraudulent RNA. However, the primary activation steps of fluorouracil involves the formation of the FdUMP by a reduction with ribonucleotide reductase to FdUMP and then by the action of phosp Malignant neoplasms of bladder horylase to FdUMP.

This active deoxynucleotide (FdUMP) interferes with the synthesis of DNA by blocking the conversion of deoxy uridylic acid to thymidylic acid by the cellular enzyme thmidylate synthetase.it can also interferes with RNA systhesis.

MATERIALS AND METHODS

Materials

Guar gum (MW 220,000) was procured from Himedia Laboratories Limited, India. Pectin and 5-fluorouracil were obtained from Dabur Research Foundation, Ghaziabad. The Eudragit L-100 & S-100 polymers were purchased from Rohm, Germany, Starch, talc and magnesium stearate used for the preparation of tablets were of Pharmacopoeial grade.

Chemicals

The various laboratory grade chemicals used for this work were Methanol, Petroleum ether (60°-80°), and Diethyl phthalate, and (99 %).Acetone (99%), Titanium di-oxide. (98%), O-Xyline, Acetonitrile (HPLC grade).

Standard Calibration Curves

A stock solution of (1 mg/ml) of standard drug in different media was accurately prepared, later required dilutions were made with the respective pH solutions (1.2, 6.8 & 7.2).

To a series of 10 ml volumetric flasks aliquots of standard solutions were taken and the volumes were made up with the respective pH solution. The absorbances of these solutions were measured at the respective wavelength of maximum absorbance, using 1 cm quartz couvette in the UV/Visible spectrophotometer. Absorbance values were plotted against respective concentration to obtain standard calibration curves shown in table 1.

Method

The preparation of the matrix tablets with guar gum and pectin containing 5-fluorouracil was done by wet granulation method.

A weighed quantity of 5-fluorouracil required for 20 tablets was mixed thoroughly with the required amount of polymers and other excipients. The ingredients in the quantities mentioned were wet granulated using starch paste (10%). Granules of the above wet mass were prepared by passing through a sieve with a nominal aperture of 1 mm. The granules were dried for 6 h at a temperature of 50^{o}C.

The dried granules were passed through a sieve with a nominal aperture of 1mm and mixed with talc (1.7%) and magnesium stearate (1.2%).
Then after weighing the granules (90 mg) per sample, all the granules were punched in the 5mm die cavity punch with the help of KBr-pellet punch machine. Total nine batches were prepared with different proportions of the polymers namely 1:1, 1: 0.5 and 1:1.5. The coating of the matrix tablet was done by dip coating technique, show in table 2.

Preparation of the coating solution
The composition of the coating solution is given in the table below. Required amount of methanol was taken in a beaker. It was stirred to get the vortex. Diethyl phthalate was added followed by the slow addition of the mixture of Eudragit L-100 & S-100 and titanium dioxide. Then the required amount of acetone was added. The mixture was stirred for 30 minutes. The suspension thus obtained was passed through muslin cloth, show in table 3.

RESULTS AND DISCUSSION
5-Fluorouracuil matrix tablets formulations
Nine batches of 5-fluorouracil matrix tablets were prepared by wet granulation method with different drug-polymer ratios (1:0.5, 1:1, and 1:1.5) by using guar gum, pectin and combination guar gum and pectin gum. The prepared formulations were given enteric coating using Eudragit L-100, S-100 and combination of both Eudragit L-100 and S-100 (1:2). The matrix tablets were evaluated with different physicochemical evaluation such as hardness, friability, average weight, and drug content and *in vitro* drug release behaviour. The results indicate the good physicochemical characteristics for matrix tablets.

Physicochemical Evaluation
The hardness of the prepared matrix tablets were determined by Monsanto hardness tester and the results of the matrix tablets are given in Table No. 4. The friability of matrix tablets were determined by friabilator and the results were shown in Table No: 4. The drug content of the formulated matrix tablets were found to be 99.8 to 104%.

In vitro dissolution data
The in vitro dissolution profile of each of prepared formulation was determined by USP paddle method by half dilution method. The in vitro dissolution profile of each of prepared formulation were carried out at different pH conditions with varying time in order to test the suitability of the developed formulations for colon specificity. These results were given in Table no.5 to 12 and graphical representation was showed in figures 1 to 8.
Form the graphical representation; it was revealed that the drug release from the developed dosage from was minimal in pH 1.2 (which found to be less than 25%). The drug release in pH 7.2 was found to range from 60% to 86%. The lowest drug was found to be in batch A6 i.e. combination batch of guar gum and pectin gum (60.85%).
The dissolution was carried out for a maximum of 24 hrs.

