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Colon Specific Matrix tablets of Oxaliplatin combined with Curcumin: Development and Evaluation

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ABSTRACT

Tablets of Oxaliplatin combined with Curcumin was prepared for colon specific delivery using guar gum as matrix carriers in varying concentrations from 40% to 65%. The drug concentration in the tablet was estimated by the newly developed and validated UV derivative spectroscopy method. *In vitro* drug release profile was studied in changing media method (0.1N HCl, phosphate buffer media, pH 7.4 and simulated colon fluid containing phosphate buffer pH 6.8 added with rat ceacal content). The drug release profiles from PB7.4 and simulated colon fluid were found to be dependent on the gaur gum concentration. Matrix tablets of Oxaliplatin and Curcumin combination showed ~65% of Oxaliplatin and 37% of curcumin release. The colon tissue homogenate studies conducted after oral administration of the optimized tablets showed the recovery of 167.5µg Oxaliplatin and 80µg. curcumin. X-ray Images of matrix tablets containing barium sulphate in Rabbit showed tablets to be intact in small intestine (3 hours after administration) but were diffused and spread out in large intestine and colon later confirming enzyme mediated erosion of the tablet in these regions.

Keywords- Oxaliplatin, Curcumin, Matrix tablets, Guar gum, Colon specific delivery, Controlled release.

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INTRODUCTION

Colorectal cancers are thought to arise from adenomatous polyps in the colon. These mushroom-like growths begins as a non-cancerous polyp on the lining of the colon or rectum that can become cancerous[1] .The risk factor for colorectal cancer includes Heredity and family history [2], Personal medical history[3], Diet[4], Alcohol and smoking[5], etc. The treatment that are generally adopted for colon and rectal cancer includes Surgery, Radiation therapy, Chemotherapy, targeted therapy, depending on the stage of the cancer, two or more of above treatment can be combined at the same time or used one after the other [6]. Oxaliplatin (OXP) is the third generation analogue of cisplatin which is recommended for the treatment of colon cancer. The most successful combination of oxaliplatin is with other drugs such as irinotecan (CPT11), for which response rates up to around 60% was reported .[7]

Many epidemiological studies reports the efficacy of non steroidal anti inflammatory drugs (NSAIDs) in inhibiting a variety of cancers including colon, skin, bladder etc [8]. They act by inhibition of COX-2 enzyme which gets up-regulated in various malignancies[9]. Among them, investigations on the improvement of the anticancer activity of oxaliplatin when combined with diclofenac sodium is well reported[10]. The effects of curcumin (CRM), derived from turmeric, has been widely investigated for anticancer properties *in vitro*. With growing evidence that it may provide antitumor efficacy, particularly when targeted against colorectal cancer, either alone or in Combination, it is worth investigating the delivery modes of OXP and CRM in combination[11,12].

Site specific delivery of drugs to colon has been investigated to reduces not only the systemic side effects but also provide safe therapy for colon cancer. Obviously, for colon delivery, oral route is the route of choice among the patients because of ease of administration with many advantageous for the treatment of diseases associated with the colon such as amaebiasis, ulcerative colitis, and colorectal cancer [13]. Guar gum is being used to deliver drug to colon due to its susceptibility to microbial degradation in the large intestine and drug release. Colonic bacteria are fundamentally *anaerobic* in nature and are involved in the fermentation of carbohydrates and proteins that have escaped digestion in the stomach and small intestine[14]. These anaerobic bacteria are responsible for the degradation of guar gum in the colon[15]. Many reports suggests the use of guar gum for colon specific drug delivery system for drugs like salicylic acid[16], Dexamethasone etc[17]. Gaur gum matrix tablet of Dexamethasone degraded completely in the colon and could release 72-82 % of the drug in the colon[18]. Combinations of guar gum with other

polymers are also studied for colonic delivery. Matrix tablet of chitosan and guar gum of Diltiazem hydrochloride coated with inulin followed by shellac showed that the tablets coated with inulin and shellac have controlled the drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment[19].

The objective of the present study was to develop and to evaluate guar gum oral matrix tablet for colon specific delivery of OXP combined with CRM. A simple and precise simultaneous analytical method was developed to estimate these drugs in tablet, dissolution media and in colon tissue homogenate using derivative spectroscopy. Optimized matrix tablets were evaluated for colon delivery in-vivo in normal rabbit animal model. Intactness of the trablets during intestinal transit was tested in rabbits by x-ray imaging.

MATERIAL AND METHODS

Materials

The Oxaliplatin pure sample was obtained from Panacea Biotech, Mohali, Punjab (India). Curcumin was obtained from Hi media laboratories Pvt. Ltd. Mumbai (India). Talc, Magnesium stearate, starch, Microcrystalline cellulose etc. were obtained from CDH Analytical Reagents New Delhi.

