

Colon specific drug delivery of tramadol HCl for chronotherapeutics of arthritis

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Abstract

Objective: The objective of present work is to develop and evaluate a matrix system for Chronotherapeutic delivery of centrally acting of opioid analgesic (tramadol HCl) to treat nocturnal symptoms of arthritis using almond gum as carrier. **Materials and Methods:** Matrix tablets of tramadol HCl were prepared by using 30, 40, 50, 60 and 70% w/w of tablet of gum badam 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 characterized by viscosity measurements and Fourier transform infrared 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 2 h, 3 h and 19 h 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. **Results and Discussion:** *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 as the concentration of polymer increased, drug release was found to be retarded. 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 gastrointestinal tract. **Conclusion:** Based on the results, selective delivery of tramadol HCl to the colon could be achieved using 60% w/w (FC4) of almond gum matrix tablets compression coated with eudragit S100.

Key words: Eudragit S100, gum almond, rat caecal content, roentgenography, tramadol HCl

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.^[1]

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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 noncompliance 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

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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 in compliance 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 h. 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]

Various natural polymers like guar gum,^[5] xanthan gum,^[6] pectin,^[7] chitosan^[3,5] and tamarind gum^[7] were used for colon specific drug delivery. In this study, the feasibility of Almond gum as a carrier for colonic delivery was studied as it is easily available and nontoxic. Almond gum is natural polysaccharide obtained from stems and branches of *Amygdalus communis* belonging to the family *Rosaceae*. The monosaccharide of almond gum contained glucose, xylose, galactose, arabinose, and little rhamnose and fucose and their molar ratios of monosaccharide were 24.35:9.25:33.75:31.60:0.74:0.31. The main chain of polysaccharide of almond gum could contain 1, 6-linked Galactose and 1, 4-linked Arabinose. The gum contains various components which have emulsifying, thickening glazing, suspending and adhesive properties. The gum obtained from tree was studied for binding property in tablet formulation. The drug release was found to be slow and suitable for delaying the drug release.^[8]

The aim of this study was to explore the feasibility of the natural gum chronotherapeutic drug delivery system, 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 polyvinylpyrrolidone (PVP) K30 was purchased from standard deviation fine chemicals, Mumbai. Hydrochloric acid, sodium hydroxide and potassium dihydrogen orthophosphate of high-performance liquid chromatography 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

Infrared (IR) spectra were recorded between 400 and 4000 cm^{-1} by a Perkin Elmer 1600 Series Fourier transform infrared (FT-IR) (Norwalk, USA). Each sample was mixed with KBr (FT-IR grade, Aldrich, Steinheim, Germany) and compressed at 70 kN with a Perkin-Elmer hydraulic press.

Determination of viscosity and swelling index of the polymer

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. 1 g of gum was added to 10 ml of distilled water. The measuring cylinder was shaken vigorously for 10 min and allowed to stand for 24 h.

Swelling capacity was expressed as:

$$\text{Swelling capacity (\%v/v)} = (X_v/X_i) \times 100$$

Where X_v is the final volume occupied by swollen material after 24 h 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) lactose and binder (PVP-K 30) were physically mixed with a mortar 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°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 9 mm 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 S100

The prepared tablets were compression coated with eudragit S100 in order to retard the drug release in the stomach. Each

Table 1: Composition of tramadol HCl matrix tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	FC1 (mg)	FC2 (mg)	FC3 (mg)	FC4 (mg)	FC5 (mg)
Tramadol HCl	100	100	100	100	100	100	100	100	100	100
Almond gum	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
Magnesium 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

PVP: Polyvinylpyrrolidone

core tablet is coated with 200 mg of dragit S100 granules (made with IPA). Initially half of the coating material (100 mg) was placed in the 11 mm die cavity upon which the core tablet is kept and the remaining half of the coating material (100 mg) 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 and FC5.

In-process quality control parameters of tablets

The formulated tablets were evaluated for different 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 (pH 1.2) for 2 h, simulated intestinal fluid (pH 7.4) for 3 h.^[10] Then the dissolution medium was replaced with simulated colonic fluid (pH 6.8), the study was continued for a period of 19 h. Sampling was done at predetermined time intervals, the samples of 5 ml were collected and replaced with fresh buffer. The samples were estimated for drug content after suitable dilution by ultraviolet method by measuring the absorbance at 271 nm.

In vitro drug release testing in presence of rat caecal content medium

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 h of dissolution (first 2 h in 0.1 N HCl and another 3 h in pH 7.4 Phosphate buffer).^[11] The albino rats weighing between 150 and 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°C ± 0.5°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 CO₂ supply into the beakers. At different time intervals, 5 ml of the samples was

withdrawn without a prefilter and replaced with 5 ml of fresh phosphate buffered saline bubbled with CO₂ and the experiment was continued for 19 h as the usual colonic transit time is 20-30 h.