The batch formulations of different matrix tablets containing 5-fluorouracil at different ratios (1:0.5, 1:1, 1:1.5) for different batches of guar gum
The cumulative percentage released at various time intervals was calculated and tabulated in table no.5 to 7. The cumulative percentage released was then plotted against time in fig. no.1 to 3. A maximum release of 68.52%, 70.49%, 67.58%, 68.70%, 68.17%, 60.85%, 70.49%, 68.52%, and 84.77% were shown by batches A_1, A_2, A_3 A_4, A_5, A_6, A_7, A_8, and A_9 respectively. A_9 prepared using 1:1.5 drug polymer ratio showed better drug release when compared to other batches.

The batch formulations of different matrix tablets containing 5-fluorouracil at different ratios (1:0.5, 1:1, 1:1.5) for different batches of pectin gum
The cumulative percentage released at various time intervals was calculated and tabulated in table no.8 to 10. The cumulative percentage released was then plotted against time in fig no. 4 to 6. A maximum release of 86.28%, 85.12%, 82.68%, 85.46%, 84.42%, 80.24%, 84.66%, 83.03% and 80.36% were shown by B_1, B_2, B_3, B_4, B_5, B_6, B_7, B_8 and B_9 respectively. B_1 using 1:0.5 drug polymer ratio showed better drug release when compared to other batches.

The batch formulations of different matrix tablets containing 5-fluorouracil at different ratios (1:0.5, 1:1, 1:1.5) for different batches of guar gum and pectin gum combination
The cumulative percentage released at various time intervals was calculated and tabulated in table no.11 to 12. The cumulative percentage released was then plotted against time in fig. no.7 to 8. A maximum release of 77.68%, 75.37%, 78.62%, 80.24% and 76.06% were shown by C_1, C_2, C_3, C_4 and C_5 respectively. C_4 1:1 drug polymer ratio showed better drug release when compared to other batches.

SUMMARY

The main objective of this project is to develop a dosage form, which can be used to provide release of drugs for local action in the GIT for diseases like colon-rectal cancer. Delivery systems such as matrix tablets were utilized for the colon specific drug delivery which is one of the seemingly interesting areas to target drugs to colon through oral route. This might be expected to localize the drug concentration and thus help in the efficient treatment of disorders associated with colon. So this matrix tablet was designed based on natural polymers such as guar gum, pectin and enteric coating employing pH sensitive polymers like Eudragit L/S, which remain undigested in the stomach and the small intestine and are degraded by only the vast anaerobic microflora of the colon to release the drug in lumen of large bowel.

For targeting the drug in colonic region, the matrix tablets with different ratios of guar gum, pectin, and combination of guar gum and pectin (1:0.5, 1:1 and 1:1.5) were prepared by wet granulation method. These tablets consist of various proportions of drug and polymer. These tablets were coated with Eudragit L-100, S-100 & combination of both L-100 & S-100.The tablet showed good physico-chemical properties such as hardness, friability, weight variation and drug content. The *invitro* drug release profile of these tablets showed delayed release characteristics.

The developed drug delivery systems was also evaluated for dissolution study by half dilution method in order to maintain the gastrointestinal transit conditions similar to human beings. All the developed systems showed a minimum release at pH 1.2 and maximum release at pH 6.8. The release of the drug from guar gum was delayed when compared to other batches such as pectin and some combination batches.

Comparison of the different developed systems indicates that the release profile of pectin were better when compared to other batches of guar gum and combination batch of guar gum and pectin.

From the results of *in vitro* evaluation of the different dosage forms, it was found that formulated drug delivery systems containing 5-fluorouracil could be used for drug targeting to colon for the treatment of colonic cancer disease.