Methods

Simultaneous estimation of OXP and CRM in combination:

Preparation of standard solutions of drugs:

OXP (20 mgs) was dissolved in 20ml of 0.1N HCl to produce a stock solution (1000 µg/ml) and was suitably diluted with 0.1N HCl to prepare aliquots of test solution in the concentration range between 20 to 200µg/ml. Similarly, stock solutions and test solutions of OXP in phosphate buffer (pH 7.4) and phosphate buffer saline (PBS) (pH 6.8) were also prepared. CRM (5 mgs) was weighed and was dissolved in 50ml of methanol to produce a stock solution of 100 µg/ml. Stock solution was suitably diluted with 0.1N HCl to prepare aliquots of test solution in the concentration range between 2 to 20µg/ml. Similarly, stock solutions and test solutions of CRM in phosphate buffer (pH 7.4) and phosphate buffer saline (PBS) (pH 6.8) were prepared. Stock solutions containing OXP-CRM combination was prepared by mixing 50 ml of individual stock solutions of OXP and CRM. Test solutions were prepared by dilution with the respective solvents as indicated above.

Simultaneous estimation of drugs in combinations:

The zero-order absorption spectrum of OXP-CRM test solutions was taken in UV/Vis

spectrophotometer in the wave length range between 200-400 nm. Since the spectrum displayed overlapping absorptions in the region, it was difficult to determine OXP in the presence of CRM. Hence, the zero order spectrum was converted to first order derivative spectra using delta lambda-4 software at scaling factor of 10, to find out the zero crossing wave lengths of OXP and CRM (Figure 1). The zero cross wave lengths observed were different with different media and is tabulated in Table 1.

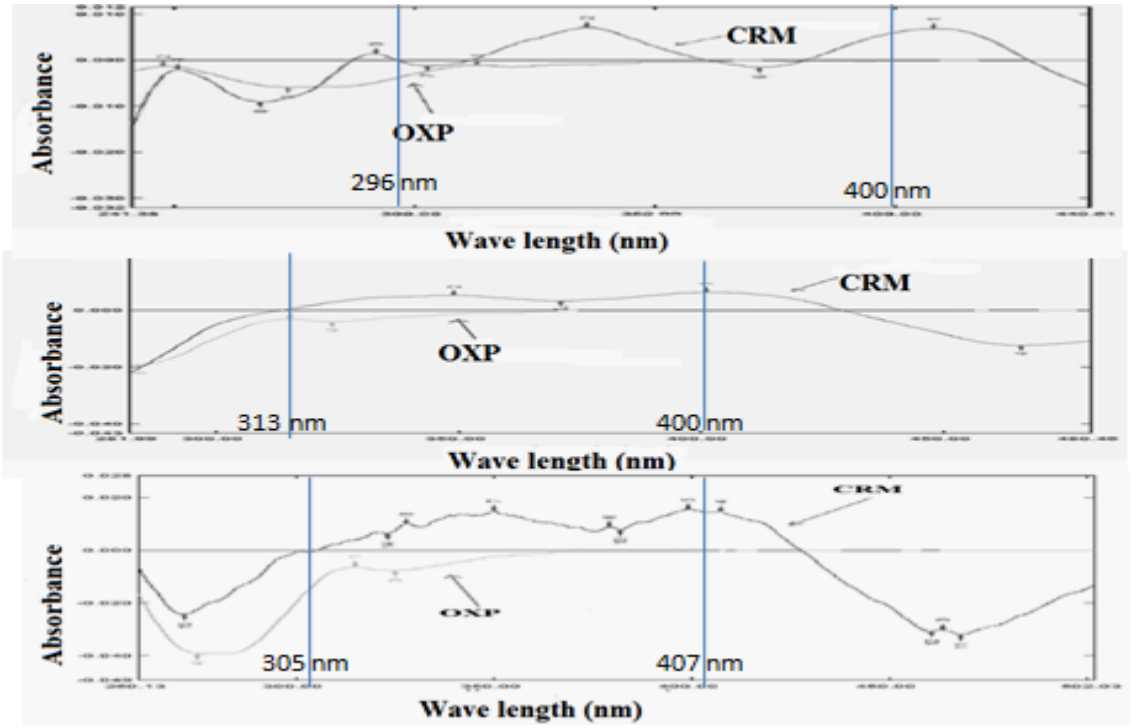


Figure 1: **Zero cross over spectra of OXP and CRM combination in (a) 0.1 N HCl (296nm and 400 nm for OXP and CRM respectively), (b) PBS pH 7.2 (313 nm and 400 nm for OXP and CRM respectively) and (c) PBS pH 6.8 in presence of cecal content (305 nm and 407 nm for OXP and CRM respectively).**

Accordingly, first derivative spectra of different concentrations of OXP + CRM were taken for the generation of calibration curve (Figure 2). Regression analysis was carried out for the data obtained to determine slope, intercept and correlation coefficient.

