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DESIGN AND EVALUATION OF CONTROLLED RELEASE COLON MATRIX TABLETS OF 5-FLUOROURACIL BY USING GUM KARAYA

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Abstract:

The applicability of gum karaya (GK), obtained from sterculia species was studied for its applicability in the design of colon drug delivery systems of 5- fluorouracil (5-FU). Colon targeted tablets of 5 FU were prepared with varying drug-GK ratios and evaluated for the drug release in colonic pH environment. The optimum concentration of drug-GK was found to be 1:1.25 w/w ratio for extending the drug release around 24 hours. The effect of channeling agents was studied and observed that soluble channeling agent lactose markedly affected the drug release compared to insoluble channeling agents and nearly 90% drug release was observed in 24 hours. The optimized formulations were evaluated in dissolution medium containing rat caecal content and 100% drug release was observed over 24 hours. The formulations followed first order without channeling agent and in rat caecal content medium where as zero order was observed for tablets with lactose as channeling agent. Non-Fickian diffusion was observed in simulated intestinal fluid. The formulations followed erosion mechanism in rat caecal content medium indicating the degradation of GK by intestinal microbial flora. No drug-GK interactions were observed in the studies carried out on optimized formulations by differential scanning calorimetry (DSC), X-ray diffraction studies (XRD) and Fourier transform infra red spectroscopy (FTIR). Based on the above findings it was concluded that GK can be explored as colon specific release polymer because of its abundant availability, reliability, efficacy, ecofriendly and economical features.

Keywords: *5-Fluorouracil, Gum karaya and colon specific drug delivery*

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INTRODUCTION:

The oral route is considered to be most convenient for administration of drugs to patients. Targeted drug delivery into the colon [1,2] is highly desirable for local treatment of diseases such as inflammatory bowel disease [3], ulcerative colitis, cirrhosis disease [4], amoebiasis [5], colonic cancer [6], local treatment of colonic pathologies and systemic delivery of protein and peptide drugs [7].

5-fluorouracil is used in the treatment of cancer for more than two decades. It is a fluorinated anti metabolite of the pyrimidine uracil. It slows tumour cell growth inhibition by inhibiting thymidine formation; thereby inhibit protein synthesis by incorporating into RNA [8,12].

Gum karaya obtained from the ‘‘*Sterculia urens (Roxburgh), Sterculia villosa (Roxburgh), Strerculia tragacanth* or other *species* of *sterculia* belonging to the family *Sterculiaceae*. It is a high molecular weight complex acidic and negative colloid polysaccharide and degraded by most of the azo reductive microorganisms. But it is neither digested nor absorbed by the body because this gum does not disintegrate or decompose in the stomach or small intestine [9].

In the present investigation UV visible spectrophotometric method was used for estimation of 5-FU as reported by earlier workers. 5-fluorouracil was estimated by measuring the absorbance at 266 nm [10] in 0.1N HCl, pH 7.4 phosphate buffer and pH 6.8 colonic fluid.

Preparation of gum karaya colon matrix tablets 5-fluorouracil:

5-FU is having poor flow properties and hence it is proposed to use wet granulation method for the preparation of matrix tablets. All the ingredients previously passed through sieve no.100 (sieve opening 149 µm as per US mesh standard) sufficient for a batch of 250 tablets were geometrically mixed with gum karaya for obtaining homogeneous blend. Granulation was done using 5% (w/v) gum karaya mucilage as granulating agent. Final blend was then compressed into tables on a 16 station rotary tablet punching machine (M/s. Rimek, India) using 6 mm/9 mm/12 mm round concave punches appropriately based on the total weight of the tablets using a compression force suitable for obtaining the hardness around 5-6 Kg/cm^2. Formulae of gum karaya colon matrix tablets of both drugs are shown in **Tables 1-2**. In each batch 200 tablets were prepared.

Table 1: **Formulae of colon matrix tablets of 5-fluorouracil**

Ingredients (mg per tablet)	**FGK1**	**FGK2**	**FGK3**	**FGK4**	**FGK5**
5-fluorouracil	125	125	125	125	125
Gum karaya	27	57	89	120	183
5% w/v gum karaya mucilage equivalent to	5	5	5	5	5
Magnesium stearate	3	3	3	3	3
Talc	2	2	2	2	2
Total weight (mg)	**162**	**192**	**224**	**255**	**318**

Table 2: Formulae of colon matrix tablets of 5-fluorouracil prepared with different channeling agents

Ingredients (mg per tablet)	FGK6	FGK7	FGK8	FGK9	FGK10	FGK11	FGK12	FGK13	FGK14	FGK15
5-Fluorouracil	125	125	125	125	125	125	125	125	125	125
Gum karaya	120	120	120	120	120	120	120	120	151	183
5%w/v gum karaya mucilage equivalent to	5	5	5	5	5	5	5	5	5	5
Microcrystalline cellulose	31	63	--	--	--	--	--	--	--	--
Dicalcium phosphate	--	--	31	63	--	--	--	--	--	--
Mannitol					31	63				
Lactose	--	--	--	--	--	--	31	63	39	94
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2
Total weight of tablet (mg)	**286**	**318**	**286**	**318**	**286**	**318**	**286**	**318**	**325**	**412**

Evaluation of prepared gum karaya colon matrix tablets of 5-fluorouracil: The prepared tablets were subjected to tableting properties viz. thickness, uniformity of weight (I.P., 2010) [12], hardness [11], friability (I.P., 2010) [12], drug content (I.P., 2010) [12] and swelling index.

Thickness:
Ten tablets were randomly selected from each batch and thickness of tablet was measured using a screw gauge. The mean thickness was determined and expressed in mm.

Uniformity of weight:
According to Indian Pharmacopoeia twenty tablets were selected at random, weighed together and individually for the determination of uniformity of weight of tablets. The mean and percent deviation was determined. Prepared tablets comply with the official Pharmacopeia standards if not more than two of the individual weights deviate from the average weight by more than the percentage and none deviate more than twice the percentage mentioned bellow.

Average weight of tablet	% deviation
80 mg or less	10.0
More than 80 mg but less than 250	7.5
More than 250 mg	5.0

Hardness:
Five tablets were randomly selected from each formulation and crushing strength of each tablet was measured using Monsanto hardness tester. The mean hardness was determined and expressed in Kg/cm^2.

