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Colon Specific Drug Delivery of Tramadol Using Almond Gum *in Vitro* & *in Vivo* Evaluation

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Keywords: Tramadol HCl; Almond gum; Eudragit S100; Roentgenography; Rat caecal content

ABSTRACT

The aim of present work is to develop colon specific matrix tablets of tramadol using natural almond gum as carrier. Matrix tablets of Tramadol HCl were prepared by using 30, 40, 50, 60 and 70% w/w of tablets of Almond gum 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 almond gum was evaluated by viscosity measurement. Drug –excipient compatibility study was done by using FT-IR &DSC. 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 and the corresponding data was fitted to popular release kinetic equations in order to evaluate the release mechanisms-kinetics. The selected formulation was subjected to *in vivo* targeting efficacy studies by Roentgenography technique**.** *In vivo* studies were conducted using rabbits. *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. Presence of rat caecal content enhances the drug release from the tablets. The release of tramadol from all the formulation followed zero order with non fickian diffusion. X-ray studies confirmed that the tablet successfully reached colon without getting disintegrated in upper G.I.T**.** The *in vivo* results confirmed that the drug release was initiated only after a lag time of 5 hrs. The bioavailability of drug was found to be improved ($AUC_{0\text{-}t^*}$ 481.82 in case of coated tablets). Based on the results, selective delivery of Tramadol HCl to the colon could be achieved using almond gum as release modifier.

INTRODUCTION

The polysaccharides gums represent one of the most widely used raw materials and have been the subject of intense research owing to their safety, biodegradability & sustainability. A large number of polysaccaharides such as guar gum pectin, inulin, dextrin, xanthan gum & chitosan were investigated. Almond gum also known as Indian gum has excellent emulsifying and swelling properties. It is found useful as food additive in USA. The gum is obtained from *Anogeissus latifolia* belong to the family Combretaceae. Recent studies exploited its complete molecular structure & physicochemical properties. In this work almond gum was selected to exploit its usage in colon specific drug delivery.

The gum is insoluble in water & ethanol. It forms viscous adhesive mucilage in water. The powder swells in water. It contains b 1, 4 linked mannose residues & 1, 6 linked galactone.

The site specificity of drugs to the colonic part is advantageous for the localized and systemic treatments of various disease conditions. Colon targeting was attained a significant role in treatment of local pathologies and Chronotherapy of various disorders includes Asthma, Rheumatoid arthritis and Hypertension[1].

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[2].

Tramadol HCl is a synthetic centrally acting aminocyclohexal analgesic that acts as an opioid agonist with selectivity for μ receptor have demonstrated that this drug is an effective agent for moderate to severe pain. It possesses good oral bioavailability and adequate colon absorption. Hence it is selected as a candidate for the colon drug delivery system. 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[3]. 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[4].

The aim of this study was to explore the feasibility of the natural gum dependent Chronotherapeutic drug delivery system (CDDS), opioid analgesic, Tramadol HCl being selected as a model drug.

MATERIALS AND METHODS

Materials:

Tramadol HCl was obtained as a gift sample from Hetero labs, Hyderabad. Almond gum 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):[5]

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.

DSC-STUDIES:

DSC thermo grams were recorded for pure drug and final formulation based on melting point values.

Determination of viscosity and swelling index of the polymer[6,7]:

Viscosity and swelling index of almond gum were measured in water, 0.1N HCl, pH 7.4 phosphate buffer and pH 6.8 phosphate buffer. Viscosity in these buffers was measured using Brookfield viscometer (Make-Brookfield, model no: DVIII+ULTRA) using spindle number SC

4-18. 1gm of gum was added to 10ml of distilled water. The measuring cylinder was shaken vigorously for 10min and allowed to stand for 24hrs.

Swelling capacity was expressed as

Swelling capacity (%v/v) = [X_V/ X_I]* 100

Where X_v is the final volume occupied by swollen material after 24hrs and X_I denotes the initial volume of the powder in graduated measuring cylinder. The results were discussed.

