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INVESTIGATION OF GUM KONDAGOGU FOR COLON SPECIFIC DRUG DELIVERY USING TRAMADOL HCL AS MODEL DRUG

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ABSTRACT

The objective of present work is to develop and evaluate a matrix system for Chronotherapeutic delivery of centrally acting opioid analgesic (Tramadol HCl) containing Gum kondagogu as carrier for the treatment of rheumatoid arthritis. If the formulation is administered at night time, symptoms that are sever in early morning hours can be treated. Core tablets of Tramadol HCl were prepared by using 30, 40, 50, 60 and 70% w/w of tablet of Gum kondagogu as carrier by wet granulation technique. These tablets were compression coated with Eudragit S100 to prevent drug release in stomach. All formulations were evaluated for hardness, friability, weight variation, drug content, in vitro and in-vivo studies. The Gum kondagogu was characterized by viscosity measurements and FTIR analysis. The coated (FC1 to FC5) and uncoated tablets (F1 to F5) were evaluated for *in vitro* release of Tramadol HCl after sequential exposure to pH 1.2, pH 7.4 and pH 6.8 respectively for 2hr, 3hr and 19hr in the absence as well as presence of rat caecal content. The selected formulation was subjected to *in vivo* targeting efficacy studies by Roentgenography technique. *In vitro* release studies indicated that the matrix tablets (F1 to F5) failed to control the drug release in the physiological environment of stomach and small intestine. On the other hand, compression coated formulations were able to protect the tablet cores from premature drug release. In the absence of rat caecal contents, compression coated FC4 and FC5 released 98.45$\pm$0.37% and 89.67 $\pm$0.43% drug respectively at the end of 24hrs. When dissolution study was continued in pH 6.8 PBS containing 4% w/v of rat caecal contents, FC4 released about 99.18 $\pm$0.29% drug at the end of 22hrs. FTIR studies confirmed that there was no interaction between the drug and the carrier. X-ray studies confirmed that the tablet successfully reached colon without getting disintegrated in upper gastro intestinal tract. Based on the results, selective delivery of Tramadol HCl to the colon could be achieved using 60% w/w (FC4) of Gum kondagogu matrix tablets compression coated with Eudragit S100.

KEY WORDS: Tramadol HCl; Gum kondagogu; Eudragit S100; Roentgenography; Rat caecal content.

INTRODUCTION

The site specificity of drugs to the colonic part is advantageous for the localized and systemic treatments of various diseases conditions. Colon targeting was attained a significant role in treatment of local pathologies and Chronotherapy of various disorders includes Asthma, Rheumatoid arthritis and Hypertension (Salunkhe, 2007).

Colon drug delivery system is valuable design, when a delay in absorption is therapeutically vital in the treatment of chronic medical conditions like nocturnal Rheumatoid arthritis. Treatment of rheumatoid arthritis is a long term therapy, where patient non- compliance is high, hence prolonged release dosage forms are useful for quality health care (Sharmin Rahman, 2012).

Tramadol HCl is a synthetic centrally acting aminocyclohexal analgesic that acts as an opioid agonist with selectivity for μ receptor that can be used for moderate to severe pain. It possesses good oral bioavailability and adequate colon absorption. Most of the water soluble drug containing formulations release the drug at a faster rate and likely to produce toxic concentrations of the drug on oral administration (Lata, 2012). Tramadol HCl is a highly water soluble and permeable drug belonging to BCS class I and likely producing toxic concentrations. So, in order to retard the drug release and to target the drug to colon for the treatment of rheumatoid arthritis this approach was selected. Tramadol HCl was frequently used for treating rheumatoid arthritis, which had apparent circadian rhythms and peak symptoms in the early morning. In case of conventional formulation, it was difficult to achieve the desired clinical effect, because it elicited patient's incompliance of administration in the early morning to coordinate the rhythm of rheumatoid arthritis, due to rapid absorption of the conventional formulation as it is having a half life of 6.3 ± 1.4 hr. However, colon specific Tramadol HCl delivery is not only effective, but also more convenient for administration than the conventional formulation to get the drug release after desired lag time (Poonam Kushwaha, 2011).