Friability:
The friability was carried out in Roche friabilator. The tablets equivalent to 6.5 g were selected randomly and initial weight (w_o) was noted down and placed in a rotating drum (SECOR, Mumbai, India). They were subjected to 100 falls of 6 inches height (25 rpm 4 min). After completion of 100 rotations, the tablets were removed de-dusted by using camel hair brush and weighed as (w). The percent loss in weight (for friability) was calculated was calculated by the formula given bellow:

$\%friability = [1- w/w_o] * 100$ - - - ------ Eq. 1

Drug content estimation:
From each batch 10 tablets were randomly collected, powdered in a glass mortar and equivalent to 50 mg of drug was placed in a 50 mL volumetric flask.5-fluorouracil was extracted with pH 7.4 phosphate buffer (as described in analytical method) with vigorous shaking on a mechanical shaker for 1 hour and filtered into a 50 ml

volumetric flask through 0.45 µm. Millipore nylon filter disk and the filtrate was made up to the mark with pH 7.4 buffer. Further appropriate dilutions were made and the absorbance was measured at 266 nm against blank using UV visible spectrophotometer.

Swelling index of colon matrix tablets:

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling index of all formulation of 5-fluorouracil were studied. Three tablets from each formulation were kept in a petri dish containing pH 7.4 phosphate buffer. At the end of 1 hr, the tablet was withdrawn, wiped with tissue paper, and weighed. Then for every 2 hrs, weights of the tablet were noted, and the process was continued till the constant weight reached and % of weight gain by the tablet was calculated by formula;

$S.I = [(w_t - w_o)/w_o] * 100$ ---------- Eq. 2

Where,

S.I = swelling index,

w_t = weight of tablet at time 't'

w_o = weight of tablet at time t =0

Reproducibility method:

Three different batches of optimized formulations FGK4 were selected to assess the reproducibility of the wet granulation method. The tablets were evaluated for thickness, uniformity of weight, hardness, friability, drug content and swelling index.

***In vitro* dissolution studies for 5-fluorouracil colon matrix tablets:**

In vitro drug release was studied for formulations of 5-fluorourail (125 mg) according to USP (USP, 2010) dissolution study procedure for delayed release dosage forms by using USP XXIV type II dissolution test apparatus (Model 1918/1916 M/s. Electronics India, Mumbai, India). 0.1N HCl (900 mL) was used as dissolution medium for first 2 hrs and pH 7.4 phosphate buffer (900 mL) was used as dissolution medium for the remaining period of dissolution and both media were maintained at 37±0.2°C and stirring rate of 50 rpm. 5 mL of samples were withdrawn with syringe fitted with a pre filter at predetermined time intervals and immediately replaced with 5 mL of appropriate fresh medium (0.1N HCl/pH 7.4 phosphate buffer) maintained at 37±0.2°C for both the drugs. The collected samples were analyzed for 5-fluorouracil at 266 nm by UV visible spectrophotometer. Each dissolution study was repeated for three times and mean values were reported.

***In vitro* release of 5-fluorouracil colon matrix tablets in the presence of rat caecal content:**

In vitro drug release studies were also investigated in the presence of rat caecal contents because of its similarity to human intestinal microflora [13]. The albino rats weighing between 105-115 g were kept on normal diet, (rat nutrition pellets, brand name KAYTEE) the care of the rats was in accordance with the institutional guidelines. 1 mL of 2% w/v aqueous dispersion of gum karaya was administered with the help of Teflon tubing directly into the oesophagus region via oral cavity for a period of 7 days to induce susceptibility of gum karaya to colonic bacterial degradation. Thirty minutes before the commencement of drug release studies, six rats were euthanized, using carbon dioxide asphyxiation. The abdomen were opened, the caecai traced, ligated at both ends, dissected and immediately transferred into pH 6.8 phosphate buffer, previously bubbled with CO_2. The caecal bags were opened; their contents individually weighed, pooled and then suspended in pH 6.8 phosphate buffer to obtain 4% w/v dilution. As the caecum is naturally anaerobic, all these operations were carried out under CO_2 [14].

Dissolution studies were continued in rat caecal medium with adopted procedure by using USP type II dissolution rate test apparatus (Model 1918/1916 M/s. Electronics India, Mumbai, India) with a 250 mL beaker containing 100 mL of dissolution medium which was immersed in the water contained in a 900 mL vessel and stirrer rotated at a speed of 100 rpm at 37±0.2°C. The formulations were subjected to *in vitro* drug release studies in 0.1N HCl (0-2 hrs), continued in pH 7.4 phosphate buffer (2-6 hrs) and later shifted in to the beaker containing colonic fluid medium (4% w/v rat caecal content in pH 6.8 phosphate buffer) with continuous supply of CO_2 for further dissolution. At a specified time intervals, 5 mL of the dissolution media was withdrawn and replaced with 5 mL of fresh colonic fluid medium maintained at the same temperature under CO_2 environment. Samples were filtered through a 0.22 µm membrane filter and the amount of drug released was measured at 266 nm by UV visible spectrophotometer. The *in vitro* drug release experiment was conducted for FGK4, FGK13 and FGK14.

Drug-polymer interaction studies:

There is always a possibility of drug-polymer interaction in the formulation due to intimate contact. The techniques employed in the present work to study the drug-polymer interactions are differential scanning calorimetry (DSC), Fourier transformed infrared (FTIR) spectroscopy and X-

ray diffraction (XRD) studies for the samples of 5-fluorouracil, gum karaya and tablets FGK14.

Differential scanning calorimetry studies (DSC):

Thermal analysis was carried out using a differential scanning calorimeter (Shimadzu Scientific Instruments, model no. DSC-50, Japan). The sample was placed in aluminum sealed pan and heated in the temperature range of 25°C to 200°C at a scanning rate of 10°C/min with an empty pan as reference.

Powder x-ray diffraction (XRD) studies:

X-ray diffraction studies were carried out by using X-ray diffractometer in N_2 environment (Rigaku Corporation, model RAPID II Japan). The sample was run at a scanning speed 56 KV and 180 mA over the range from 2° to 40° with a chart speed of 2°/2 cm (2θ) with an increment of 0.02°.

Fourier transformed infrared (FTIR) spectroscopy studies:

The sample was analyzed for Infrared absorption spectrum by using FTIR spectrophotometer (Perkin Elmer, model No.841, Japan). The pellets were prepared by pressing the samples with potassium bromide and the spectrum was recorded in the region of 400 to 4000 cm^{-1}.

***In vitro* drug release kinetics of the 5-fluorouracil colon matrix tablets:**

The drug release kinetics and mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in case of matrix systems. It is evident from the pharmaceutical literature that no single approach is widely accepted to determine if dissolution profiles are similar. The model dependent methods are an acceptable model approach to establish the true relationship between the dependent and independent variables of dissolution data.