Table 1: Standard Calibration Curves

Concentration (µg/ml)	For pH 1.2		For pH 6.8		For pH 7.2	
	Absorbance		Absorbance		Absorbance	
2 (µg/ml.)	0.168		0.190		0.116	
4 (µg/ml.)	0.345		0.365		0.297	
6 (µg/ml.)	0.524		0.548		0.446	
8 (µg/ml.)	0.692		0.717		0.609	
10 (µg/ml.)	0.854		0.892		0.760	
	k=11.665	**b=-0.0077**	**k=11.247**	**b=-0.0871**	**k=13.097**	**b=0.0763**

Table 2: Tablets Resulting After Coating Were Given Batch Codes

Batch	***Ratio***	***Coated with Eudragit***		
		L-100	***S-100***	***L-100+S-100 combination***
Guar gum	***1:0.5***	A_1	A_2	A_3
	1:1	A_4	A_5	A_6
	1:1.5	A_7	A_8	A_9
Pectin	***1:0.5***	B_1	B_2	B_3
	1:1	B_4	B_5	B_6
	1:1.5	B_7	B_8	B_9
Combination of Guar gum and Pectin	***1:0.5***	--	C_1	--
	1:1	C_2	C_3	C_4
	1:1.5	C_5	--	--

Table 3: Composition of Coating Suspension

Ingredients	Qty. for 100 ml.	Qty. for 30 ml.
Eudragit L-100 & S-100	7g.	2.1g
Titanium Di-oxide	2.9g	0.87 g.
Di ethyl phthalate	3.3 g.	0.99 g
Methanol	50.9 ml.	15 ml.
Acetone	35.9 ml.	10.77 ml.

Table 4: Physico-Chemical Evaluation Data for Matrix Tablets

Batch details	Hardness	% friability	Weight gain*									Drug content (%)
			Before coating			After coating			% weight gain			
			L	S	L+S	L	S	L+S	L	S	L+S	
Guar gum												
1:0.5	3.8 (0.27)	0.7425	0.0905 (0.002)	0.0905 (0.002)	0.0905 (0.02)	0.094 (0.005)	0.095 (0.006)	0.096 (0.005)	4.32 (0.701)	5.03 (0.510)	5.20 (0.590)	10.22
1:1	3.9 (0.41)	0.6944	0.0906 (0.002)	0.0907 (0.002)	0.0907 (0.02)	0.095 (0.008)	0.095 (0.009)	0.096 (0.006)	5.10 (0.850)	4.32 (0.650)	5.23 (0.650)	10.25
1:1.5	3.9 (0.41)	0.7328	0.0907 (0.002)	0.0906 (0.002)	0.0906 (0.02)	0.097 (0.009)	0.095 (0.008)	0.095 (0.008)	5.20 (0.651)	4.32 (0.590)	4.90 (0.061)	09.98
Pectin												
1:0.5	4 (0.5)	0.6888	0.0907 (0.002)	0.0906 (0.002)	0.0905 (0.02)	0.096 (0.008)	0.096 (0.007)	0.096 (0.009)	5.56 (0.512)	5.56 (0.630)	5.20 (0.620)	09.39
1:1	3.8 (0.44)	0.7449	0.0905 (0.002)	0.0905 (0.002)	0.0904 (0.02)	0.094 (0.008)	0.094 (0.008)	0.094 (0.008)	4.90 (0.590)	4.90 (0.610)	5.90 (0.510)	10.02
1:1.5	3.9 (0.41)	0.5720	0.0906 (0.002)	0.0905 (0.002)	0.0905 (0.02)	0.095 (0.008)	0.095 (0.008)	0.095 (0.008)	5.71 (0.590)	5.71 (0.515)	5.03 (0.641)	10.33
Combination												
1:0.5	4 (0.5)	0.6278	0.0905 (0.002)	0.0907 (0.002)	0.0905 (0.02)	0.095 (0.008)	0.094 (0.008)	0.094 (0.009)	4.90 (0.490)	5.10 (0.465)	4.90 (0.528)	10.05
1:1	3.9 (0.41)	0.6325	0.0904 (0.002)	0.0907 (0.002)	0.0905 (0.02)	0.094 (0.009)	0.096 (0.009)	0.095 (0.008)	4.20 (0.545)	4.32 (0.560)	4.98 (0.590)	10.40
1:1.5	4 (0.5)	0.6864	0.0906 (0.002)	0.0906 (0.002)	0.0905 (0.02)	0.095 (0.009)	0.095 (0.008)	0.096 (0.008)	5.32 (0.581)	5.21 (0.564)	4.51 (0.581)	10.23

Table 5: In vitro release profile of 5-fluorouracil matrix tablets using Guar gum (ratio 1:0.5)