Various natural polymers like guar gum (Srujana, 2011), xanthan gum (Indira Muzib, 2012), pectin (Lakshmi prasanna, 2012), chitosan (Lata, 2012; Srujana, 2011), and tamarind gum (Lakshmi prasanna, 2012) were used for colon specific drug delivery. In this study, the feasibility of Gum kondagogu as a carrier for colonic delivery was studied as it is easily available and non-toxic. Gum kondagogu is natural polysaccharide obtained from stems and branches of Cochleospermum gossypium belonging to the family Bixaceae. The back bone structure of gum kondagogu consists of α-D-GalpA-(1→4)-α-L-Rhap and can be grouped under rhamnogalacturonans type of gum, as it is rich in rhamnose, galactose and uronic acids residues [12].

MATERIALS AND METHODS

Tramadol HCl was obtained as a gift sample from Hetero labs, Hyderabad. Gum kondagogu was purchased from Girijan co-operative society, Tirupathi. Lactose and PVP K30 was purchased from SD fine chemicals, Mumbai. Hydrochloric acid, sodium hydroxide and potassium dihydrogen orthophosphate of HPLC grade were purchased from Merck India Ltd., Mumbai, India. All reagents and chemicals were of analytical grade and used as received.

Drug and excipient compatibility studies:

Fourier Transform Infrared Spectroscopy (FTIR): IR spectra were recorded between 400 and 4000 cm^{-1} by a Perkin Elmer 1600 Series FTIR (Norwalk, USA). Each sample was mixed with KBr (FT-IR grade, Aldrich, Steinhelm, Germany) and compressed at 70 kN with a Perkin-Elmer hydraulic press. The FTIR spectra were shown in Figure.1.

Determination of viscosity and swelling index of the polymer: Viscosity and swelling index of Gum kondagogu was measured in water, 0.1N HCl, P^H 7.4 phosphate buffer and P^H 6.8 phosphate buffer. Viscosity in these buffers was measured using Brookfield viscometer using spindle number SC 4-18.

Preparation of core tablets: Accurately weighed quantities of drug, polymer (gum kondagogu) lactose and binder (PVP-K 30) were physically mixed with a motar and pestle. Required quantity of solvent (Isopropyl alcohol) was added and was mixed thoroughly to form a damp mass suitable for the preparation of granules. The dough mass was passed through sieve # no 10 to form granules which were dried in an oven at 50^0 C. Finally talc and magnesium stearate were added to granules before punching the tablet. Now the granules were compressed to form tablets in a Rotary punch tablet machine using 9mm round concave punches at an optimum pressure. Ten formulations were prepared by varying the amount of gum kondagogu, 30, 40,50, 60 and 70%w/w of the tablet and coded as F1, F2, F3, F4 and F5 and FC1, FC2, FC3, FC4 and FC5 respectively. The composition of different formulations was shown in the Table.1.

Compression coating of core tablets using Eudragit S 100: The prepared tablets were compression coated with Eudragit S 100 inorder to retard the drug release in the stomach. Each core tablet is coated with 200mg of Eudragit S 100 granules (made with IPA). Initially half of the coating material (100mg) was placed in the 11mm die cavity upon which the core tablet is kept and the remaining half of the coating material (100mg) was placed on it. Then the contents are compressed under optimum pressure to form coating on the core tablets.

In-process quality control parameters of tablets: The formulated tablets were evaluated for different IPQC parameters like drug content, weight variation, hardness and friability. The results were tabulated in Table.2.

***In-vitro* drug release studies:** Dissolution studies were carried out using USPXXII, Paddle method (apparatus II). The stirring speed was maintained at 100 rpm. The tablets were placed in simulated gastric fluid (SGF- P^H 1.2) for 2 hr, simulated intestinal fluid (SIF P^H 7.4) for 3 hr as the average small intestine transit time is about 3hrs. Then the dissolution medium was replaced with simulated colonic fluid (SCF P^H 6.8) and the study was continued for a period of 19 hr. Sampling was done at predetermined time intervals and the samples of 5ml were collected and estimated for drug content after suitable dilution by UV method.