Preparation of core tablets:

Accurately weighed quantities of drug, polymer (almond gum) were physically mixed with a mortar and pestle. Required quantity of water was added and 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 60^0C. 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. The matrix tablets were prepared by varying the amount of almond gum, 30, 40, 50, 60, and 70%w/w of the tablet. These tablets were coded as F1, F2, F3, F4 and F5. 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 in order 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. The coated tablets were represented by FC1, FC2, FC3, FC4 & FC5 and shown in Table 1.

In-process quality control parameters of tablets

The formulated tablets were evaluated for different IPQC (in process quality control) tests like drug content, weight variation, hardness and friability.

***In vitro* drug release studies[8, 9]**

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- pH 1.2) for 2 hr, simulated intestinal fluid (SIF pH 7.4) for 3 hr[13]. Then the dissolution medium was replaced with simulated colonic fluid (SCF pH 6.8), the study was continued for a period of 19 hr. Sampling was done at predetermined time intervals, the samples of 5ml were collected and replaced with fresh buffer. The samples were estimated for drug content after suitable dilution by UV method by measuring the absorbance at 271 nm.

***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/VIII/9/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 pH 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 almond gum 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 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 pH 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 pH 6.8, which was kept in the water bath of the apparatus. The best formulation were placed in the Paddle of the apparatus and immersed in the rat caecal content medium. 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 hr.

Drug release mechanism & kinetics[11]:

The drug release pattern was evaluated by zero order, first order, higuchi kinetics and Peppa's drug release kinetics.

***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 rabbit of 1.58kg was 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 in different parts of G.I.T.

Pharmacokinetic Studies[12]

Optimised formulation with respect to aim of study was selected for *in vivo* study and compared with *in vivo* pharmacokinetic parameters of Marketed tablets of tramadol using rabbits as animal model (2.5-3 kg). The study protocol was approved by animal ethical committee clearance IAEC/III/31/BCOP/2014. The entire study was conducted in Bapatla College of Pharmacy. The optimised formulation, marketed formulations were administered to rabbits with sufficient flush of water to a group of four animals in fasting conditions. The rabbits have access to water throughout the study.

Blood samples were collected from marginal ear vein before dosing (zero time) and at definite time intervals after dosing namely 1, 2, 5, 7, 12, 16 & 19 hrs using EDTA tubes. The collected

samples were immediately centrifuged at 2000 rpm for 15 min and plasma was separated and stored at -20^{0}C until analysis.

Analysis of samples was done by using HPLC method[13, 14]. Mobile phase was acetonitrile: water (70:30 v/v), with a flow rate of 1 ml/min, volume of injection is 20 micro lt. the wave length used for detection was 237 nm.

RESULTS AND DISCUSSION

The present study was aimed at developing oral colon targeted formulations for Tramadol HCl using natural polymer, almond gum in various concentrations. Predictable pulsatile release of tramadol for chronotherapeutics of arthritis[15] was previously reported using combination of natural polymer delonix regia gum and HPMCK4M. The lag time in drug release was controlled by selection various combinations of natural & synthetic polymer. In this work an attempt was made to control the lag time by the use of almond gum.

3.1 FTIR analysis:

The characteristic IR absorption peaks of Tramadol HCl were characterized by the presence of a very strong and sharp absorption band at 3344.011 cm^{-1} is assigned to OH bond stretching, while the absorption band located at 3062.151 cm^{-1} may be attributed to CH group stretching by aromatic proton. The absorption band appearing at 2929.018 cm^{-1} is due to CH stretching contributed by the methyl groups. CH_2 group stretching is assigned to an absorption band located at 2859.883 cm^{-1}. Figure 1(a-c) revealed the presence of peaks nearby at 3344 cm^{-1}, 3062 cm^{-1}, 2929 cm^{-1} & 2857cm^{-1}. Frequencies of functional groups and unique absorption bands of pure drug remained intact in physical mixture containing polymer. Hence there was no major interaction between the drug and excipient used in the study.