Time (hrs.)	Cumulative % release (%)		
	Guar gum 1:0.5 (L)	Guar gum 1:0.5 (S)	Guar gum 1:0.5 (L+S)
0.5	0.39	0.6	1.3
1	0.5	0.9	1.7
2	0.9	1.3	2.2
3	1.4	1.5	2.4
4	2.7	2.2	4.8
5	5.4	2.8	5.9
6	6.2	3.8	6.3
8	7.6	4.7	7.7
10	8.5	6.4	8.8
12	11.3	10.9	10.3
15	20.8	17.22	17.8
17	57.7	52.9	52.2
20	63.9	60.78	62.33
22	67.5	62.9	64.7
24	68.521	67.3	68.8

Table 6: In vitro release profile of 5-fluorouracil matrix tablets using Guar gum (ratio 1:1)

Time (hrs)	Cumulative % release (%)		
	Guar gum 1:1 (L)	Guar gum 1:1 (S)	Guar gum 1:1 (L+S)
0.5	0.7	0.9	0.7
1	0.9	1.1	1
2	1.3	1.7	1.3
3	1.7	1.8	1.5
4	3.2	4	3.4
5	3.6	4.6	3.6
6	4.2	5.4	4.8
8	5.5	6.5	5.8
10	8.8	8.9	6.9
12	11.4	10.7	7.7
15	16	14.6	16.7
17	47.7	49.9	36.55
20	56.9	59.5	53.6
22	60.9	64.8	59.4
24	65.6	66.7	68

Table 7: In-vitro release profile of 5-fluorouracil matrix tablets using Guar gum (ratio 1:1.5)

Time (hrs)	Cumulative % release (%)		
	Guar gum 1:1.5 (L)	Guar gum 1:1.5 (S)	Guar gum 1:1.5 (L+S)
0.5	0.61	0.63	0.74
1	1.23	0.9	0.9
2	1.4	1.2	1.11
3	1.9	1.4	1.69
4	3.1	3.2	3.2
5	3.3	3.8	3.7
6	3.6	4.6	3.5
8	3.9	5.23	4.56
10	4.4	5.3	7.2
12	5.3	5.7	8.2
15	12.3	14.5	16.7
17	42.1	44.21	46.8
20	46.7	45.2	51.8
22	56.3	54.5	57.5
24	66.8	65.2	67.7

Table 8: In vitro release profile of 5-fluorouracil matrix tablets using Pectin (ratio 1:0.5)

Time (hrs)	Cumulative % release (%)		
	Pectin 1:0.5 (L)	Pectin 1:0.5 (S)	Pectin 1:0.5 (L+S)
0.5	1.1	1.2	0.6
1	1.7	0.5	2.2
2	2.5	1.5	3.1
3	2.8	1.7	3.7
4	4.6	4.6	5
5	5.1	5	6
6	6	5.3	6.6
8	7	6.2	7.5
10	7.5	6.4	7.9
12	7.9	9.5	8.3
15	29.9	32.1	27.5
17	58.3	56.3	61.3
20	63.1	64.6	69
22	76.97	74.7	81.1
24	80.6	82	83.7

Table 9: In vitro release profile of 5-fluorouracil matrix tablets using Pectin (ratio 1:1)

Time (hrs)	Cumulative % release (%)		
	Pectin 1:1 (L)	Pectin 1:1 (S)	Pectin 1:1 (L+S)
0.5	0.5	0.8	0.6
1	1.3	1.7	1.2
2	2	2.5	1.6
3	2.8	2.7	2
4	5	3.7	3.3
5	6	4.3	4.3
6	6.3	6.2	4.5
8	7.1	7.8	5.9
10	7.5	8.7	7.2
12	9.6	9.3	8.4
15	19.6	18.4	18.4
17	60.9	51.6	63.224
20	73	73.5	75.6
22	76.9	82.4	78.9
24	79	84.428	80.249

Table 10: In vitro release profile of 5-fluorouracil matrix tablets using Pectin (ratio 1:1.5)

Time (hrs)	Cumulative % release (%)		
	Pectin 1:1.5 (L)	Pectin 1:1.5 (S)	Pectin 1:1.5 (L+S)
0.5	0.3	0.2	0.8
1	1	1.6	1.2
2	1.5	1.6	1.5
3	1.8	2.3	2.1
4	3.5	3.7	3.5
5	3.9	3.7	4
6	4.2	3.7	4.6
8	5.4	4.9	5
10	7.4	6	5.6
12	9.1	7.8	6.7
15	16.3	17.7	16.8
17	57.7	54.6	62.889
20	71.8	72.7	74.8
22	76.5	74.8	77.3
24	77.9	78.8	79.8