Costa *et al.*, reviewed the model dependent approaches for studying the kinetics and mechanisms [15]. The drug release kinetics from matrix systems can be studied by using zero order [16] or first order [17]. The mechanism of drug release from matrix systems was also studied by using Higuchi diffusion model [18] and Hixon-Crowell erosion model Korsenmeyer-Peppas [19] support to understand the drug release mechanism for further judgment. The related equations for these models are described in **Table 3**. According to equation the release exponent 'n' value is used to characterize different release mechanisms for a dosage form with cylindrical shape and it is summarized in **Table 4.**

Table 3: Kinetic models for comparison of dissolution data

Model	Equation
Zero order	$Q_t = Q_0 + K_0t$
First order	$\text{Log } C = \log C_0 - K_1t/2.303$
Higuchi	$Q = K_Ht^{1/2}$
Hixon-Crowell	$(W_0^{1/3} - W_t^{1/3}) = Kt$
	$M_t/M_n = K_k.t^n$
Q_t: Amount of drug released in time t; Q_0: Initial amount of drug in the tablet; C: Concentration of drug; C_0: Initial concentration of drug in the dosage form; W_t: Remaining amount of drug in the dosage form at time t; M_t: The amount of drug released at time t; M_n: Amount released at time t; M_t/M_n: Fraction of drug released at time t; K_0, K_1, K_H, K, K_k: Rate constants.	

Table 4: Interpretation of diffusional drug release mechanisms from colon matrix tablets

Diffusion exponent (n)	Drug release mechanisms
0.45	Fickian diffusion
$0.45 < n < 0.89$	Anomalous (non-Fickian) diffusion
0.89	Case II transport
$n > 0.89$	Super Case II transport

Appropriate models for the release kinetics and mechanism can be judged by their highest correlation coefficient (r) values compared to other models. The dissolution data was fitted to the models to assess the dissolution behavior of the prepared colon matrix tablets of both the drugs.

RESULTS AND DISCURSIONS:

Evaluation of prepared colon matrix tablets of 5-fluorouracil:

The prepared gum karaya colon matrix tables of 5-fluorouracil were evaluated for their tableting properties. The results of the thickness, uniformity of weight, hardness, friability, drug content, and swelling index are presented in **Table 5.** All the tablets prepared were found to have uniformity of weight and the percent deviation complied with compendial standard. The drug content of each individual preparations of 5-fluorouracil were found to be within the limits of 98-101% indicated that the drug content test complies with the official compendial tests for tablets as per I.P (I.P, 2010). The thickness of the tablets varied depending on the weight of each tablet. The hardness of all the formulations was found to be in the range of 5.5 to 6 kg/cm^2.

Friability is a measure of the ability of the tablet to withstand abrasion during packaging, handling and transportation. It was observed that the friability values of the formulations were <0.5%. The prepared 5-fluorouracil gum karaya based matrix tablets were swollen in distilled water; the swelling index was studied to know the influence of polymer swelling on drug release. Formulations FGK5 showed maximum swelling index (1.79) in pH 7.4 phosphate buffer. This may be due to high concentration of polymer used for the matrix tablets formulation.

Table 5: Tableting properties of 5-fluorouracil colon matrix tablets

Formulae code	Uniformity of weight [a] (%)	Drug content [b] (%)	Hardness [e] (kg/cm^2)	Thickness [b] (mm)	Friability [d] (%)	Swelling Index[e]
FGK 1	1.74	99.12±1.35	5±0.50	3.3±0.12	0.24	0.82±1.20
FGK 2	1.98	98.25±1.10	5±0.72	3.7±0.09	0.38	1.05±0.15
FGK 3	2.14	98.96±1.20	5±0.48	4.0±0.11	0.45	1.23±1.00
FGK 4	2.30	98.78±1.92	5±0.82	4.1±0.03	O.21	1.66±0.25
FGK 5	2.13	98.19±1.45	5±0.61	4.2±0.15	0.29	1.79±0.45
FGK6	1.38	98.72±1.32	5±0.59	4.2±0.32	0.24	1.62±1.30
FGK7	2.49	99.22±1.02	5±0.65	4.4±0.22	0.38	1.72±1.12
FGK8	2.34	98.61±1.22	5±0.78	4.2±0.10	0.45	1.60±0.52
FGK9	2.13	98.72±1.62	5±0.57	4.4±0.06	O.21	1.70±1.15
FGK10	1.91	98.27±1.25	5±0.77	4.2±0.21	0.2	1.63±0.31
FGK11	1.43	99.08±0.22	5±0.45	4.4±0.19	0.3	1.75±1.15
FGK12	2.30	98.51±1.15	5±0.88	4.2±0.34	0.25	1.66±1.30
FGK13	2.04	99.11±1.25	5±0.75	4.4±0.09	0.59	1.71±1.12
FGK14	1.51	98.18±1.25	6±0.10	4.6±0.14	0.62	1.76±0.52
FGK15	2.74	97.79±1.25	5±0.75	4.2±0.22	0.19	1.82±1.15

a: mean±% deviation, n=20; b: mean ± s. d., n=10; c: mean, n=5; d: Tablets equivalent to 6.5 g.; e: mean± s.d., n=3

Reproducibility of method:
Tablet formulations FGK4 prepared under similar conditions were evaluated for tableting characteristics. No differences were observed between friability, hardness and weight variation as shown in **Table 6.**

Table 6: Reproducibility of wet granulation method on formulation FGK4

Tableting characteristics	FGK4		
	Batch I	Batch II	Batch III
Uniformity of weight[a] (%)	2.14	2.15	2.12
Drug content[b] (%)	98±1.49	98±1.09	99±1.19
Hardness[c] (Kg/cm^2)	5±0.50	5±0.51	5±0.50
Friability[d] (%)	0.30	0.29	0.25

***In vitro* dissolution studies of 5-fluorouracil colon matrix tablets:**
The prepared colon matrix tablet formulations of 5-fluorouracil FGK1, FGK2, FGK3 with 1:0.25, 1:0.50 1:0.75 drug-polymer ratio showed 100% drug release in 6, 8, 16 hrs which was less time than the proposed time (24 hrs) and FGK4 formulation with 1:1 showed 100% drug release in 28 hrs and FGK5 with 1:1.5 ratio showed 100% drug release in 36 hrs respectively. The results are shown in **Fig.1**.
The results indicated that the percentage drug release of 5-FU depends on the concentration of gum karaya used in the tablet preparation. Formulations FGK4 showed 100% drug release within 28 hrs and FGK5 showed maximum swelling index, they released 100% drug over a period of 36 hrs. The higher the concentration (more than 1:1) of the gum, drug release decreased due to the rigidness of polymer, slow diffusion and erosion. As a result of increasing the polymer concentration swelling index of matrix tablets was also increased which may help in increasing the diffusion of drug at a faster rate up to some extent. However, this may even retard the drug release due to increase in the diffusion path length due to high swelling nature of polymer at higher concentrations.
Hence, it was decided to incorporate the channeling agents into formulation FGK6 to FGK15 for achieving required percentage of drug release in 24 hrs.