In-vitro drug release testing in presence of rat caecal content medium[10]: Before commencement of the experimentation on animals, the experimental protocol was subjected to the scrutiny of the Institutional Animal Ethical Committee (IAEC/III/30/BCOP/2014) and was approved by the same in time.

In-vitro drug release studies were investigated in the presence of rat caecal content after 5 hrs of dissolution (first 2 hrs in 0.1 N HCl and another 3 hrs in P^H 7.4 Phosphate buffer). The albino rats weighing

between 150-200 g were kept on normal diet and administered the 2.5 ml of 1% w/v solution of Gum kondagogu in water with the help of Teflon tubing directly into the oesophagus region via oral cavity. The treatment was continued for 7 days to induce enzyme responsible Gum kondagogu degradation, animals were sacrificed before 30 min of commencing drug release studies and the caecum was exteriorized for content collection. The caecal content (anaerobic) were immediately transferred into buffer saline solution P^H 6.8 to obtain an appropriate 4%w/v concentration solution which was bubbling with carbon dioxide gas to maintain anaerobic environment. Using USP dissolution rate testing apparatus Paddle type (100 rpm, 37±0.5^{o}C) in anaerobic conditions with modifications the procedure was done. A beaker containing 250 ml of 4% w/v rat caecal content medium was immersed in dissolution bowl and the bowl volume was adjusted to 900 ml with phosphate buffer P^H 6.8, which was kept in the water bath of the apparatus. As the caecum is naturally anaerobic, the experiment was carried out with continuous CO_2 supply into the beakers. At different time intervals, 5 ml of the samples was withdrawn without a pre-filter and replaced with 5 ml of fresh phosphate buffered saline (PBS) bubbled with CO_2 and the experiment was continued for 19 hr as the usual colonic transit time is 20-30 hours. The result was shown in Figure.2.

In-vivo targeting efficacy: In-vivo targeting efficiency study was carried out to check the efficiency of the formulation to target to colon after obtaining ethical clearance (IAEC/III/31/BCOP/2014). The evaluation of dosage form in animal model renders support to the *in vitro* studies. To closely simulate the human physiological environment of the colon, rabbits were selected as animal model for evaluating the colon specific delivery. Roentgenography study; a comparatively safer technique was carried out in healthy male albino rabbits to access the *in vivo* performance of the selected batch. The behaviour of Tramadol HCl tablets in rabbit was observed using a radiographic imaging technique. It involves the use of radio-opaque markers such as barium sulphate, incorporated in the formulation to determine the position of the tablet. Healthy rabbits of 1.58kg were fasted overnight and on the next day morning tablet was administered followed by giving 25ml of water. At different time intervals of 2hrs, 5hrs, 8hrs, 17hrs, and 20hrs X-ray images were taken under the supervision of a radiologist, to follow the nature, movement, location and the integrity of the tablets indifferent parts of Gastro intestinal tract. The result was shown in Figure.3.

Table.1.Composition of Tramadol HCl matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	FC1	FC2	FC3	FC4	FC5
Tramadol HCl	100	100	100	100	100	100	100	100	100	100
Gum kondagogu	150	200	250	300	350	150	200	250	300	350
PVP K30	25	25	25	25	25	25	25	25	25	25
Lactose	215	165	115	65	15	215	165	115	65	15
Mg. Stearate	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5
Eudragit S100	----	-----	------	-----	-----	200	200	200	200	200
Total	500	500	500	500	500	700	700	700	700	700

Table.2.Physical properties of the Tramadol HCl matrix tablets Formulated With gum kondagogu by Wet granulation method

Formulation	Weight variation (mg)	%Drug content	Hardness kg/cm	% Friability
F1	501±0.7	99.23±0.18	7.2±0.02	0.39
F2	502±0.4	99.85±0.1	7.8±0.25	0.31
F3	499±0.6	101.39±0.21	7.9±0.34	0.35
F4	501±0.2	99.93±0.23	8.2±0.12	0.41
F5	498±0.5	101.88±0.39	8.8±0.06	0.39
FC1	702±0.8	100.16±0.51	8.2±0.58	0.32
FC2	701±0.3	99.64±0.63	8.5±0.40	0.38
FC3	699±0.1	101.24±0.17	8.6±0.24	0.35
FC4	698±0.6	101.16±0.39	8.8±0.45	0.28
FC5	702±0.9	100.18±0.69	8.9±0.67	0.19

RESULTS AND DISCUSSION

The present study was aimed at developing oral colon targeted formulations for Tramadol HCl using natural polymer, Gum kondagogu in various concentrations.