Table 11: In vitro release profile of 5-fluorouracil matrix tablets using combination of guar gum and pectin. (Ratio 1:1)

Time (hrs)	Cumulative % release (%)		
	Combination 1:1 (L)	Combination 1:1 (S)	Combination 1:1 (L+S)
0.5	0.70	0.87	0.94
1	1.27	1.01	1.30
2	1.84	1.27	1.40
3	2.25	1.90	2.09
4	3.25	2.97	3.16
5	3.55	3.40	3.97
6	4.27	3.86	5.10
8	4.77	4.80	5.24
10	5.27	5.67	5.50
12	7.72	8.22	7.17
15	17.24	16.93	17.85
17	60.35	59.30	62.40
20	71.70	73.21	71.23
22	77.67	76.94	77.60
24	82.20	80.60	80.25

Table 12: In vitro release profile of 5-fluorouracil matrix tablets using combination of guar gum and pectin. (Ratio 1:0.5 and 1:1.5)

Time(hrs)	Cumulative % release	
	Combination 1:0.5(S-100)	Combination 1:1.5 (L-100)
0.5	0.59	0.63
1	1.02	1.47
2	1.39	1.76
3	1.74	1.84
4	3.65	2.64
5	3.16	3.65
6	3.53	3.84
8	3.72	4.14
10	4.27	4.53
12	5.17	6.35
15	16.47	16.72
17	50.64	57.74
20	70.32	69.65
22	74.35	76.27
24	77.69	79.12

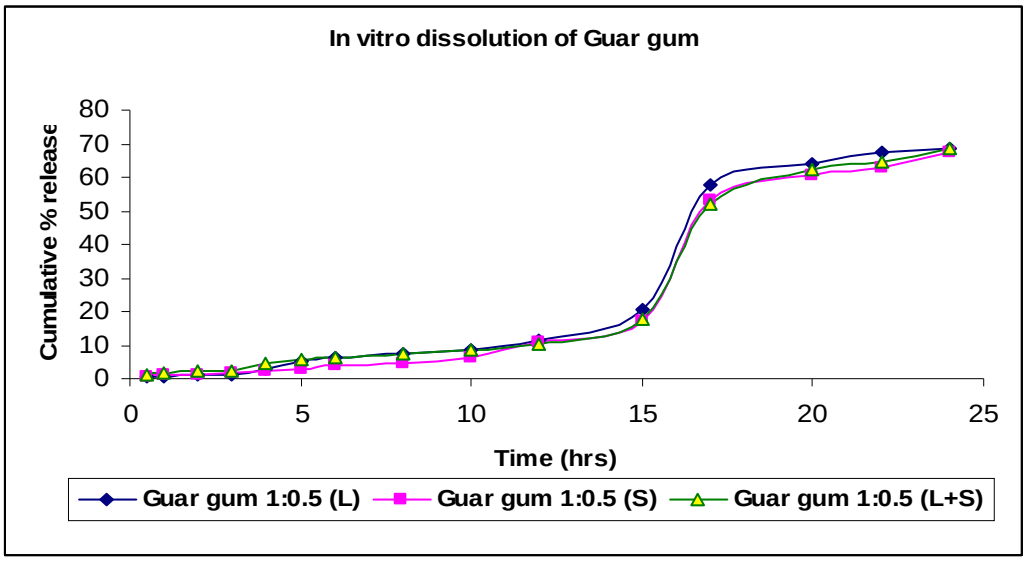

Fig. 1: *In vitro* release profile of 5-fluorouracil matrix tablet using Guar gum (ratio 1:0.5)

