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Research Article

FORMULATION AND EVALUATION OF MODIFIED ORAL CHRONOTROPIC DRUG DELIVERY SYSTEMS OF TRAMADOL HYDROCHLORIDE FOR RHEUMATOID ARTHRITIS PAIN

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ABSTRACT

Objective: The main aim was to develop a modified oral chronotropic system for timed release tramadol hydrochloride (tramadol HCl). Biological rhythms are highly organized for all functions of the human body both in health and in disease. Hence, drug delivery systems were designed to make possible the treatment of illness based on biological rhythms for improving therapeutic efficacy.

Materials and Methods: These systems consist of immediate release core tablet of tramadol HCl using different materials such as SSG, crospovidone, pregelatinized starch and then coated with Tamarindus gum, hydroxypropyl methylcellulose (HPMC), and their combination. This coated tablet is enteric coated with Eudragit L 100, Eudragit S100 to produce lag time period of 5 h.

Results: Immediate release systems are optimized with formulation F6 containing pregelatinized starch as an immediate release agent, the formulation is coated with Tamarindus gum, HPMC, and their combination. The release retardant behavior of Tamarindus gum was evaluated in compressed coated formulations. This coated tablet is enteric coated with Eudragit L 100, Eudragit S100 to release the drug after the lag time period of 5 h.

Conclusion: A modified oral chronotropic system for timed release of tramadol HCl was made possible with the compressed coated tablets CF3 which shows better drug release followed by enteric coating with Es c coat fulfilled our objective of work.

Keywords: Rheumatoid arthritis, Chronotropic delivery, Tramadol HCl, Biological rhythms.

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INTRODUCTION

Rheumatoid arthritis is an inflammatory condition affecting synovial joints severely. Arthritic pain affects millions of people worldwide [1,2]. Nonsteroidal anti-inflammatory drugs are commonly used to treat the rheumatoid arthritis pain. They help to manage pain, inflammation, and swelling at the relevant area of rheumatoid arthritis [3]. Opioids are powerful pain-relieving substances which range from relatively mild (codeine) to strong (morphine). Examples of weak opioids are codeine and tramadol. Examples of strong opioids are oxycodone, morphine, and fentanyl [4,5].

Chronotherapeutics refers to treatment for a disease which is timed to match the biological rhythms of that disease to optimize the therapeutic benefits and minimize side effects by increasing *in vivo* bioavailability. The benefits of chronotherapeutics have been very helpful in the management of a number of diseases. They have a potential role in chronotherapy which benefits the patients suffering from allergic rhinitis, rheumatoid arthritis, and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease [6,7].

Tramadol HCl is a synthetic centrally acting amino-cyclohexyl analgesic that acts as an opioid agonist with selectivity for μ receptor which is treated like the drug of choice and an effective agent for moderate to severe pain. It is having good oral bioavailability and adequate colon absorption [8]. Tramadol HCl has a special role in treating rheumatoid arthritis, which had apparent circadian rhythms and shows peak symptoms in the early morning [9,10]. The HCl salt of tramadol is a widely used narcotic analgesic for severe pain.

MATERIALS AND METHODS

Tramadol HCl was obtained from Hetero labs, Hyderabad, Sodium Starch Glycolate, crospovidone, pregelatinized starch, HPMCK100, Eudragit L100, and Eudragit S100 were obtained from yarrow chem products. Microcrystalline cellulose, magnesium stearate, Talc, and all other reagents were of analytical grade. Tamarindus gum was extracted by a suitable analytical procedure given below.

Compatibility studies by Fourier-transform infrared spectroscopy (FTIR)

Active drug blended with individual excipients taken in 1:0.5 and 1:1 ratio. It was filled in closed vials and placed in the refrigerator and open workbench. The drug-excipient compatibility studies were done by FTIR, i.e., using Kerr pellet method. Samples were observed under Bruker FTIR scanned in the wavelength region between 400 and 4000 cm^{-1}. The spectra were analyzed and interpreted in Figs. 1 and 2.