Influence of channeling agents on drug release from 5-fluorouracil colon matrix tablets:
To select suitable channeling agent a preliminary study was made by using varying concentrations polymer-channeling agent (1:0.25 and 1:0.50) of insoluble and erodible channeling agents microcryalline cellulose (MCC) and dicalcium phosphate (DCP) and soluble channeling agents lactose and mannitol.
Formulations FGK6 to FGK13 showed 86-87% drug release for insoluble channeling agents MCC, DCP and 88-94% for soluble channeling agents mannitol and lactose. Enhanced drug release with the channeling agent was observed when compared to earlier formulations (FGK1 to FGK5). The channeling agents containing formulations of 5-fluorouracil could be able to control the drug release in the period of 24 hrs. Among all the channeling agents lactose (1:0.25) showed 93-94% of drug release in 24 hrs for both the drugs. Hence, these formulations were selected for further study.
In order to determine the optimum concentration of drug-polymer-channeling agent ratio further formulations FGK14 and FGK15 were prepared in the ratio of 1:1.25:0.25 and 1:1.5:0.50 and tested for *in vitro* drug release. Among all the channeling agents lactose (1:1.25:0.25) showed 96% of drug release in 24 hrs for both the drugs. Hence, these formulations were selected for further study.
The formulations FGK14 with 1:1.25:0.25 (drug-polymer-excipient) ratios showed 93%, 96% and FGK15 with 1:1.5:0.50 showed only 80% of drug release in 24 hrs for both the drugs. This might be due to more polymer concentration used for matrix tablets. It was clearly evident from the *in vitro* release data that upon increasing the gum karaya minimized the drug release. The results are shown in **Figs**.**2**
The results indicated that the formulations FGK4 released 100% of drug in 28, 32 hrs which was more time than the required period (24 hrs). FGK13, FGK14 could able to released 93-96% of drug in 24 hrs. Formulations FGK13, FGK14 showed 94-96% drug release with channeling agents in 24 hrs. As the formulations containing lactose as channeling agent could release more than 90% of drug in 24 hrs, these formulations were further subjected for drug dissolution in a medium of phosphate buffer pH 6.8 containing rat caecal content to evaluate the microbial degradation of gum karaya by intestinal microflora for releasing the drug.

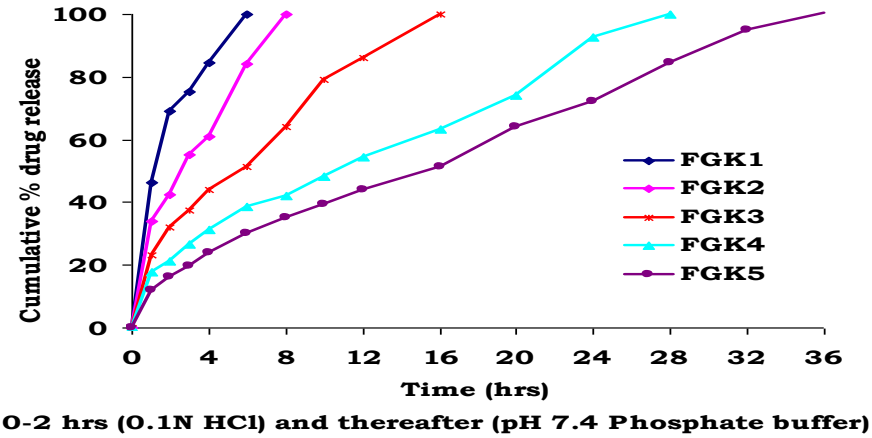


Fig.1: Dissolution profiles of colon matrix tablets of 5-fluorouracil

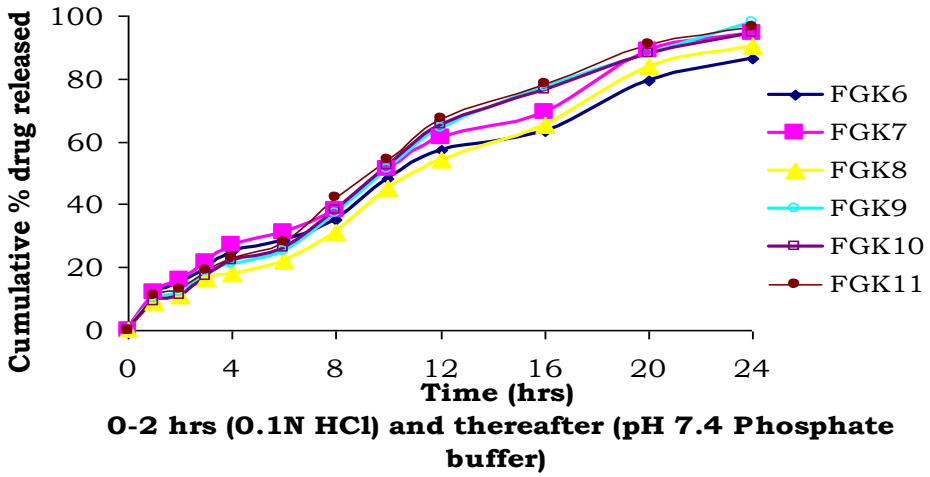


Fig.2: Dissolution profiles of colon matrix tablets of 5-fluorouracil prepared with channeling agents (DCP, Mannitol and MCC)

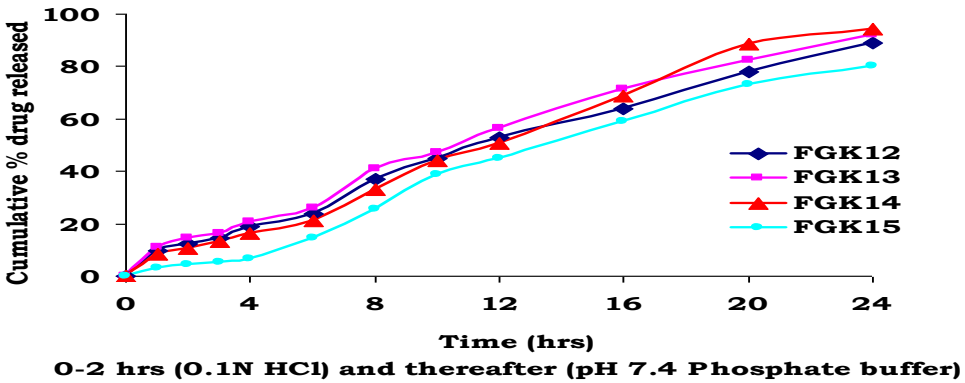


Fig.3: Dissolution profiles of colon matrix tablets of 5-fluorouracil prepared with lactose