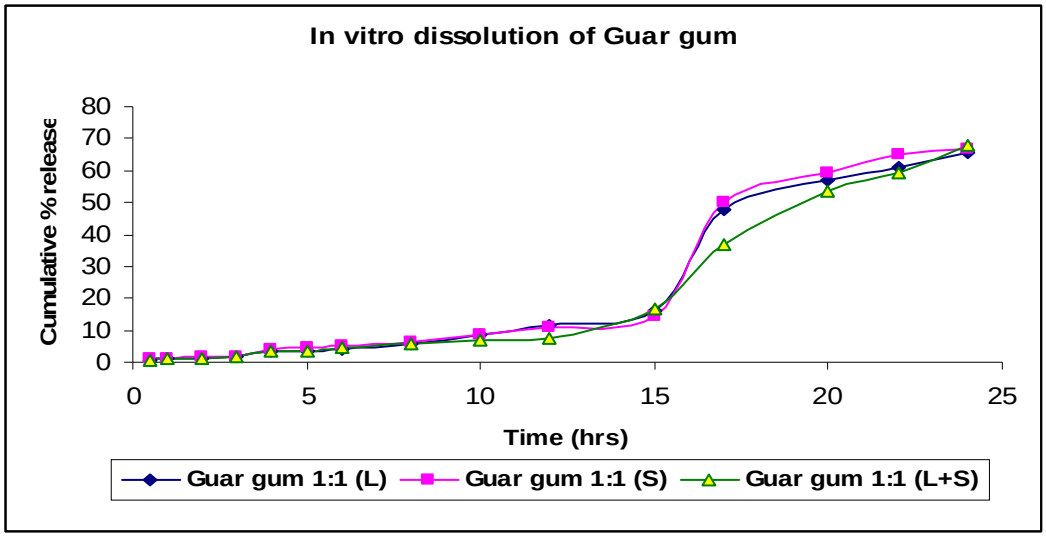

Fig. 2: *In vitro* release profile of 5-fluorouracil matrix tablets using Guar gum (ratio1:1)

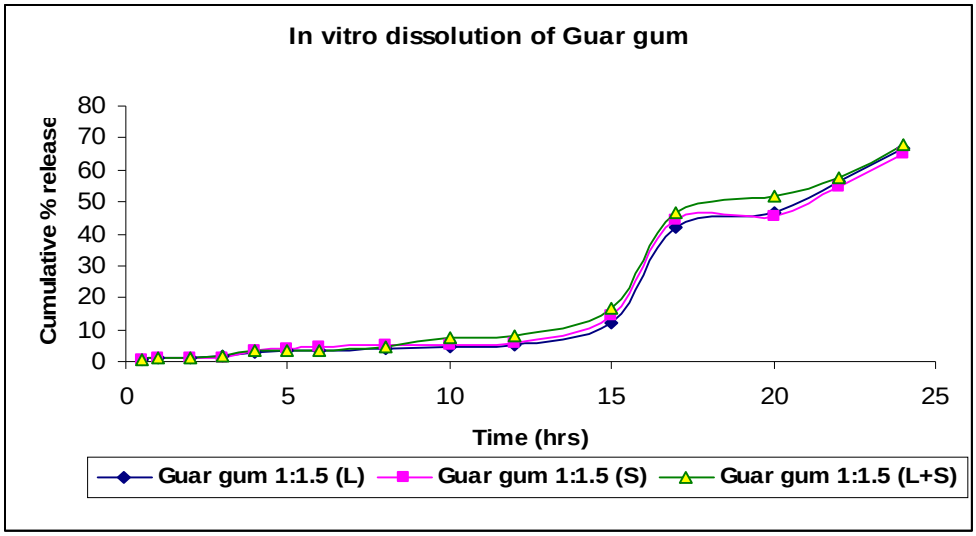

Fig. 3: *In vitro* release profile of 5-fluorouracil matrix tablets using Guar gum (ratio 1:1.5)