DSC-analysis:

DSC analysis Figure 2 (a&b) shows that melting point of tramadol starts at 174.6^{0}C in formulation (peak at 179.3^{0}C) and in case of pure drug melting point starts at 178.98^{0}C (peak at 182.2^{0}C). The result conformed that there was no interaction between drug and additives employed in formulation.

3.2 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.

3.3 EVALUATION PARAMETERS:

a) Physicochemical characteristics of tablets:

The hardness of the tablets was found to be 7-9 kg/cm^2. Weight variation, Friability and drug content were within the pharmacopoeia limits (Table 2).

b) Viscosity and Swelling indexes:

Determination of viscosity and swelling index are helpful in deciding the gum suitable for delaying the drug release. These were observed for almond gum in water, 0.1N HCl, pH 7.4 phosphate buffer and pH 6.8 phosphate buffer. Viscosities of almond gum were found to be high. The highest viscosity was found in 7.4 phosphate buffer which was about 122.1Cp. Swelling index of almond gum was measured by using the same buffers. Swelling index of Almond gum was found to be low and the lowest swelling index was observed in pH 7.4 phosphate buffer which was about 8.3% v/v (Table3).

c) Uniformity of drug content:

The matrix tablets were found to contain 99.1-101.5% of the labelled amount of Tramadol HCl indicating uniformity of drug content.

***d) In vitro* drug release studies:**

In order to investigate the extent to which Almond gum 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

Almond gum formulations respectively (Figure 3). Whereas, all the compression coated formulations (FC1, FC2, FC3, FC4 and FC5) released 0% drug during the same period (Figure 4). This indicates that compression coating with Eudragit S 100 succeeds in preventing the drug release in stomach. This indicates that, almond gum by increasing the concentration of polymer the drug release can be retarded. It was also observed that throughout release study; almond gum compression coated tablets containing high concentration of polymer released the drug at slower pace.

The present investigation has revealed that, in spite of using the natural polymer alone, the hydrophilic nature of the polymer makes vulnerable to release the drug to some extent in the upper digestive tract. As a result, the use of the polymer alone may not successfully target the drug to the colon. Hence there is a need of further coating of the tablet with pH dependent enteric polymer.

Among all the formulations, FC4 containing 60% of almond gum has shown maximum drug release (98%) within 24 hrs study period. Whereas in FC5 containing 70% gum the drug release was 85% in 24 hrs study period. So FC4 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 glycosidase and degrade the polysaccharide polymers (Figure 5).

The drug release from Formulation FC4 was 0% in the first 2h. The drug release was negligible i.e. it was only 9.83% at the end of 5hr. However, the release may be complete once the drug reaches the colon. Hence, a delayed action was observed. It was seen that formulation FC4 released 99.18% at the end of 22hrs in the presence of rat caecal contents, whereas, formulation FC4 released 98.45% at the end of 24hrs in the absence of rat caecal contents. This indicates that the drug release from formulation is mainly due to the presence of enzymes released by micro-organisms of rat cecal contents (degradation). The formulation FC4 & FC5 developed and followed zero order & peppas drug release mechanism.

From this data, it can be concluded that almond gum can be used for targeting the drug to the colon. Further, if they are coated with enteric polymer, efficiently can be targeted to the colon by avoiding the release in the upper intestinal part and the release of the drug are basically dependent upon the colon microflora degradation rather than any other factors.

e) *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 (Figure 6(a)), then it has reached the small intestine and remained intact for next 3hrs (Figure 6(b)). Then it has reached large intestine and colon (Figure 6(c)) and remained intact for 17hrs (Figure 6(d)).

***In vivo* Pharmacokinetic Study**

The study was performed in rabbits and parameters like C_{max} .t_{max} are the values directly obtained from plasma concentration time curve. *In vivo* pharmacokinetic parameters for optimised batch (F5) were determined and compared with marketed formulation. Plasma concentration v/s time profiles for prepared & marketed formulation was shown in (Figure 7). t_{max} for prepared & marketed formulations was found to be 7 hr & 5 hrs respectively with C_{max} of 1.48 mcg/ml & 1.32 mcg/ml respectively. From these results, it can be concluded that lag phase of 5 hrs was observed in optimised formulation and bioavailability was improved compared to marketed tramadol (Table 4).