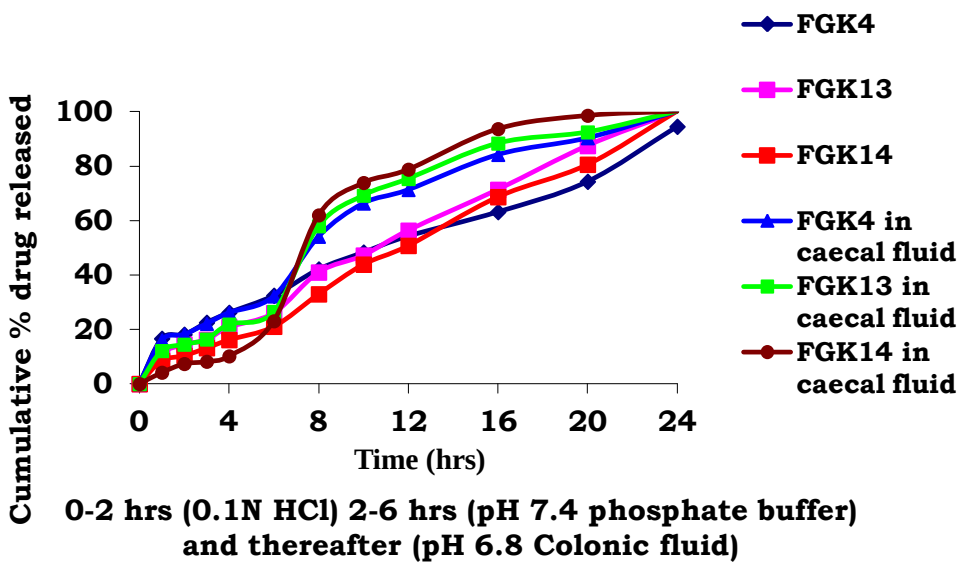


Fig. 4: Dissolution profiles of matrix tablets of 5-fluororacil in rat caecal fluid

***In vitro* release of 5-fluorouracil colon matrix tablets in the presence of rat caecal contents:**

In vitro drug release studies of 5-fluorouracil formulations FGK4, FGK13 and FGK14 were carried out in colonic fluid (4% w/v rat caecal content in phosphate buffer pH 6.8). The above said formulations selected as optimized because FGK4 released 92.5% of drug without channeling agent in 24 hrs compared to other formulations which extended the release up to 36 hrs. FGK13 and FGK14 released 91% of drug with lactose as channeling agent in the dissolution period of 24 hrs.

At the end of 24 hrs dissolution study in colonic fluid, formulations of 5-flurouracil released 95% for FGK4, 97% for FGK13 and 100% for FGK14. The results are shown in **Fig. 4.** It was evident from *in vitro* drug release data that the formulations FGK14 in caecal content medium released 100% of drugs during the dissolution testing period of 24 hrs.

The higher drug release in rat caecal medium was due to microbial degradation of gum karaya present in the matrix tablet by intestinal microflora. It was evident from the results that the polymer weights used for tablet had a marked effect on drug release in the rat caecal fluid. As the polymer ratio increased degradation of gum karaya in rat caecal medium was also increased this caused an increment of drug release from the formulations.

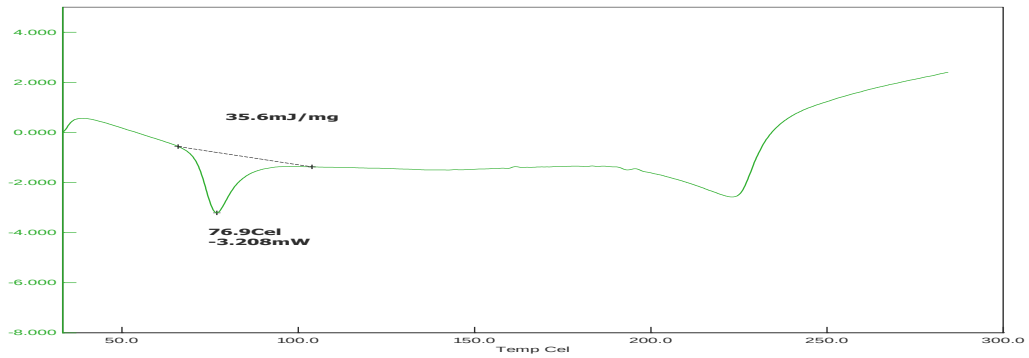
Drug-polymer interaction studies:

The drug polymer interactions were studied by using differential scanning calorimetry (DSC), Fourier transformed infrared (FTIR) spectroscopy and x-ray diffraction (XRD) studies.

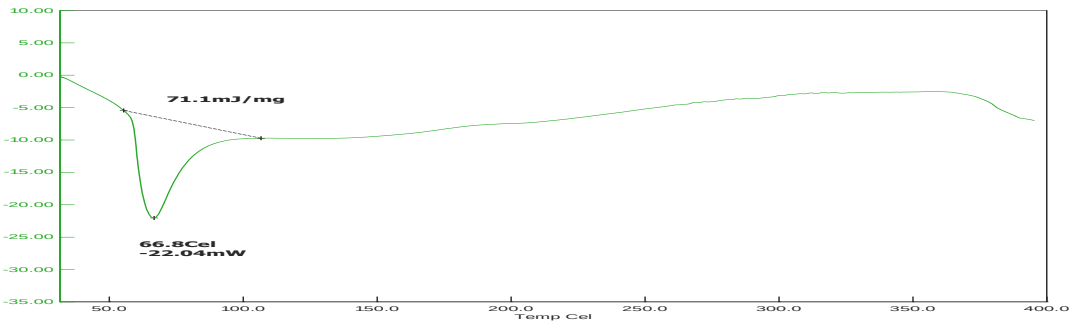
Differential scanning calorimetry (DSC):