Drug release mechanism and kinetics

The drug release pattern was evaluated by zero order, first order, Higuchi kinetics and Peppas's drug release kinetics.^[12]

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 1.58 kg was fasted overnight and on the next day morning tablet was administered followed by giving 25 ml of water. At different time intervals of 2 h, 5 h, 8 h, 17 h, and 20 h 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 gastrointestinal tract (g.i.t).

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^[13] 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 and synthetic polymer. In this work an attempt was made to control the lag time by the use of almond gum.

Fourier transform infrared analysis

The characteristic IR absorption peaks of tramadol HCl were characterised 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. CH₂ group stretching is assigned to an absorption band located at 2859.883 cm⁻¹. Figure 1a-c revealed the presence of peaks nearby at 3344 cm⁻¹, 3062 cm⁻¹, 2929 cm⁻¹ and 2857 cm⁻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.

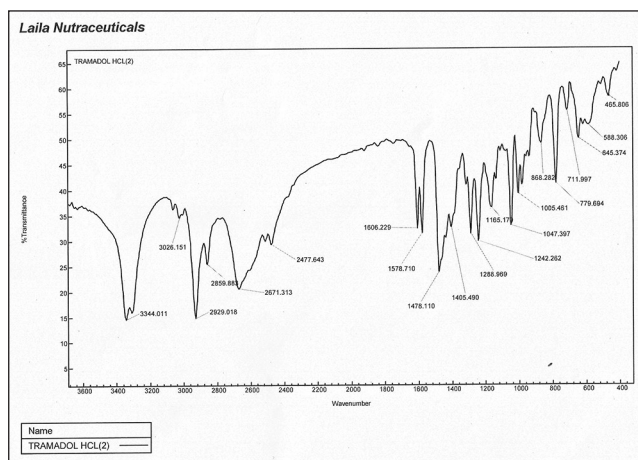


Figure 1a: Fourier transform infrared spectrum of pure drug

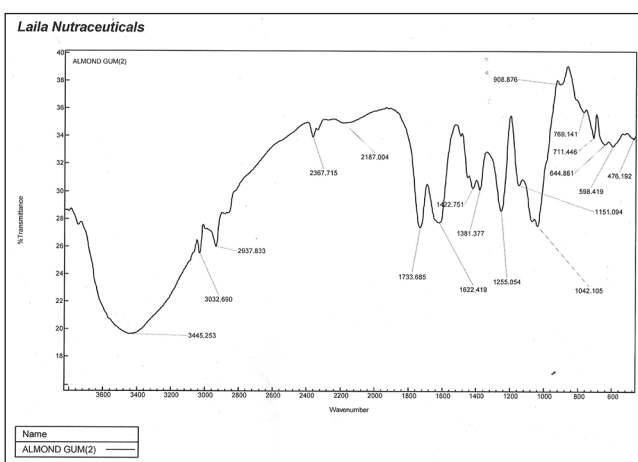


Figure 1b: Fourier transform infrared spectrum of almond gum

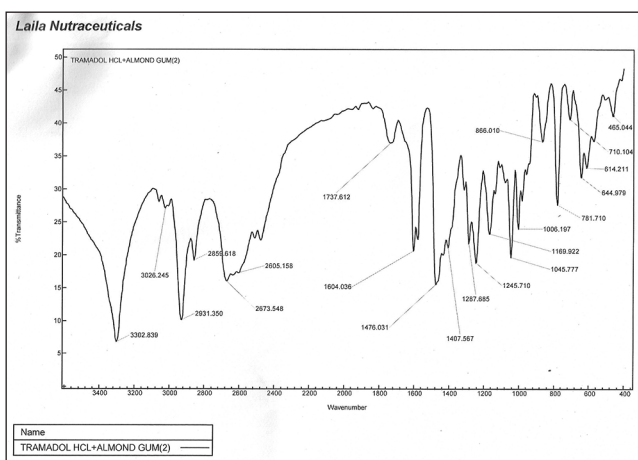


Figure 1c: Fourier transform infrared spectrum of drug and almond gum

Precompression 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.

Evaluation parameters

Physico chemical characteristics of tablets

The hard ness of the tablets was found to be 7-9 kg/cm². Weight variation, Friability and drug content were within the pharmacopocia limits [Table 2].

Viscosity and swelling indexes

Determination 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 Gum almond 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.

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.