Analytical method validation:

The analytical method for the simultaneous estimation of OXP with CRM was Validated. The parameters of linearity, accuracy, inter-day precision, intra-day precision, limit of detection (LOD) and limit of quantification (LOQ) were evaluated to validate the process. Regression analysis of the analytical data was conducted to obtain regression equation and correlation co-efficient (r^2). Accuracy of the method was determined by the recovery studies conducted with the

prepared tablet formulations containing OXP with CRM by the addition of known quantities of standard drug solution to pre-analyzed samples. Experiments were repeated three times in a day to determine intra-day precision and on three different days to establish inter-day precision. The relative standard deviation (RSD) was calculated for each analysis. LOD and LOQ were calculated by repeating the blank measurements six times at first order λmax determined previously for OXP with CRM.

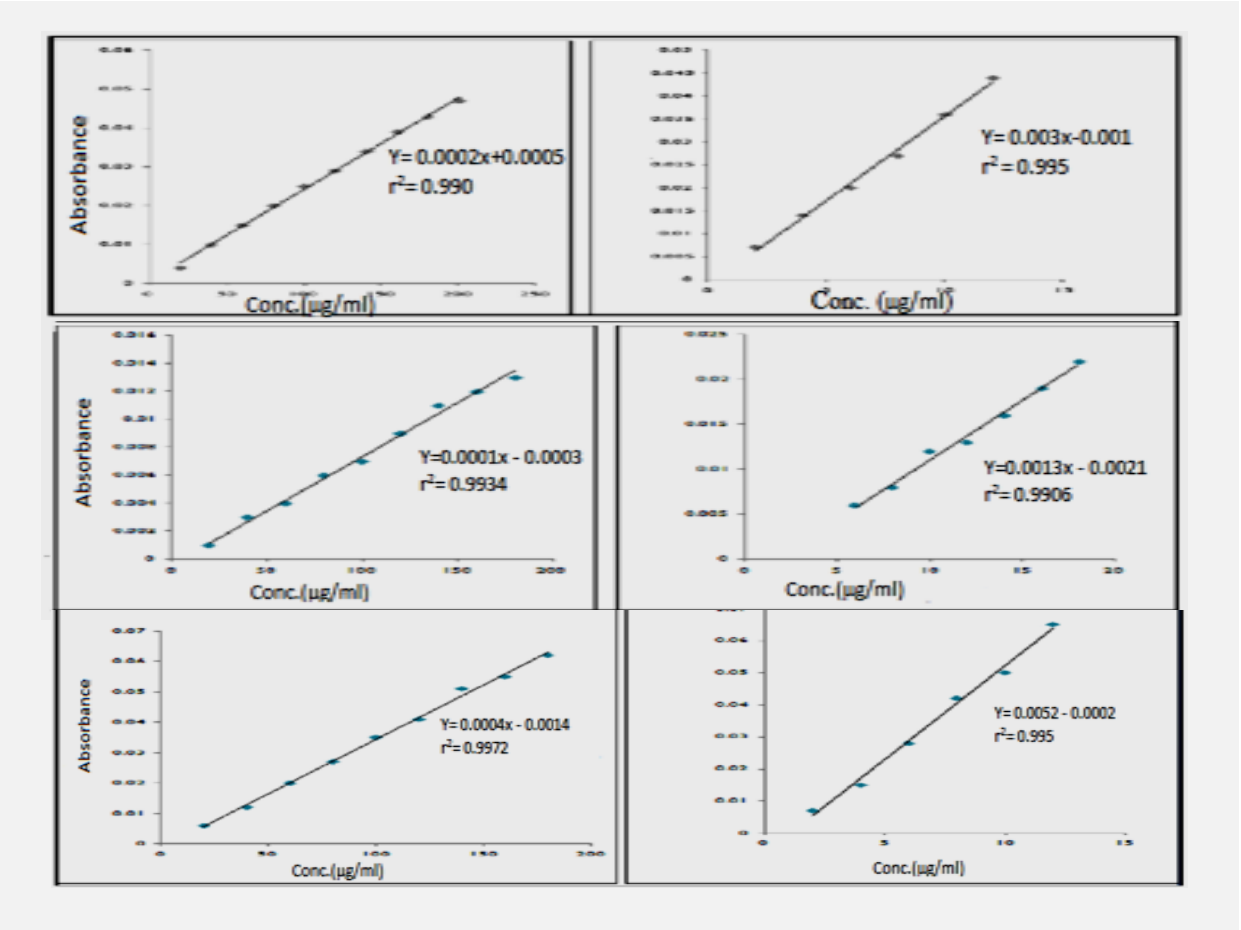


Figure 2: **Calibration curve of OXP (Left) and CRM (Right) for their simultaneous estimation by first derivative spectroscopy in (a) 0.1 N HCl at 296 nm and 400 nm respectively, (b) in PBS pH 7.2 at 313 nm and 400 nm respectively and (c) in PBS pH 6.8 in presence of cecal content at 305 nm and 407 nm respectively.**

Preparation of Matrix Tablets:

Matrix tablet was prepared by wet granulation technique using MCC as diluent, talc and Magnesium stearate as Lubricant[20]. Guar Gum was included in Formulations in various proportions (40 to 65%) to prepare various batches of guar gum matrix tablets of oxaliplatin and curcumin (GG/OC). Firstly, the Guar gum was sieved separately and mixed with drug and MCC.

Curcumin being hydrophobic was added in the form of solution in minimum quantity of absolute alcohol during mixing for uniform distribution. Then the Powder is well blended and then granulated with 10 % (w/v) starch paste. The Wet Mass obtained was passed through a mesh (#16). The Granules obtained after passing the wet mass through the sieve was dried at 60 ^{0}C. The Dried granules were again passed through a mesh (#22). Lubrication was done with mixture of Talc and Magnesium Stearate. The Granules were compressed with 8mm punch using 10 station rotary tablet press (M/s Karnavati Engineering Ltd, Ahmedabad, India).

Evaluation of Matrix tablet

All the Guar gum matrix tablet formulations were evaluated for Weight variation, Hardness and Friability as per pharmacopoeial methods[21]

Drug content uniformity- Five matrix tablets were weighed and powdered quantitatively and mixed in 50ml methanol. The mixture was shaken well and added sufficient methanol to produce 100 ml, mixed well and filtered. Diluted 10 ml of the above solution to 100 ml with methanol. The drug content was estimated by the method described above.