The pure drugs, pure polymers and selected formulation (FGK14) used in this study. The results are shown in **Fig. 5.** Thermogram of 5-fluorouracil showed a single sharp endothermic peak at 282.16°C due to melting (with decomposition) of 5-fluorouracil in the temperature range of 282 to 286°C, by removal of the moisture from the pure drug. DSC thermogram of gum karaya showed endothermic peaks at 91.6°C and 316°C. The first peak was assigned to the loss of water because polysaccharides usually have a strong affinity for water and therefore may be easily hydrated. The second peak due to the thermal decomposition of gum karaya. The decomposition temperature of gum karaya was found to be 316°C. This result indicated that gum karaya exists as a stable in thermal analysis. The DSC thermogram of selected formulations showed characteristics endothermic peaks of drug as well as polymer which indicated that there was no physico-chemical interaction or complexation between drugs and polymer.

a) 5-Fluorouracil



(b) Gum karaya



(c) Tablet FGK14

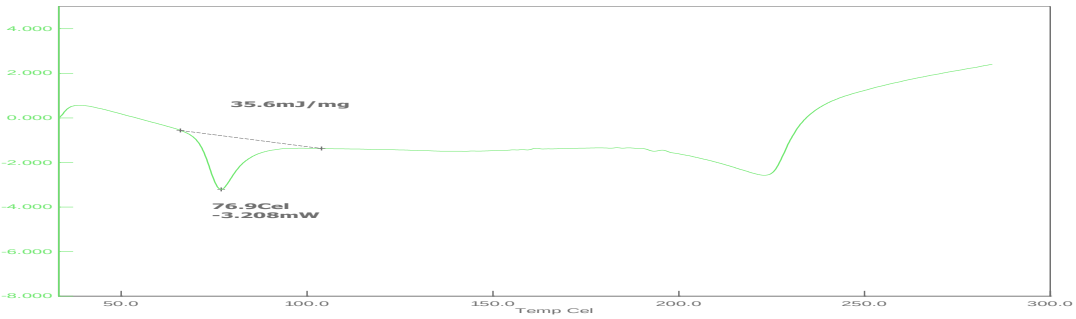


Fig. 5: DSC thermogram of (a) 5-fluorouracil (b) gum karaya (c) Tablet FGK14

Powder x-ray diffraction (XRD) studies:

XRD analysis was applied to detect the crystallinity of the 5-fluorouracil, gum karaya and selected formulations (FGK14). The X-ray diffractograms are shown in **Fig. 6.** The XRD of 5-fluorourail exhibited sharp peak indicating the crystalline nature.Gum karaya XRD showed five sharp reflections at 10.4°, 20.8°, 30.2°, 34.1° and 41.2°. X-ray diffraction exposed the characteristics more clearly due to the different arrangements adopted by these polymorphs. The XRD of gum karaya also exhibited well resolved and intense peaks while a broad diffuse scattering and less intense peaks were found at 10.4° and 20.8°. This indicated that gum karaya is a partially amorphous because of its anti parallel compact structure. However the intense and sharp peaks of drug were not seen in the XRD pattern of selected formulations as the area under the peaks is very small hence, it was concluded that the selected formulations are partially amorphous rather than crystalline nature which may be due to compression.

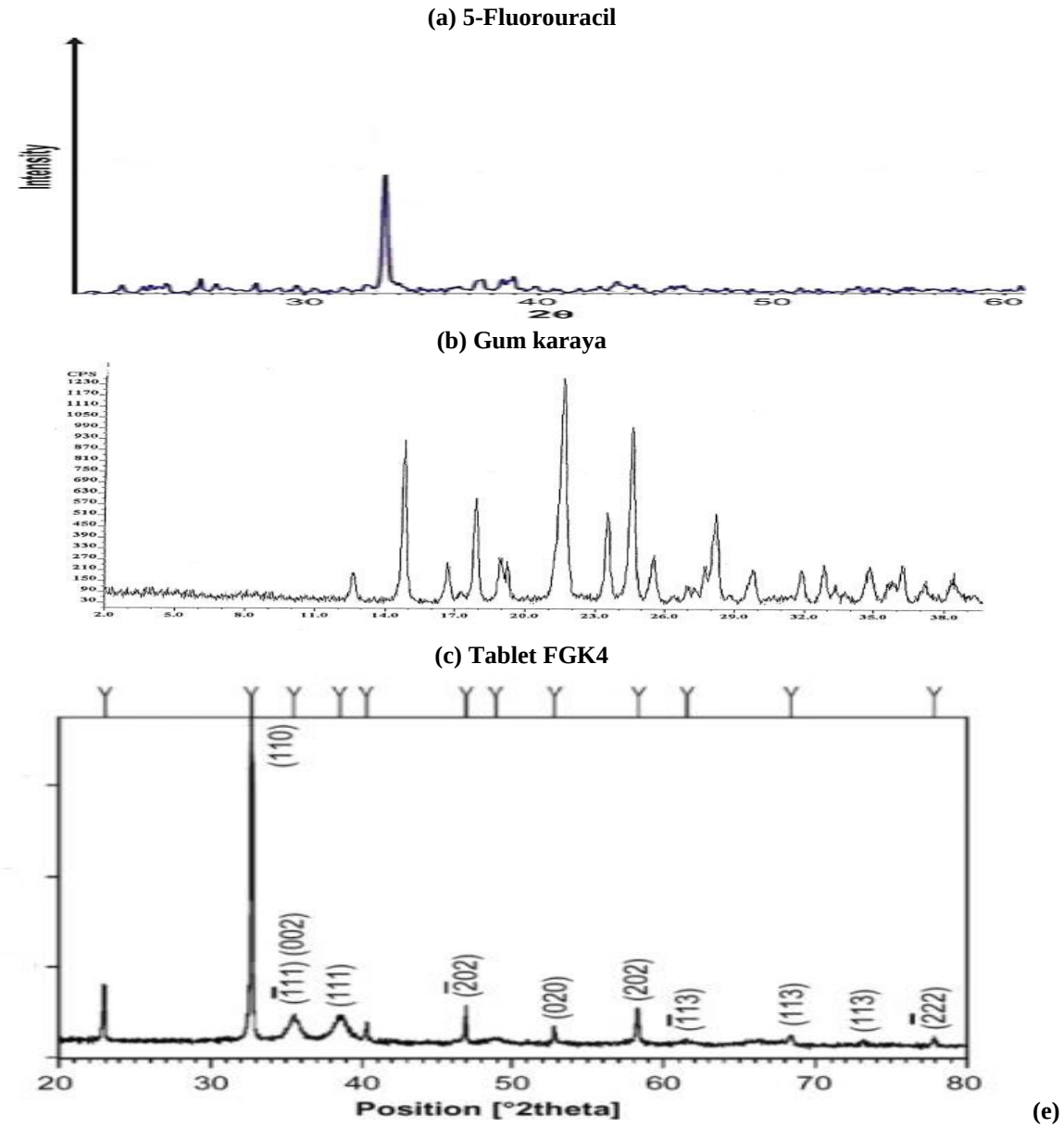


Fig. 6: X-ray diffractograms of (a) 5-fluorouracil (b) gum karaya (c) Tablet FGK14