In vitro drug release studies

In order to investigate the extent to which Gum almond 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 g.i.t. 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 2 h 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 almond formulations respectively [Figure 2]. Whereas, all the compression coated formulations (FC1, FC2, FC3, FC4 and FC5) released 0% drug during the same period [Figure 3]. This indicates that compression coating with eudragit S100 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 h study period. Whereas in FC5 containing 70% Gum the drug release was 85% in 24 h study period. So FC4 formulation (60%) was

Table 2: Physical properties of the tramadol HCl matrix tablets formulated with almond gum by wet granulation method

Formulation code	Weight variation (mg) (mean \pm SD)	Percentage drug content (mean \pm SD)	Hardness kg/cm ² (mean \pm SD)	Percentage friability (mean \pm SD)
F1	501 \pm 0.7	99.23 \pm 0.18	7.2 \pm 0.02	0.39
F2	502 \pm 0.4	99.85 \pm 0.1	7.8 \pm 0.25	0.31
F3	499 \pm 0.6	101.39 \pm 0.21	7.9 \pm 0.34	0.35
F4	501 \pm 0.2	99.93 \pm 0.23	8.2 \pm 0.12	0.41
F5	498 \pm 0.5	101.88 \pm 0.39	8.8 \pm 0.06	0.39
FC1	702 \pm 0.8	100.16 \pm 0.51	8.2 \pm 0.58	0.32
FC2	701 \pm 0.3	99.64 \pm 0.63	8.5 \pm 0.40	0.38
FC3	699 \pm 0.1	101.24 \pm 0.17	8.6 \pm 0.24	0.35
FC4	698 \pm 0.6	101.16 \pm 0.39	8.8 \pm 0.45	0.28
FC5	702 \pm 0.9	100.18 \pm 0.69	8.9 \pm 0.67	0.19

SD: Standard deviation

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 caecal content there was a significant increase in the drug release as compared to that of the release studies performed in the absence of rat caecal content. The rat caecal 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 4].

The drug release from Formulation FC4 was 0% in the first 2 h. The drug release was negligible that is, it was only 9.83% at the end of 5 h. 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 22 h in the presence of rat caecal contents, whereas, formulation FC4 released 98.45% at the end of 24 h 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 caecal contents (degradation). The formulation FC4 and FC5 developed followed zero order and peppas drug release mechanism [Figure 5].

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 micro flora degradation rather than any other factors.

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 2 h [Figure 6a] then it has reached the small intestine and remained intact for next 3 h [Figure 6b]. Then it has reached large intestine and then reached colon [Figure 6c] and remained intact for 17 h [Figure 6d] and finally tablet disintegrated in the 20 h [Figure 6e]. It can be concluded from the X-ray images that the enteric coated tablets have remained intact

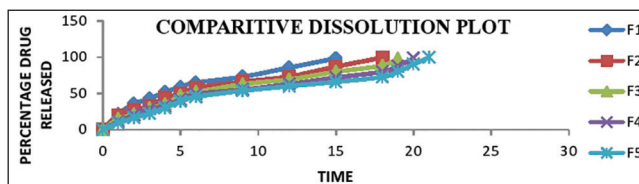


Figure 2: Comparative dissolution profile of tramadol HCl matrix tablets (F1 to F5)

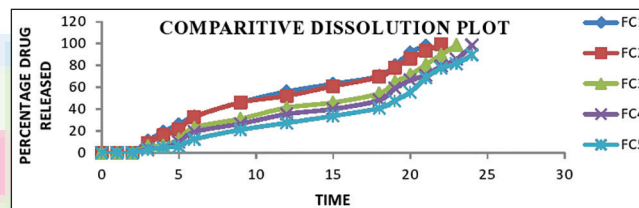


Figure 3: Comparative dissolution profile of tramadol HCl matrix tablets (FC1 to FC5)

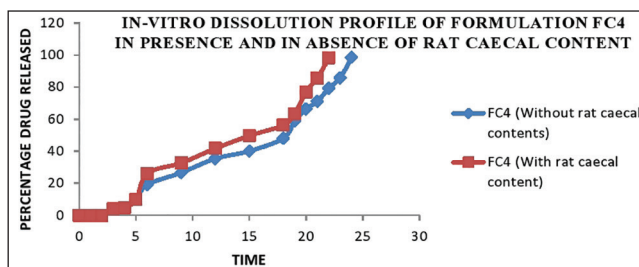


Figure 4: Percentage drug release plots for formulation FC4 in presence and in absence of rat caecal contents

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 almond gum 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.

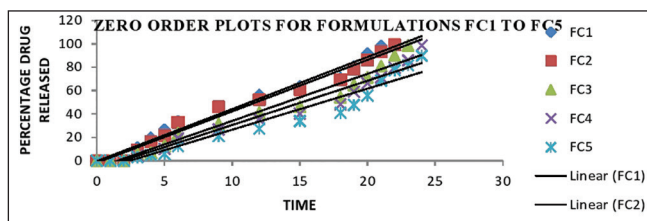


Figure 5: Zero order plots for formulations FC1 to FC5



Figure 6a: X-ray image showing the tablet in stomach at 2nd h



Figure 6b: X-ray image showing the tablet in intestine at 5th h



Figure 6c: X-ray image showing the tablet in descending part of small intestine at 8th h



Figure 6d: X-ray image showing the swollen tablet in colon at 17th h



Figure 6e: X-ray image showing the disintegration of tablet at 20th h

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 Peppa's 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 $n > 1.0$.

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 almond 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. 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.

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