Calibration curve for tramadol Hcl

100 mg of tramadol HCl was taken in a 100 mL volumetric flask and dissolved with 100 mL of 0.1 N HCl to give the concentration of 1000 μg/mL. From the above stock solution, aliquots of concentrations 40–300 μg/mL were prepared for pH 1.2 buffer and concentrations 20–160 μg/mL were prepared for pH 7.4 buffers. When this solution was scanned in the ultraviolet (UV) range, i.e., from 200 nm to 800 nm λ_{max} was found to be 271 nm for tramadol HCl. The absorbance of these solutions was measured at 271 nm and a graph of concentration versus absorbance was plotted and are shown in Figs. 3 and 4.

Isolation of Tamarindus gum

Take the tamarind seeds and peel out the outer cover and obtain the white part of seeds and crush them. The crushed seeds of Tamarindus were soaked in water for about 24 h, then take this soaked crushed seeds into a muslin cloth and press them for the release of gum. The marc was removed from the gum and to the extracted gum equal quantity of absolute ethyl alcohol was added to precipitate the gum, and it was

separated by filtration. The marc was for multiple extractions with decreasing quantity of extracting solvent i.e., water with the increase of the number of extractions. The isolation process was continued until the material was free of gum. The separated gum was dried in a hot air oven at temperature 40°C. Then, the extracted dried gum was powdered and stored in an airtight container at room temperature [11,12].

Purification and standardization of gum

Loss on drying

The 5 g gum was dried at 105°C ± 5°C till the constant weight of gum was obtained. The loss on drying was found to be <7% w/w.

Ash value

1 g of gum was accurately weighed and evenly distributed it in the crucible. It was dried at 105°C for 1 h and ignited in a muffle furnace at 700°C ± 25°C. Percentage of ash content was found to be <6% w/w.

pH

The binder gum is natural and has a pH between 7.0–7.5.

This gum was also tested for flow properties as per I. P. and shown in Table 1 [12].

Swelling property of mucoadhesive materials

Natural mucoadhesive material obtained from the fruits of Tamarindus indica is nontoxic. 250 mg of Tamarindus indica gum was allowed to hydrate in 25 ml of distilled water at 25°C in a 25 ml graduated cylinder and volume measured at 5 min. Intervals until there was no further hydration observed. The swelling property was determined at different time intervals (Table 2) [13,14].

Formulation development of immediate release core tablet

Tramadol HCl and all other ingredients listed in Table 1 were collected. Except for magnesium stearate and talc remaining ingredients was passed through sieve no 60 to get uniform sized particles and weighed accurately. Finally, magnesium stearate and talc (passed through a Wsh) were introduced to the powder mixture. The final mixture was shaken manually for 5–10 min. This powder was passed through the hopper of 16 station rotary tableting machine and punched into tablets using 6 mm punch by direct compression method. This process is similar for all core formulations.

Formulation development of compression coat tablet

The core tablets were compression coated with the coating mixture given in Table 2. All the constituents of the coating mixture consisting of HPMC alone, HPMC, and Tamarindus gum in the ratios of 3:1, 1:1, and 1:3 were uniformly mixed together and then used for the compression coating. MCC was added for its cushioning effect so as to protect the core tablet from any damage during the compression coating procedure. To prepare compression-coated tablets of crushing strength of about 6 kg, one-third of the powder was placed in 8-mm die, the core tablet was placed centrally, and the remaining two-third of powder was placed over it in the die cavity and finally compressed using 8-mm punch to obtain the compression coated tablets [15,16].

Table 1: Flow properties of dried tamarind gum

S.No.	Parameter	Value
1	Bulk density (g/cm^3)	0.45±0.8
2	Tapped density (g/cm^3)	0.32±0.2
3	Carr's index (%)	24.5±0.24
4	Angle of repose (0)	26.0±0.22

Number of experiments (n)=3

Table 2: Swelling property of *Tamarindus indica* gum

S.No.	Time interval	Swelling property (mL)
1	After 5 min	0.8
2	After 10 min	1.0
3	After 15 min	1.1
4	After 20 min	1.3
5	After 25 min	1.4
6	After 30 min	1.5