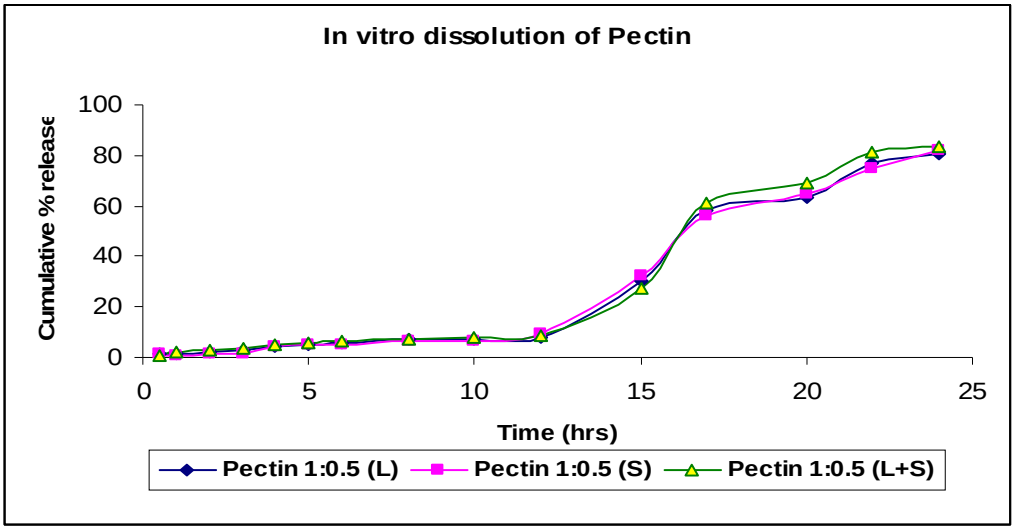

Fig. 4: *In vitro* release profiles of 5-fluorouracil matrix tablets using Pectin (ratio 1:0.5)

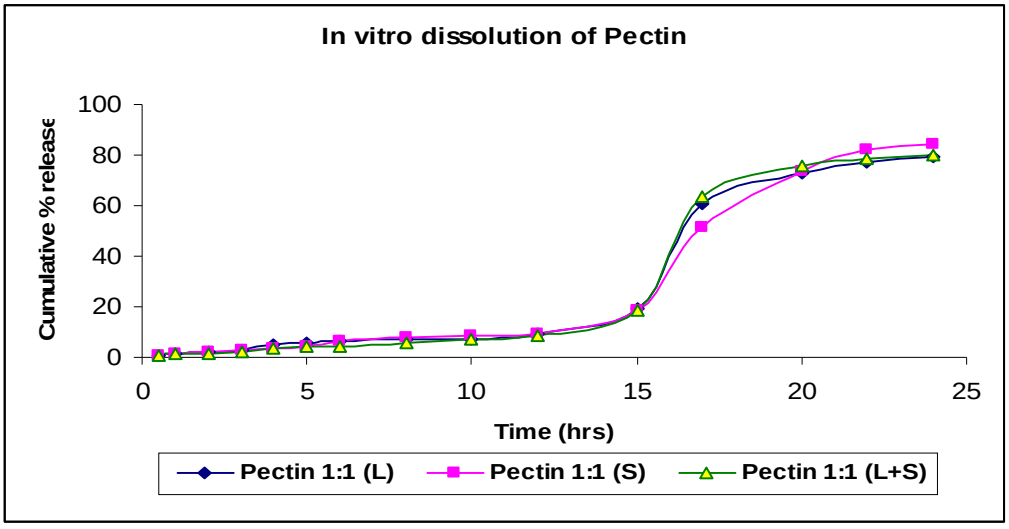

Fig. 5: *In vitro* release profile of 5-fluorouracil matrix tablets using Pectin (ratio 1:1)

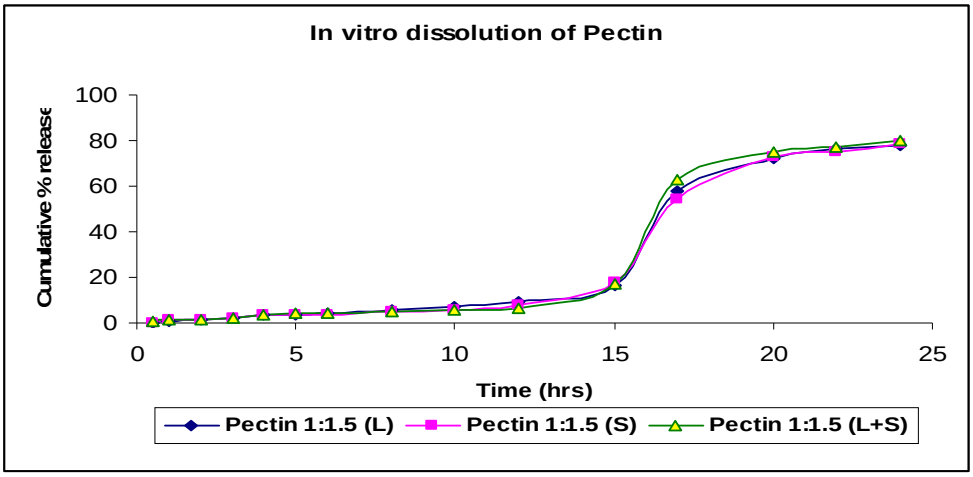

Fig. 6: *In vitro* release profile of 5-fluorouracil matrix tablets using Pectin (ratio1:1.5)