FTIR analysis: The FTIR spectra of the pure drug and formulations of Gum kondagogu indicated that no chemical interaction occurred between the drug, Tramadol HCl and the carriers used Figure.1.

Pre-compression parameters: Flow properties of the pure drug alone were poor when compared with the formulated granules. This may be due to the attractive forces between the molecules of the pure drug which are not allowing the particles to flow easily. So in order to improve the flow properties, wet granulation technique is employed.

Physico chemical characteristics of tablets: The hard ness of the tablets was found to be 7 $kg/cm^{2.}$ Weight variation, Friability and drug content were within the pharmacopoeial limits. (Table 2).

Viscosity and swelling indexes: Viscosity and swelling index was observed for Gum kondagogu in water, 0.1N HCl, P^H 7.4 phosphate buffer and P^H 6.8 phosphate buffer. Viscosities of Gum kondagogu were found to be high. The highest viscosity was found in 7.4 phosphate buffer which was about 189.7Cp. Swelling index of Gum kondagogu was measured by using the same buffers. Swelling index of Gum kondagogu was found to be low and the lowest swelling index was observed in P^H 7.4 phosphate buffer which was about 5.2% v/v.

***In- vitro* drug release studies:** In order to investigate the extent to which Gum kondagogu succeed in targeting the drug to the colon, ten formulations have been formulated and *in vitro* drug release studies have been conducted in the pH range, which normally accounted in the GI tract. Further to mimic the colon environment, the colonic micro flora was also taken into consideration for the *in vitro* release study, as polysaccharide polymers release the drug faster in the presence of colonic micro flora as they release glycosidase. At the end of 2hrs the Formulations without compression coat released 32.41%, 29.65 %, 22.93%, 19.03% and 17.11%of the drug from F1, F2, F3, F4 and F5 Gum kondagogu formulations respectively. Whereas, all the compression coated formulations (FC1, FC2, FC3, FC4 and FC5) released 0% drug during the same period. This indicates that compression coating with Eudragit S 100 succeeds in preventing the drug release in stomach. This indicates that, Gum kondagogu by increasing the concentration of polymer the drug release can be retarded. It was also observed that throughout release study; Gum kondagogu compression coated tablets containing high concentration of polymer released the drug at slower pace.

Among all the formulations belonging to Gum kondagogu FC4containing 60% of Gum kondagogu has shown the desired drug release profile compared to FC5 containing 70% Gum. So this formulation (60%) was selected to carry out the dissolution in the presence of rat caecal content.

When the drug release studies were carried out in the presence of rat cecal content there was a significant increase in the drug release as compared to that of the release studies performed in the absence of rat cecal content. The rat cecal content in the release study was considered to mimic the human colonic environment as it contains micro flora which releases many glycosidases and degrade the polysaccharide polymers.

In- vivo targeting efficacy: To strengthen the in-vitro release study finding, *in vivo* targeting efficiency study was carried out using formulation FC4. It is shown from the X-ray studies that the tablet remained in the stomach for the first 2hrs (fig 3(a)) then it has reached the small intestine and remained intact for next 3hrs (fig 3(b)). Then it has reached large intestine and then reached colon (fig 3(c)) and remained intact for 17hrs (fig 3(d)) and finally tablet disintegrated in the 20hr .It can be concluded from the X-ray images that the enteric coated tablets have remained intact in the upper part of the intestinal tract and swollen tablet picture in the colon indicates that the formulation releases the drug in the colon and hence the colon specificity and the tablet remained intact without disintegration proving that the formulation is ideal for colon targeting.

From these results Gum kondagogu can be successfully used for targeting the drug to colon. The drug release from the polymer is dependent on the concentration of the polymer used, the more the concentration of the polymer the lesser is the drug release.