In-vitro dissolution studies

In–vitro dissolution studies were conducted using USP II Dissolution apparatus (paddle type) at 100rpm,in 900 ml of 0.1 N HCL for 2h (average gastric emptying time). Then the medium was replaced with Phosphate buffer (pH 7.4) for 3h (average small intestine transit time). Then the medium was replaced by Phosphate Buffer (pH 6.8) for 19hrs in one set and in the other, the medium was replaced by Phosphate Buffer (pH 6.8) contain 2% w/v rat cecal content. At specified time intervals (2h, 5h, 8h, 12h, 16h, 20h, 25h) 5ml of sample was withdrawn and replaced with 5 ml of respective fresh buffer. The withdrawn sample was analyzed for percent drug content by UV Derivative Spectroscopy method developed individually for both Formulations. Mean results of triplicate measurements and standard deviation were reported.

For rat ceacal content the abdomen of rats were opened, the cecum was traced, ligated at the both ends, dissected and immediately transferred into PB(pH 6.8) previously bubbled with carbon dioxide. This was finally added to dissolution media and study was continued [20]

Colon tissue homogenate studies

The tissue homogenate study for the optimized Guar gum matrix tablet (GG/OC-60) was conducted in New Zealand Rabbits (2 to 3kg). Animals were housed with free access to water and food. The study protocol as approved by Institutional Animal Ethical committee of I.S.F College of pharmacy was followed. The studies were carried out as per the guidelines of council for the purpose of control and supervision of experiment on animals (CPCSEA), Ministry of

social justice and environment, Govt. of India. GG/OC matrix tablet was administered to Rabbits by oral route. After 12hr the rabbits were sacrificed and colon was isolated, homogenized and the homogenate was subjected to extraction and was estimated for the percentage of drugs by UV derivative spectroscopy method as described below.

Estimation of drugs in colon tissue homogenates:

Estimation of Oxaliplatin and Curcumin in colon tissue, were conducted by the first derivative spectroscopic method described above. Rabbit was sacrificed by cervical dislocation and the colon was removed. The colon was washed thoroughly both out side and inside the lumen with phosphate buffer and colon sample was homogenized in Phosphate buffer. One portion was kept aside which served as blank and the other portion was divided in to required number of portions and added with known quantities of both the drug solution separately and stirred well. These suspensions were centrifuged (8000-10000 rpm) for 20 minutes at ambient temperature. After centrifugation, supernatant was transferred into a clean, fresh volumetric flask; volume made up to mark and was estimated by the UV Derivative Spectroscopy method developed individually for both the drugs. Calibration curve was plotted.