CONCLUSION

The present work was aimed at developing colon targeted drug delivery of Tramadol HCl for treatment of Rheumatoid arthritis. A comparison study was done by using various concentrations of almond gum 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) almond gum had slow drug release when compared with other formulations. The study shows that ghatti 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 G.I.T. *In vivo* study reveals that the lag

phase was maintained indicating the potential of almond for targeting the drug towards colon. It was concluded that the compression coated matrix tablets of Tramadol HCl prepared by employing almond gum, could be used for chronotherapy of Rheumatoid arthritis to treat nocturnal symptoms.

REFERENCES

1. Salunkhe KS, Kulakarni MV,"Colon specific drug delivery",*Journal Of Pharmaceutical Research*., Oct 2007, vol 6, No 4, 248-250.

2. Sharmin Rahman, Md. Abdullah Al Masum, Florida Sharmin, S. M. Ashraful Islam and Md. Selim Reza "Formulation and Evaluation of Bi-layered Sustained Release Matrix Tablets of Tramadol Hydrochloride", *Journal of Applied Pharmaceutical Science 02 (06); 2012: 129-134.*
3. Ms. Lata a. Panchal, dr. Pragna k. Shelat, dr. Maitreyi n. Zaveri "Development of sustained release matrix tablet of tramadol hydrochloride using natural gums", *International journal of pharmacy and pharmaceutical sciences ,Issn- 0975-1491 vol 4, suppl 4, 2012.*
4. Poonam Kushwaha, Sheeba Fareed, Sanju Nanda and Anuradha Mishra "Design & Fabrication of Tramadol HCl loaded Multiparticulate Colon Targeted Drug Delivery System", *J. Chem. Pharm. Res., 2011, 3(5):584-595.*
5. Srujana. N, valluru ravi, pramod kumar, vinay, kulkarni R. Ajay "Feasibility of kondagogu gum as a carrier for colon targeted drug delivery system for metaprolol succinate", *IRJP 2 (7) 2011 68-79.*
6. Y.Indira muzib, Padma sree kurri, "Effect of kondagogu on the release behaviour of Ambroxol HCl matrix tablets", *IRJP 2012, 3 (11);158-162.*
7. Lakshmi prasanna J, Deepthi B, Rama Rao N, " Influence of diluents on diclofenac sodium release from Gum kondagogu based matrix tablets", *International journal of Pharma research and review, august 2012: 1(4); 12-20.*
8. G.Subba Rao, TEGK Murthy, "Formulation and evaluation of diltiazem HCl colon targeted tablets", *IJRPC 2013, 3(4).819-827.*
9. Mallikarjuna Gouda M, Somashekar Shyale, Putta Rajesh Kumar and S. M. Shanta Kumar, "Design and evaluation studies on colon specific ciprofloxacin matrix tablets for Inflammatory Bowel Disease treatment", Der Pharmacia Lettre, 2011, 3(2): 383-395.
10. Valluru Ravi, T.M. Pramod Kumarand Siddaramaiah, "Investigation of almond gum as a carrier to develop sustained release floating tablets of diltiazem hydrochloride", *Thai J. Pharm. Sci. 36 (2012) 155-164.*
11. Dash S, Murthy PN, Nath L, Chowdhury Kinetic modelling on drug release from controlled drug delivery systems. Acta Pol Pharm 2010; 67:217-223.
12 12.Krishnaiah YSR[1], Seetha Devi A, Nageswara Rao L, Bhaskar Reddy PR, Karthikeyan RS, Satyanarayana V "Guar gum as a carrier for colon specific delivery; influence of metronidazole and tinidazole on *in vitro* release of albendazole from guar gum matrix tablets**"**J Pharm Pharmaceut Sci (www.ualberta.ca/~csps) 4(3):235-243, 2001
13 R.M.Kotadiya,V.A.Patel " *In vitro In vivo* evaluation of Okragum:guargum compression coated diclofenac sodium tablets for colonic deliovery:a factorial approach" Int.journal of Pharm.Biological Archieves 2012;3(1):228-236.
14. YALDA H.Ardakani, Mohammad-Reza Rouini " Pharmacokinetics of tramadol and its three main metabolites in healthy male and female volunteers." Biopharmaceutics &Drug disposition 28:526-533(2007).
15. Dabhi Cl, Randale S, Belgamwar V, "Predictable pulsatile release of tramadol hydrochloride for chronotherapeutics of arthritis." Drug Deliv.2010 Jul;17(5):273-281