Fourier transformed infrared (FTIR) spectroscopy studies:

The infrared absorption spectrum of pure 5-fluorouracil, gum karaya and selected formulation (FGK4) analyzed using Perkin Elmer 841 FTIR spectrophotometer and are shown in **Fig.** 7**.** FTIR spectra of 5-fluororuacil showed bands at 3053 cm^{-1}, 3014 cm^{-1} and 2825 cm^{-1} are attributed to both aromatic and aliphatic C−H stretching vibrations. A band at 1726 cm^{-1} represents the imide group stretching of heterocyclic ring. A band at 1661 cm^{-1} is due to the tertiary amide group stretching vibration. N−H bending vibration was observed at 1517 cm^{-1}. A band at 1236 cm-1 shows C−N stretching vibrations. The C-F stretching band was observed at 806 cm^{-1}. The spectra of gum karaya a single band was observed in spectrum at 3441.56 cm^{-1} which is commonly assigned to the stretching of the CO group hydrogen bonded to amide group of the neighboring intra sheet chain. The band at 1430 cm^{-1} and a distinct band at 1416 cm^{-1} were also occurred in the spectrum. The band due NH stretching at 3264 cm^{-1} and 3107cm^{-1} can be seen clearly these bonds assigned to CO-NH intermolecular bonding and H bonded NH group. OH out-of plane bending at 703 cm^{-1} and NH out-of plane bending at 750 cm^{-1} can be observed in the spectrum. This is due to a relatively low crystalline and loosely ordered structure showing weaker inter and intramolecular hydrogen bonding in gum karaya. FTIR spectra of 5-fluorouracil, and gum karaya were compared with selected formulations spectra there was no change in the bands. This was further confirmed that the integrity of pure drugs and their compatibility with polymer as well as matrix tablets.

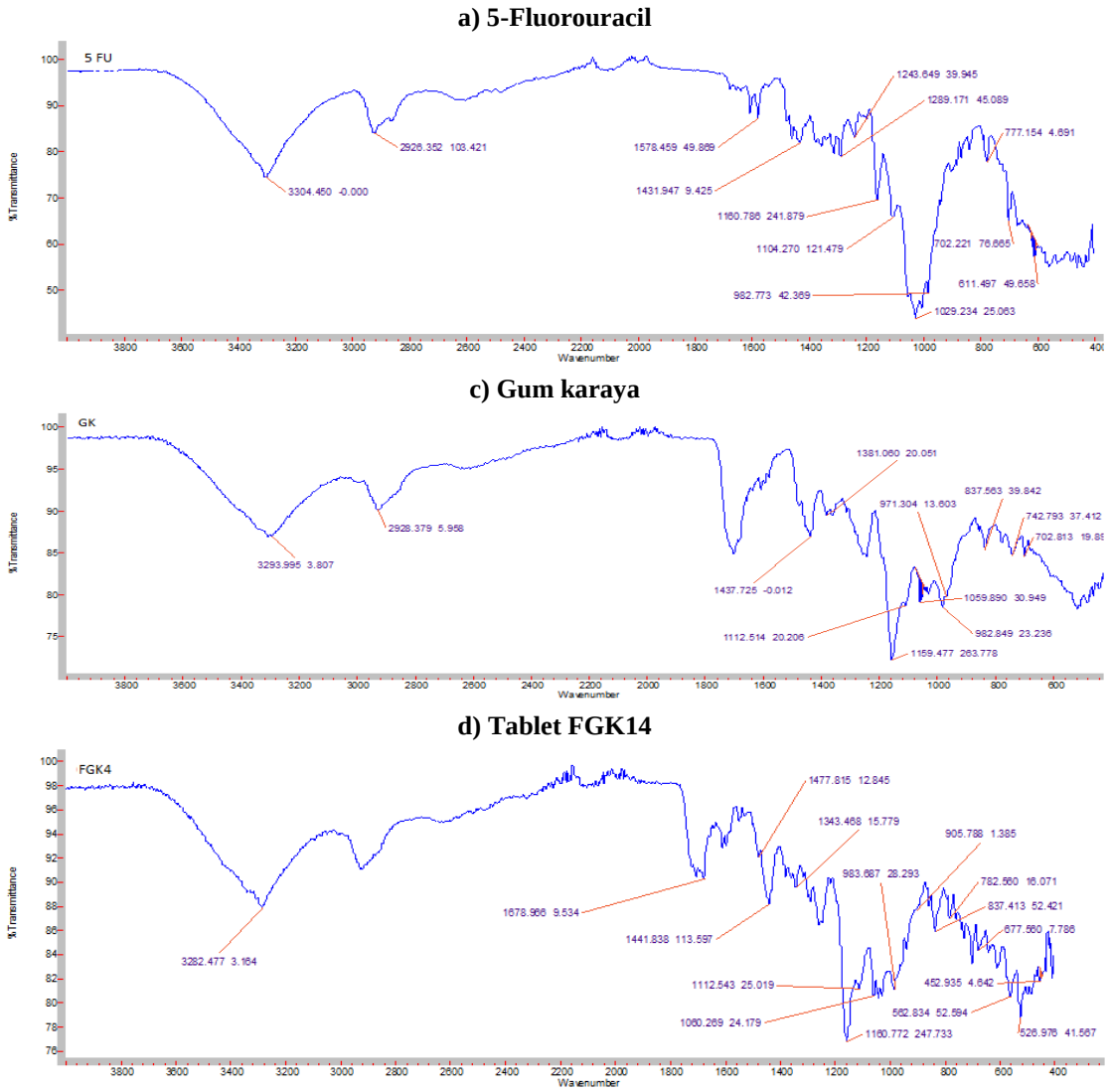


Fig. 7: FTIR Spectra of (a) 5-fluorouracil (b) gum karaya (c) Tablet FGK14

Drug release kinetics and mechanism of the colon matrix tablets of 5-fluorouracil:

The dissolution data was fitted to zero order and first order for establishing the rate of release of drug. The mechanism of drug release was tested by fitting the data to Higuchi, Hixson-Crowell and Korsmeyer-Peppas equations. The mathematical treatment for the data was done for the entire time period as well as for the individual buffer time periods i.e. 0-2 hrs in 0.1N HCl and from 2 hrs to the end of dissolution in pH 7.4 phosphate buffer. However, no significant changes in the order of release or mechanism were observed for the individual treatments and hence the data for the entire time period was presented. The correlation coefficient values were presented and no graphs were presented in the thesis.