Radiographic monitoring of orally administered tablet:

The radio-opaque tablets were prepared using barium sulphate as per the optimized formulation just by replacing Drugs with sufficient quantity (20 mg) of barium sulfate and diluents. The other parameters of tablet formulation were kept constant. The *in-vivo* GIT study was carried out by administering a Barium sulphate tablet using a feed tube to the overnight fasted New Zealand Rabbits (2.5-3.0 kg) and monitoring them through radiological method for 6 hours.

RESULTS AND DISCUSSION

Simultaneous estimation of OXP+CRM in combination:

First derivative spectroscopic method was adopted for the simultaneous estimation of OXP in presence of CRM and visa versa. Zero order spectra of the drug combination showed interference with each other and hence first order derivative spectra (Figure 1) was developed. Zero crossing wave lengths were identified and recorded (Table 1). Calibration curves generated for OXP and CRM estimation in their combination showed linearity with coefficient of determination (r^2) near unity in the concentration range between 50 to 200 µg/ml for OXP and 2 to 12 µg/ml for CRM. Regression parameters are presented in table 1.

Table 1: Summary of validation Parameters for the simultaneous estimation of OXP and CRM by first derivative spectroscopy.

Parameters*	**0.1N HCl**		**PBS (pH 7.2)**		**PBS (6.8) With Colonic fluid**	
	OXP	**CRM**	**OXP**	**CRM**	**OXP**	**CRM**
Zero Cross λ(nm)	296	400	313	400	305.3	407
Linearity Range(μg/ml)	50-200	2-12	50-200	2-12	50-200	2-12
Slope (Mean)	0.00212	0.00308	0.00108	0.00125	0.00408	0.00517
Intercept	+0.0005	-0.001	-0.0003	-0.0021	-0.0014	-0.006
R^2	0.9980	0.995	0.9934	0.9906	0.9972	0.993
Accuracy (% Recovery)	97.347± 2.648	95.437± 2.948	97.84± 3.24	95.06± 1.78	96.89± 3.64	95.75± 2.15
Std Dev.(SD)	0.000264	0.00038	0.00015	0.00031	0.00022	0.00029
RSD	0.1245	0.1222	0.1399	0.2464	0.0529	0.05534
LOD	0.4109	0.4033	0.4617	0.8131	0.1747	0.1826
LOQ	1.2453	1.222	1.399	2.464	0.5294	0.5534
%RSD (Intra day)	0.952	0.988	0.972	1.264	0.926	1.624
% RSD (Inter day)	1.192	1.624	1.534	2.453	1.112	2.824

*n=6

Validation:

Validation parameters determined for the analytical method under different media are tabulated in table 1. The intra-day and inter-day precision of the method was evaluated by means of six determinations at 100% of their respective test concentration. The RSD values for intra-day (n=6) precision were less than 2% except in case of CRM estimations conducted after 12 hours in PBS media. The RSD values for inter-day (n=6) precision were less than 2% in case of OXP but were marginally higher than 2% in case of CRM estimations in PBS media. These results indicate both inter day and intraday precision of the method for the estimation of OXP while, the method was not precise for the estimation of CRM in acidic media and alkaline media after 12 hours due to lack of stability of CRM in pH more than 6.0 for long time. Inter-day precision for CRM in both PBS media (pH 7.2 and pH 6.8) indicate the instability of CRM in these media and hence their absorption reading should be taken on the same day. Accuracy was evaluated by the standard addition method for both the combinations. The mean percentage recovery values were very well within the limits (>95%) for both OXP and CRM. These recovery values indicate the accuracy of the method developed. Linear regression analysis of the analytical data showed very low intercept values (0.005 and zero for OXP and CRM respectively) indicating no interference of the drugs mutually in their estimation.

3.2. Preparation of Matrix Tablets:

Different batches of GG/OC matrix tablets prepared are listed in table 2. Six formulations were

prepared with different concentration of Guar gum ranges from 40 to 65%.