Table 1: Composition of Tramadol HCl matrix tablets

S. No.	Ingredients	F1	F2	F3	F4	F5	FC1	FC2	FC3	FC4	FC5
1.	Tramadol HCl	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg
2.	Almond gum	30mg	40mg	50mg	60mg	70mg	30mg	40mg	50mg	60mg	70mg
3.	Mg. Stearate	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
4.	Talc	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
5.	Eudragit S100	----	-----	------	-----	-----	200mg	200mg	200mg	200mg	200mg
6.	Total	140mg	150mg	160mg	170mg	180mg	340mg	350mg	360mg	370mg	380mg

Table 2: Physical properties of the Tramadol HCl matrix tablets Formulated with almond gum by Wet granulation method

Formulation Code	Weight variation (mg) (Mean±sd)	%Drug content (Mean±sd)	Hardness kg/cm^2 (Mean±sd)	% Friability (Mean±sd)
F1	143±0.7	99.23±0.18	7.2±0.02	0.39
F2	155±0.4	99.85±0.1	7.8±0.25	0.31
F3	166±0.6	101.39±0.21	7.9±0.34	0.35
F4	171±0.2	99.93±0.23	8.2±0.12	0.41
F5	185±0.5	101.88±0.39	8.8±0.06	0.39
FC1	342±0.8	100.16±0.51	8.2±0.58	0.32
FC2	355±0.3	99.64±0.63	8.5±0.40	0.38
FC3	367±0.1	101.24±0.17	8.6±0.24	0.35
FC4	375±0.6	101.16±0.39	8.8±0.45	0.28
FC5	385±0.9	100.18±0.69	8.9±0.67	0.19

DRUG EXCIPIENT COMPATABILITY STUDIES:

Figure 1.FT-IR compatibility studies:

Figure 1a) mixture of drug & polymer **Figure 1b) spectra of almond gum**

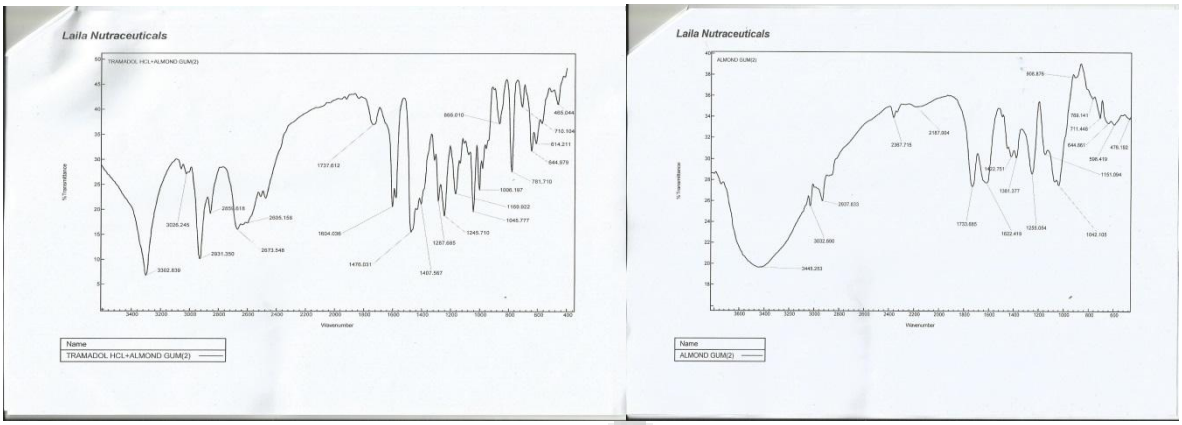


Figure 1c) spectrum of drug

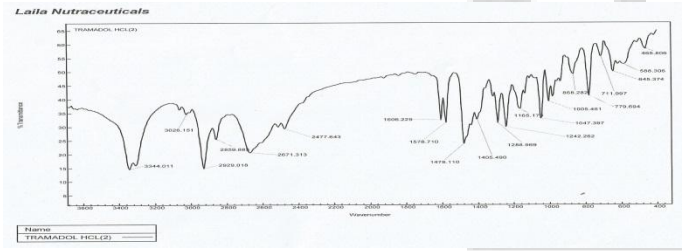


Figure 2: DSC GRAPHS

a) tramadol formulation **b) pure tramadol**

:

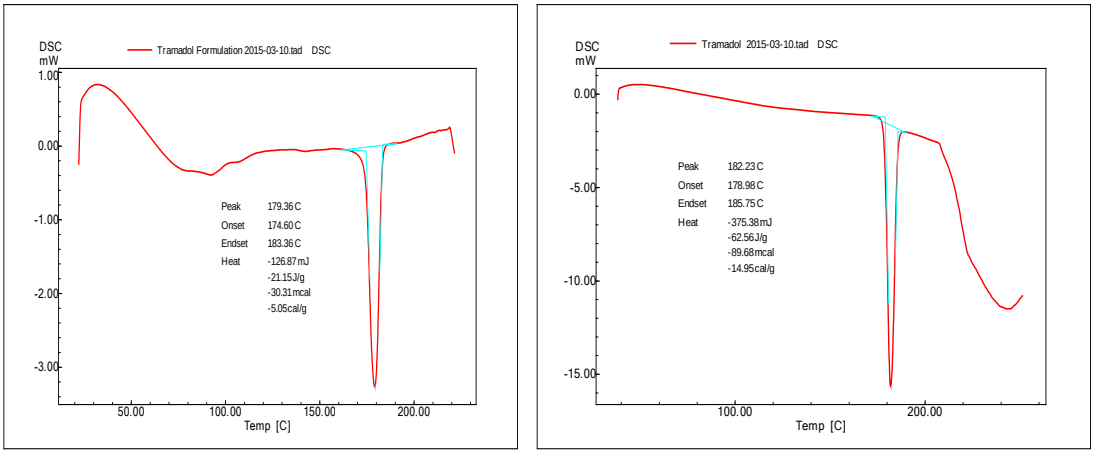


TABLE 3: VISCOSITY & SWELLING INDEX OF ALMOND GUM

Polymer Dispersion Almond Gum (1%) W/V	Water	IN 0.1 N HCl	IN pH 7.4 Phosphate Buffer	IN pH 6.8 Phosphate Buffer
VISCOSITY(cps)	117.9	109.6	122.1	116.5
SWELLING INDEX	8.1	8.9	8.3	8.4