In all the formulations developed the results were subjected to study the release kinetics. The values of correlation coefficient indicated that the drug release followed zero order drug release kinetics with Peppas drug

release mechanism. The values of T50% and T90% were found to be increased with increasing the proportion of polymers. The drug release mechanism was super case II transport as n>1.0

Table.3.Release kinetics for Tramadol HCl matrix tablets

Formulation	Zero order (R^2)	First order (R^2)	T50(hr)	T90(hr)	Higuchi (R^2)	Peppas (R^2)	K (µg/hr)	n
F1	0.980	0.968	8.98	15.17	0.893	0.905	5.56	0.598
F2	0.988	0.954	9.46	20.64	0.946	0.992	5.28	0.625
F3	0.990	0.977	11.36	22.86	0.943	0.978	3.48	1.175
F4	0.993	0.935	14.62	28.97	0.862	0.996	4.29	0.756
F5	0.996	0.980	16.77	30.20	0.965	0.997	4.98	0.254
FC1	0.996	0.912	11.46	17.69	0.938	0.987	4.36	1.026
FC2	0.991	0.973	15.43	21.77	0.842	0.993	3.24	1.236
FC3	0.996	0.921	18.91	29.61	0.872	0.994	3.87	1.021
FC4	0.997	0.978	19.16	31.08	0.924	0.978	2.48	1.642
FC5	0.995	0.959	21.06	34.11	0.933	0.917	3.68	1.365