Table 2: Tablet formulation

Ingredients (per Tablet) in mg	GG/OC-40*	GG/OC-45*	GG/OC-50*	GG/OC-55*	GG/OC-60*	GG/OC-65*
Oxaliplatin	20	20	20	20	20	20
Curcumin	20	20	20	20	20	20
Guar gum	80	90	100	110	120	130
MCC	54	44	34	24	14	4
Starch	20	20	20	20	20	20
Magnesium stearate	2	2	2	2	2	2
Talc	4	4	4	4	4	4
Total weight (Theoretical)	200 mgs	200 mgs	200 mgs	200 mgs	200 mgs	200 mgs

***Indicate gaur gum 40%, similarly other batches.**

Evaluation of Matrix tablets:

Pharmacopoeial tests:

The results of GG/OC matrix tablet evaluation parameters are listed in table 3. Weight variation (3.4 to 5.1 %) percentage Friability (< 1%) and drug content (>90%) were in compliance with the standard limits. Tablets being a matrix tablet Hardness was kept high enough (4.4 to5.3 kg/cm^2) to avoid disintegration before reaching colon.

Table 3: Evaluation of various parameters

Formulation	Hardness (kg/cm^2)	Weight Variation %	%Friability	Drug content% (Curcumin)	Drug content% (Oxaliplatin)
GG/OC-40	4.4±0.14	3.4±0.1	0.59±0.01	94.83±1.08	97.53±1.98
GG/OC-45	4.5±0.05	4.1±0.26	0.68±0.01	94.37±1.04	94.56±0.97
GG/OC-50	4.6±0.05	4.3±0.05	0.37±0.015	95.43±1.78	95.06±1.06
GG/OC-55	5.0±0.05	3.9±0.1	0.46±0.01	92.48±0.47	92.63±2.22
GG/OC-60	5.2±0.05	3.4±0.05	0.25±0.015	95.3±0.62	91.66±1.57
GG/OC-65	5.3±0.05	5.1±0.1	0.26±0.005	94.86±0.86	97.37±0.62

In-vitro drug release studies from GG/OC matrix tablets:

GG/OC-40 and GG/OC-45 matrix tablets disintegrated within 6 hours and so were rejected and the remaining tablets (GG/OC-50, GG/OC-55, GG/OC-60 and GG/OC-65) were subjected to in-vitro release studies in changing media with and without cecal content.

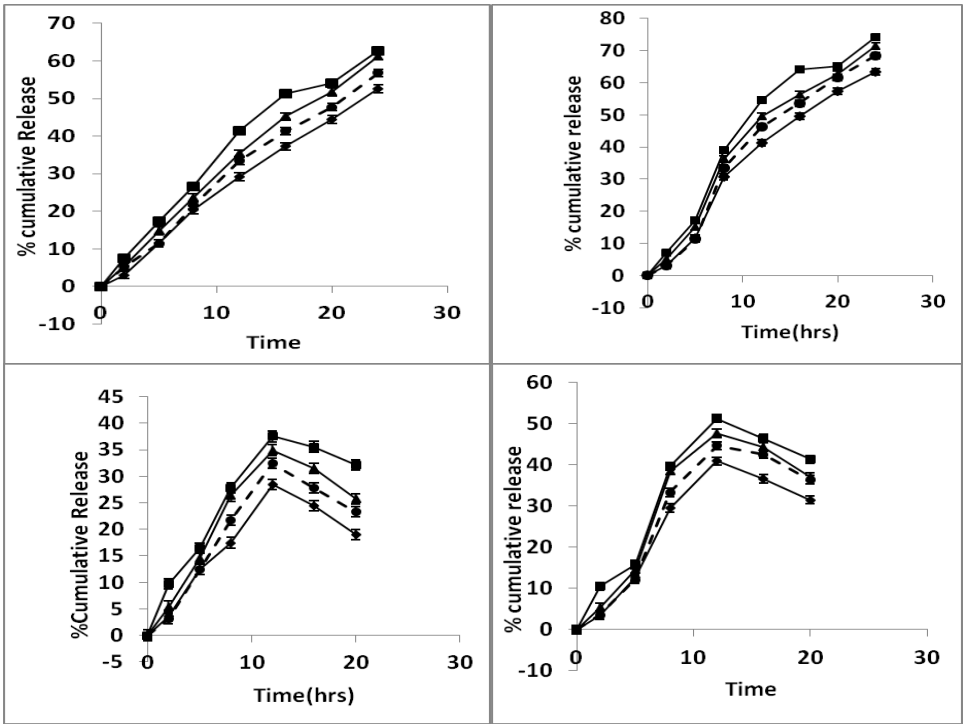
In-vitro Release of Oxaliplatin:

In- vitro dissolution of all formulations was carried out in different medium; 0.1 N HCL for 2hr, Phosphate Buffer (pH 7.4) for 3hr and Phosphate Buffer (pH 6.8) for 19 hr with or without Rat cecal content. Concentration of gaur gum used was from 40%-65% at 6 levels. Selection of gaur gum percentage was made based on the in-vitro drug release data looking in to the following

criteria;