The correlation coefficient values for zero and first order along with their release rate constants for formulations FGK1 to FGK15 are shown in **Table 7.** The correlation coefficients (r) values of 5-fluorouracil formulations, FGK1 to FGK5 for zero order were found to be lower (0.8272 to 0.9713) than that of first order (0.9763 to 0.9948) indicating that they followed first order. Formulations FGK6 to FGK12 followed zero order due to higher correlation coefficient values (0.9730 to 0.9878) compared first order correlation coefficient values (0.9491 to 0.9656). However in FGK13 to FGK15 no significant difference was observed between zero order (0.9615to 0.9708) and first order (0.9703 to 0.9852) release kinetics. This may be due the higher concentration of channeling agent, lactose present in the formulation which is dissolving during the dissolution and creating pores for the penetration of the dissolution medium into the core of the matrix tablet thereby improving the dissolution of the drug.

Table 7: Zero and first order release rate constants and correlation coefficients (r) of 5-fluorouracil colon matrix tablets

Formulae Code	Zero order		First order	
	K_0 (%h^{-1})	r	k_1 (h^{-1})	r
FGK1	14.9	0.8272	0.10	**0.9790**
FGK2	11.36	0.9420	0.12	**0.9763**
FGK3	5.76	0.9503	0.10	**0.9919**
FGK4	3.21	0.9615	0.06	**0.9775**
FGK5	2.60	0.9713	0.07	**0.9948**
FGK6	3.50	**0.9775**	0.08	0.9594
FGK7	3.86	**0.9799**	0.09	0.9603
FGK8	3.85	**0.9878**	0.10	0.9491
FGK9	4.20	**0.9806**	0.10	0.9635
FGK10	4.12	**0.9730**	0.10	0.9589
FGK11	4.22	**0.9753**	0.09	0.9599
FGK12	3.46	**0.9830**	0.09	0.9656
FGK13	4.03	0.9708	0.11	0.9852
FGK14	5.73	0.9697	0.09	0.9703
FGK15	9.23	0.9615	0.14	0.9783

The drug release mechanism was also studied for the formulations of 5-fluorouracil by using model dependent methods. The correlation coefficient (r) values of Higuchi, Hixon-Crowell and exponential values (n) of Korsmeyer-Peppas models are represented in **Tables 10.** Higuchi correlation coefficient (r) values were higher (0.9273 to 0.9925) for all 5-fluorouracil formulations except FGK13 indicating that the drug release mechanism followed diffusion i.e. the polymer swelling and dissolution governs the drug release from the matrix. Further application of Korsmeyer-Peppas model indicated that the exponential 'n' value was found to be more than 0.45 indicating that the release mechanism followed anomalous (non-Fickian) diffusion.

The correlation coefficient values were more favourable for Hixon-Crowell model compared to Higuchi for formulations FGK13 and FGK14 indicating the dominance of erosion model. This may again attributed to higher concentrations of lactose present in the formulation which may be causing pores in the matrix for penetration of dissolution fluid into the matrix. Peppas 'n' value also indicated the dominance of anomalous diffusion for these formulations.

Table 10: Correlation coefficient (r) and Peppas diffusion exponent (n) values of 5-fluorouracil colon matrix tablets for release mechanism

Formulae Code	Higuchi equation	Hixson-Crowell equation	Korsmeyer-Peppas Model	
	r	r	r	n
FGK1	**0.9925**	0.9643	0.8285	0.46
FGK2	**0.9850**	0.9339	0.7463	0.52
FGK3	**0.9785**	0.9631	0.7999	0.56
FGK4	**0.9732**	0.9243	0.7299	0.53
FGK5	**0.9846**	0.9437	0.7828	0.50
FGK6	**0.9635**	0.9299	0.8253	0.52
FGK7	**0.9608**	0.9373	0.8211	0.54
FGK8	**0.9273**	0.9053	0.8903	0.46
FGK9	**0.9348**	0.9264	0.8811	0.45
FGK10	**0.9437**	0.9407	0.8879	0.45
FGK11	**0.9476**	0.9392	0.8668	0.48
FGK12	**0.9503**	0.9348	0.8253	0.52
FGK13	0.9318	**0.9415**	0.8211	0.54
FGK14	0.9627	**0.9906**	0.8993	0.65
FGK15	**0.9424**	0.9382	0.8811	0.48

The drug release kinetics and mechanisms were also established for the optimized formulations (FGK4, FGK13 and FGK14) dissolution in rat caecal content and the results are shown in **Tables 11** and **12**. The optimized formulations followed first order kinetics. FGK4 followed anomalous diffusion, whereas the formulations prepared with lactose as channeling agent followed erosion model. This may be due to degradation of gum karaya by the colonic microflora and hence the swelling ability of the polymer was lost.

Table 11: Zero and first order release rate constants and correlation coefficients (r) of colon matrix tablets in rat caecal fluid

Formulae Code	Zero order		First order	
	k_0 (%h^{-1})	r	k_1 (h^{-1})	R
FGK4	4.05	0.9298	0.06	**0.9470**
FGK13	4.38	0.9102	0.09	**0.9330**
FGK14	4.97	0.8870	0.13	**0.9770**

Table 12: Correlation coefficient (r) and Peppas diffusion exponent (n) values of colon matrix tablets for release mechanism in rat caecal fluid

Formulae Code	Higuchi model	Hixson Crowell model	Korsmeyer-Peppas model	
	r	r	r	n
FGK4	**0.9514**	0.8769	0.9558	0.54
FGK13	0.9197	**0.9529**	0.9346	0.62
FGK14	0.8780	**0.9659**	0.9233	0.69

CONCLUSION:

The applicability of gum karaya for colon specific drug release of 5-fluorouracil was studied successfully and optimum *in vitro* drug release over a period of 24 hrs was obtained by incorporating soluble channeling agent lactose. And prepared 5-Fluoruracil tablets exhibited good tabletting characteristics. The colon matrix tablets exhibited good drug release characteristics even in phosphate buffer of pH 6.8 containing rat caecal content in which the microbial degradation of gum karaya by rat intestinal microflora was observed. The optimum drug-gum karaya ratio (1:1.25) was found to be the same indicating the consistency of the polymer for controlling the drug release. The release mechanisms were also not effected significantly for selected drug. Hence it can be concluded that the selected polymer, gum karaya can be studied in the design of colon drug delivery systems.

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