***IN VITRO* DRUG RELEASE STUDIES**

Figure 3 Drug release profile of F1-F5

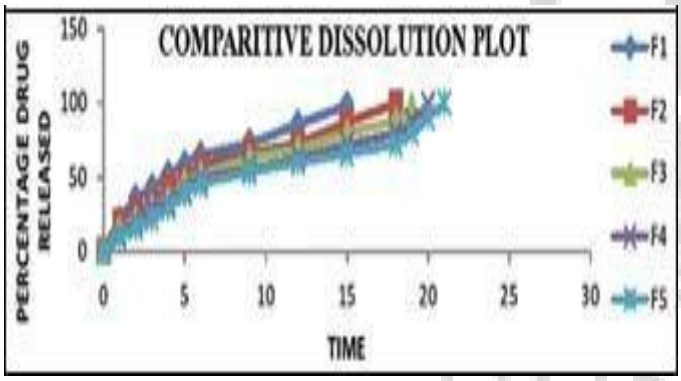


Figure 4 Drug release profile of FC1-FC5

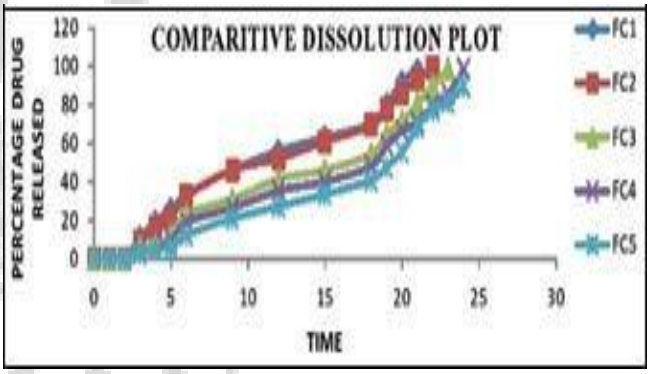


Figure 5 Drug release profile of FC5 in presence and in absence of caecal content

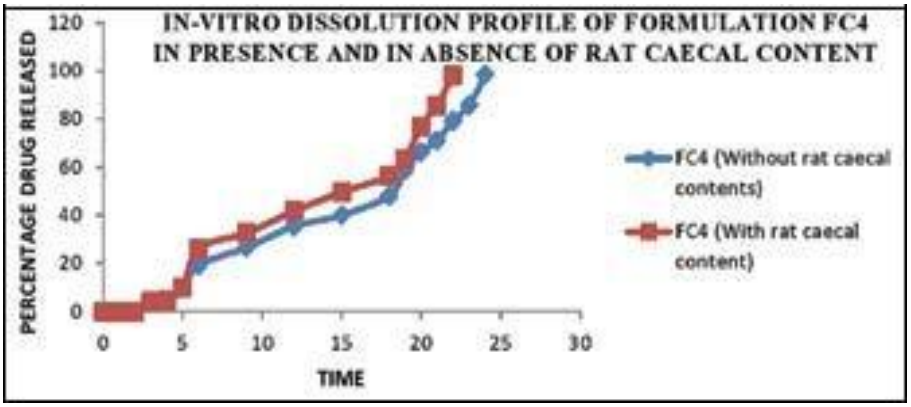
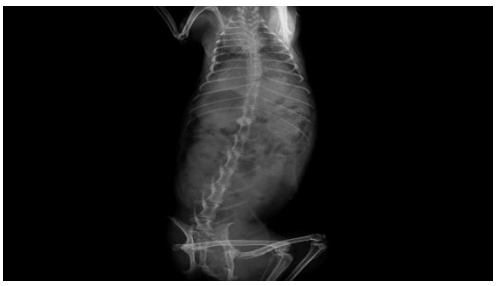
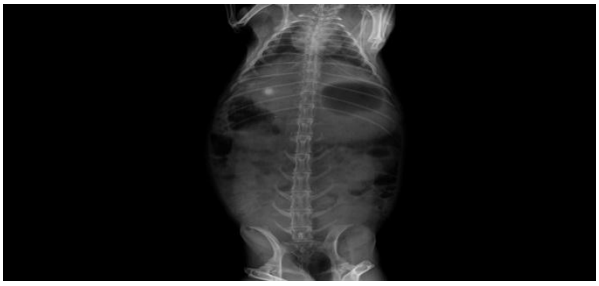