1. Tablet integrity throughout the GI transit up to colon
2. Minimum drug release in stomach and small intestine (First 5 hours)
3. Maximum drug release in colon

GG/OC-40 and GG/OC-45 matrix tablets disintegrated within 6 hours and so were rejected and the remaining tablets (GG/OC-50, GG/OC-55, GG/OC-60 and GG/OC-65) were subjected to in-vitro release studies in changing media with and without cecal content. Release profile of oxaliplatin and curcumin from GG/OC matrix tablets in to the combined media without cecal content and with cecal content are shown in figure 3. In both the cases, tablets containing lower Gaur gum content (GG/OC-50 and GG/OC-55) showed high percentage release in first 5 hours but GG/OC-60 and GG/OC-65 showed convincing release behavior (~10%) in first 5 hours.



Figure–3: *In –vitro* Release of OXP (Upper) and CRM (Lower) from GG/OC-50(■), GG/OC-55(▲), GG/OC-60(●) and GG/OC-65(♦) matrix tablets in to changing pH media without caecal content (Left) and with caecal content (Right). Note the reduction of curcumin concentration after 12 hours due to degradation of curcumin at higher pH.

In-vitro drug release from GG/OC matrix tablets:

Total drug release in the last Phase of 19 hours of release study in media with cecal content was high from GG/OC-60 than GG/OC-65 obviously due to higher resistance for break down and drug release from GG/OC-65 tablets. Hence GG/OC-60 was selected for in-vivo studies. Total

drug release from GC-60 tablets into medium without ceacal content was 56.78 % (Oxaliplatin) and 23.32 % (curcumin) at the end of 24 hrs while with caecal content medium; the release was 64.83% of Oxaliplatin and 36.39% of curcumin in 24 hours. In other words release studies carried out in presence of rat caecal content showed 10% increase in oxaliplatin release and 13% more drug release of curcumin. A similar observation was also reported in case of oxaliplatin release from gaur gum matrix tablet containing oxaliplatin and diclofenac sodium[10] This indicates the importance of the intestinal bacteria and the enzyme they secrete in the degradation of polysaccharide like gaur gum and drug release specifically in colon. In comparison, percentage release of oxaliplatin was higher than that of curcumin in all tablets. This may not only due to low solubility of curcumin which has low bio-availability but also due to its multiple pKa values in aqueous solutions (8.38, 10.0 and 10.2 corresponding to the deprotonation of the three hydroxyl groups (Figure 4)[22]. This makes curcumin less absorbable in lower intestine and colon than in the upper intestine. In addition, Curcumin is unstable in alkaline condition and has been observed that it starts degradation about 12 hours after solution preparation.

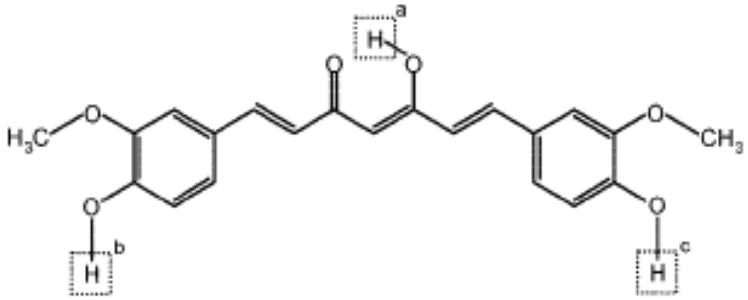


Figure 4: **Chemical structure of the keto-enol form of curcumin. The pKa values at 8.31, 10.0 and 10.2 in aqueous solution correspond to deprotonation of the three hydroxyl groups of curcumin with the (a) enolic and (b and c) phenolic protons highlighted.**

Solubility and Dissolution characteristics of curcumin are an important subject of discussion and have been investigated widely in various media. In addition, instability of curcumin makes the oral delivery much complicated. Undoubtedly, curcumin exhibits extremely low solubility in water and accordingly, its dissolution rate in distilled water has been reported to be about 2.6% in 90 minutes[23]. However, the dissolution of curcumin is pH dependent, having lower solubility in acidic and neutral condition[24]. Dissolution studies conducted in pH 4.5 acetate buffer[25] showed 39% release in 60 minutes while the study conducted[24] in simulated gastric media in presence /absence of pepsin and in pH 6.5 simulated intestinal fluid in presence/ absence of pancreatin showed negligible release (1%). However, the curcumin dissolution was improved in

presence of surfactant[26]. Overall Increase in dissolution of curcumin observed in our study (36.4% in 24 hours) in combined media and particularly in the colonic fluid containing cecal content could be due to many reasons. Firstly, due to major proportion of drug release in the colon as a result of enzymatic degradation of gaur gum and the second reason could be due to reduced exposure of the drug in the intestine and eventually impeding curcumin degradation in the intestine substantially. Since Curcumin solution in alcohol was mixed with other excipients during granulation, micro crystals of curcumin formed after drying gets deposited on the gaur gum particles. Hence curcumin is embedded in the gaur gum metrix as microcrystalline phase has showed significant dissolution once the gaur gum matrix is broken down in colon.