Where k = release rate constant, n = Diffusion exponent for Peppas

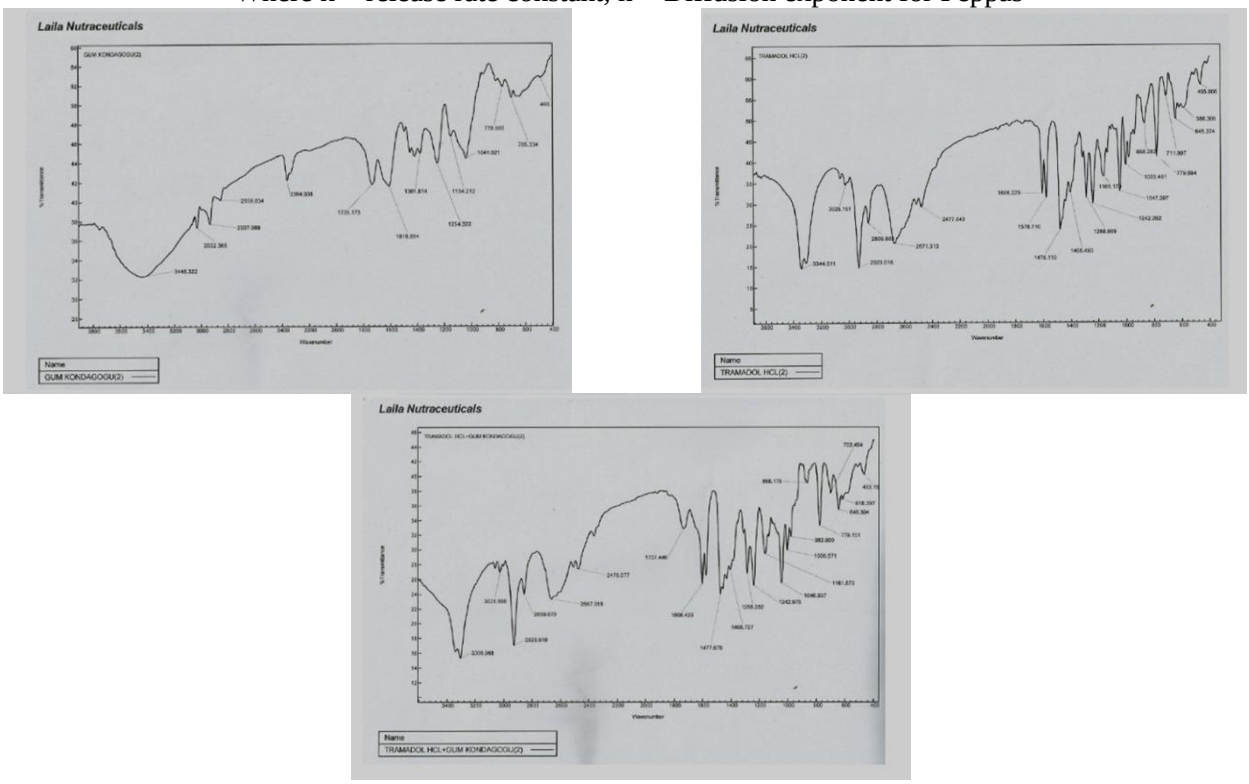


Figure.1.FTIR graphs of plane gum, drug & formulation

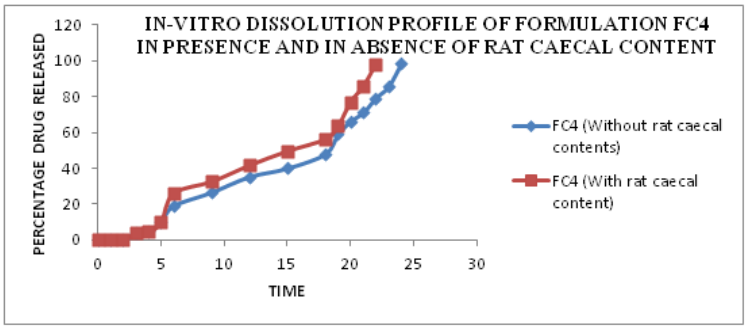
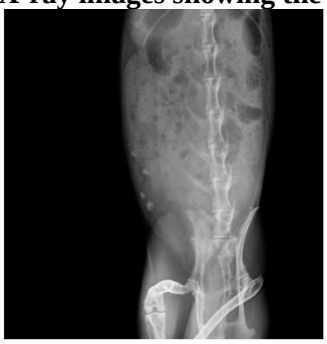
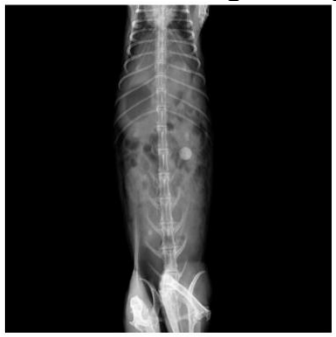


Figure.2.Percentage drug release plots for formulation FC4 in presence and in absence of rat caecal contents

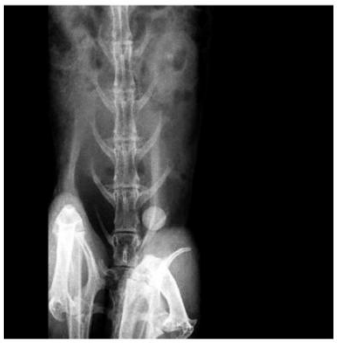
Figure.3(a,b,c&d) X-ray images showing the tablet in various regions of gastro intestinal tract



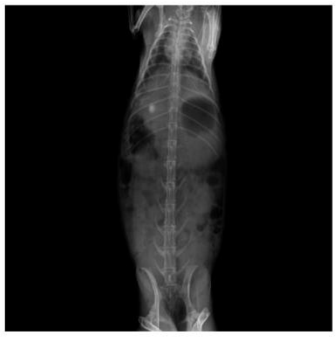
x ray image showing the tablet in stomach(1hr)



x ray image in the region of intestine(5hr)



x ray showing the presence of tablet in colon(7 hr)



x ray showing the disintegration of tablet (19 hr)

CONCLUSION

The present work was aimed at developing colon targeted drug delivery of Tramadol HCl for treatment of Rheumatoid arthritis. A comparision study was done by using various concentrations of Gum kondagogu in the preparation of matrix tablets of Tramadol HCl and matrix tablets are compression coated with Eudragit S100. Tramadol Hcl matrix tablets prepared with 60% (FC4) Gum kondagogu had slow drug release when compared with other formulations. The study shows that Gum kondagogu is able to target the drug to the colon. But it is dependent on the concentration of the polymer used. The release of the drug was more in the presence of caecal content than without the caecal content. The X-ray studies revealed that the formulated tablets are able to target the colon without getting disintegrated in the upper part of gastro intestinal tract. It was concluded that the compression coated matrix tablets of Tramadol HCl prepared by employing Gum kondagogu, could be used for chronotherapy of Rheumatoid arthritis to treat nocturnal symptoms.

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