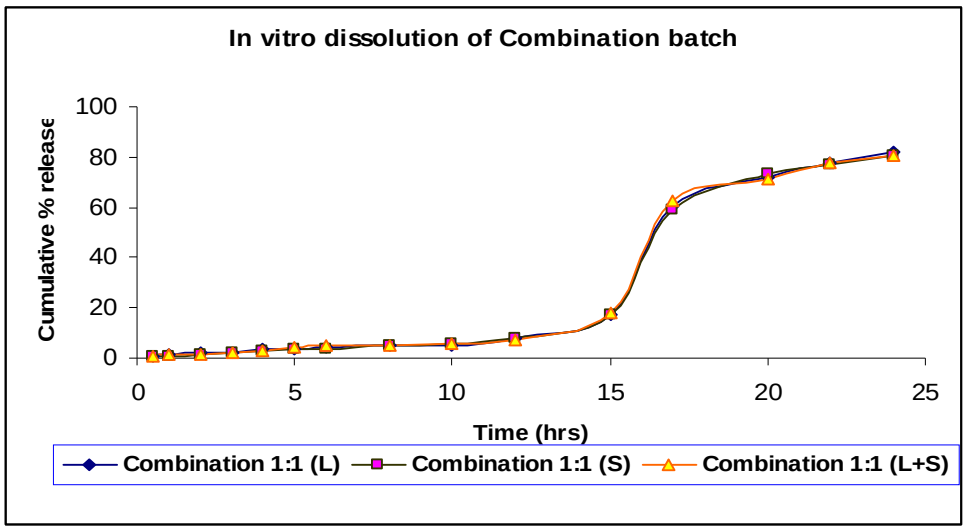

Fig. 7: *In vitro* release profile of 5-fluorouracil matrix tablets using combination of guar gum and pectin. (Ratio 1:1)

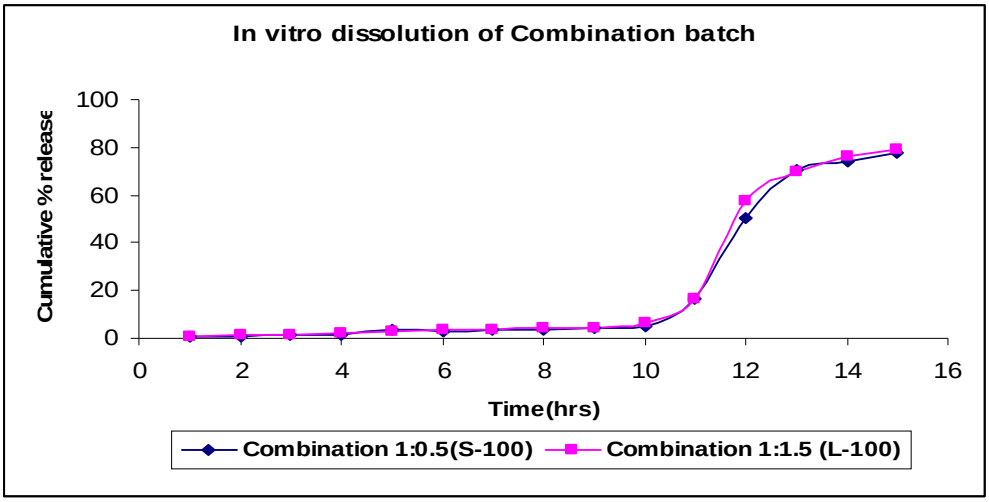

Fig. 8: *In vitro* release profile of 5-fluorouracil matrix tablets using combination of guar gum and pectin. (Ratio 1:0.5 and 1:1.5)

CONCLUSION

This polysaccharide composition consisting of guar gum and pectin as a drug release retarding agent in combination with colon degradable polysaccharides such as guar gum which can be successfully used to protect the drug from being released under conditions mimicking mouth-to-colon transit. If properly projected this kind of dosage forms can lead to a major key role for overcoming the different problems associated with the disease. Though the preliminary data based on *in vitro* dissolution profiles proved that the drug release from these tablets takes place at a highly retarded rate till it is digested by the microflora of the colon. So, these systems seem to be site specific and shall be useful for the effective local action for diseases like colo-rectal cancer. However, *in vivo* studies are needed to carryout to establish its potential.

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