Tissue homogenate studies

Tissue sample homogenates were subjected to extraction and were estimated for both the drugs. Percentage of the total drug recovered in colon was also calculated. Concentration of oxaliplatin and curcumin were estimated by first order derivative spectrometric method at the absorption maxima 289.8 nm (Oxaliplatin) and 400nm (curcumin) respectively. The percentage recovery of Oxaliplatin and curcumin in the colon tissue excised 12 hrs post drug administration were 33.75 % and 20% respectively. At the outset the percentage recovery seems to be low for a colon delivery system. But looking in to the procedure adopted for colon homogenate study, where, the tissue was thoroughly washed and cleared off from the colon content before homogenization and analysis, the recovered drug is essentially the amount absorbed and retained in the colon tissue. As such, the maximum bio-availability reported for curcumin is not more than 60%[23]. The prime aim of this study being to understand the availability of the drug combination in colon tissue, comparison of our results with earlier reported bio-availability results seems to be irrelevant. However, the studies are in progress to address the problems of curcumin degradation in colon to further improve the availability of the curcumin in the colon tissue.

X-Ray imaging studies:

X-ray Images of Rabbit were taken for 6hr after oral administration of Barium sulphate containing gaur gum matrix tablet. Images obtained after 3 hours showed that the tablet was intact as shown in figure 5 (the region indicated in circle) at the lower abdominal cavity probably in the small intestine. Image taken later showed diffused images in colon region indicating disintegration of the tablet.

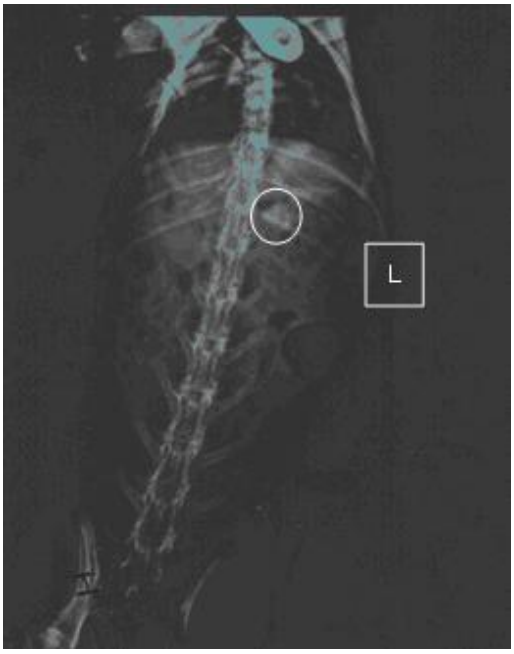


Figure 5: X-ray Images of Rabbit were taken 3hr after oral administration of Barium sulphate containing gaur gum matrix tablet. Image above shows the intact tablet (circled) in the region of small intestine in the lower abdominal cavity.

CONCLUSION

From these studies it was concluded that the 60% guar gum matrix tablet gives significantly less drug release in first 5hr (stomach and small intestine transit time) but the release in colon media was found significant. The release of oxaliplatin in the colon media is to the order of 65 to 70% of the total amount in the tablets. However, the amount of curcumin estimated in colon media was less (39%) due to the fact that Curcumin was found to be stable only up to 12 hrs in alkaline pH and thus might have degraded partially in the samples taken at later time points. Colon tissue homogenization studies followed by oral administration of the tablet showed 33.75% and 20% recovery of Oxaliplatin and curcumin respectively after 12 hours. X ray imaging studies conducted in rabbit for 6 hours showed the tablets intact in small intestine 3 hours after administration but were diffused and spread out in large intestine and colon later confirming enzyme mediated erosion of the tablet in these regions. Further studies are required to increase the stability of curcumin at alkaline medium in order to exploit the excellent observations made by us on high degree of potentiating action of oxaliplatin when combined with curcumin in vitro (Unpublished work). This warrants for a detailed study for effectively using this combination to reduce the dose of Oxaliplatin not only to potentiate the activity but also avoids adverse effects of Oxaliplatin by dose reduction in colorectal cancer.

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