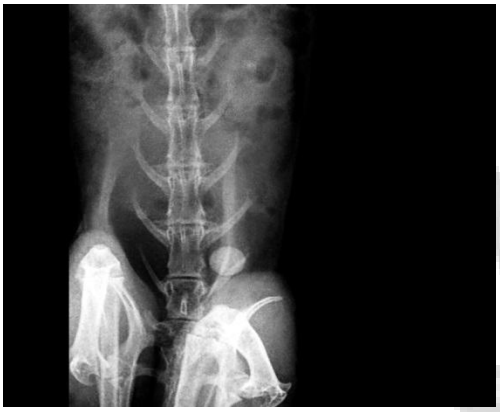
Figure 6) X Ray images taken at various time intervals:

6a) Image showing the tablet in stomach 6b) Image showing the tablet in intestine at 5th hr





6d) In the region of colon at 17 hr



6c) Image in the region of intestine at 7hrs

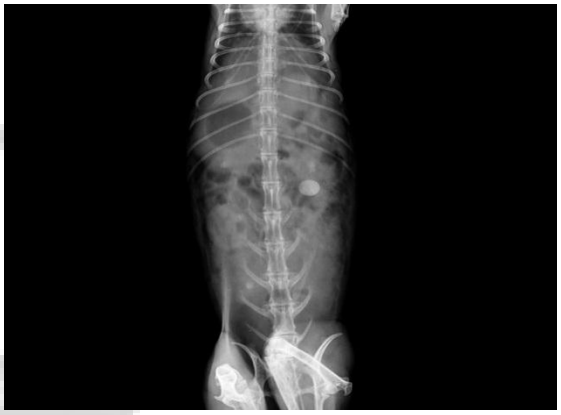


Figure 7: *In vivo* Pharmacokinetic Analysis: Plasma Concentration Time Profile of Marketed Formulation & Optimized Formulation

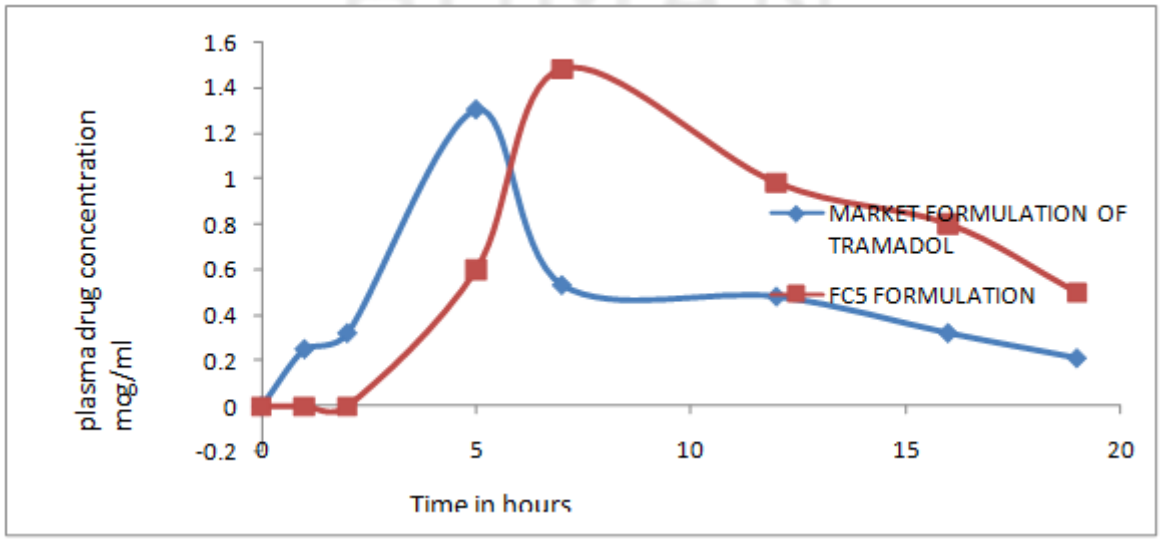


Table 4. Pharmacokinetic parameters:

Pharmacokinetic parameter	**T_{max}**	**C_{max}**	**AUC**
TRAMADOL MARKETED FORMULATION	5 hr	1.25	185.55
FC5	7 hr	1.48	481.25