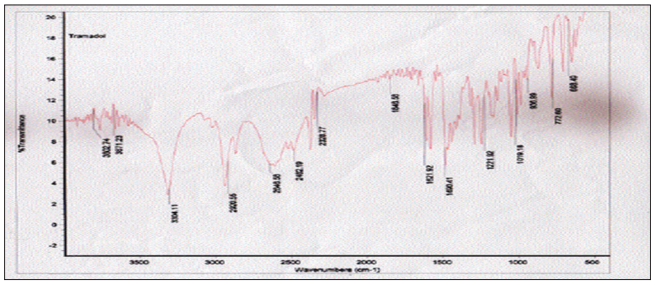

Fig. 1: IR spectrum of pure tramadol HCl

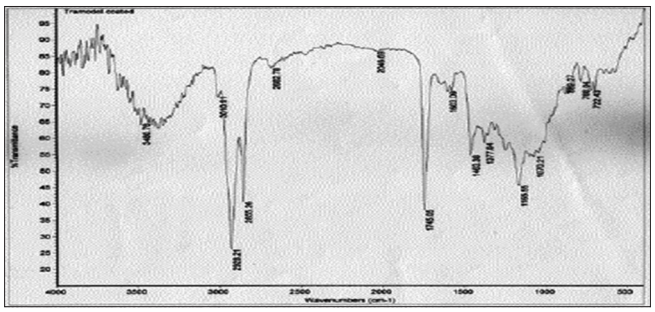

Fig. 2: IR spectrum of tramadol HCl with polymers

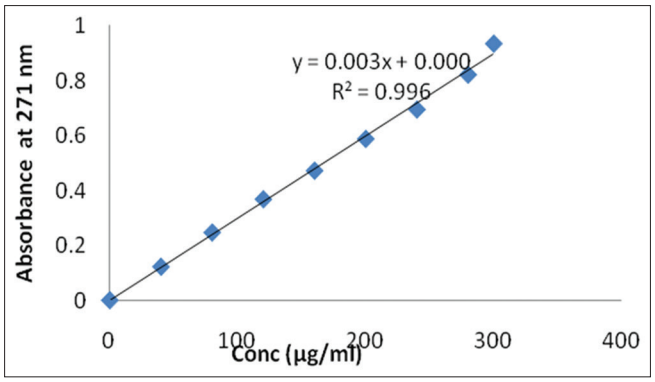

Fig. 3: Calibration curve of tramadol HCl at pH 1.2

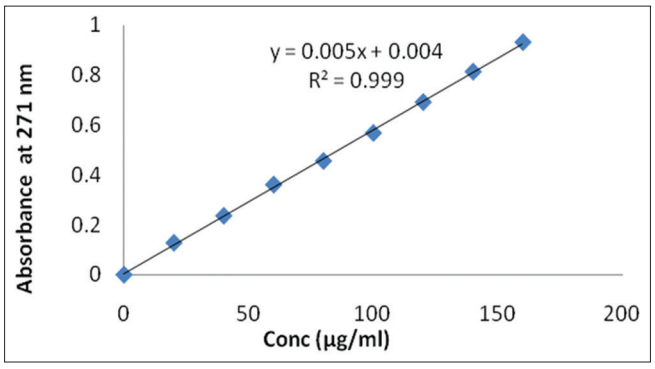

Fig. 4: Calibration curve of tramadol HCl at pH 7.4

Formulation development of enteric coated tablet

The compressed core tablets were then coated with enteric polymers such as Eudragit L-100 and Eudragit S-100 until the compressed core tablets percentage total weight gain (%TWG) of 5, 10, 15, and 20% were obtained. Their compositions and respective formulation codes are given in Tables 3 and 4.

Evaluation parameters

Pre-compressional parameters

The flow properties of powder blends were evaluated by determining the bulk density, tapped density, Carr's index, angle of repose, and Hausner's ratio.

Post-compressional parameters

Weight variation test

The weight variation test is carried out to detect the uniformity in the weight of tablets. First, the total weight of 20 tablets from the randomly selected formulations is determined, and the average weight is calculated. The individual weight of each tablet is also determined. Then, the weight variation is calculated by the below formula [15].

% wt variation = (average weight of tablet-weight of each tablet/ average of tablet) *100.

Hardness and friability

For each formulation, the hardness of at least three tablets was determined using Monsanto hardness tester, an average is calculated. Friability represents the mechanical strength of tablets. Roche friabilator was used to determine the friability by rotated at 25 rpm for 100 rotations. After the test, tablets were reweighed; percentage friability from the loss in the weight is calculated by the following expression.

% Friability = ([Initial weight– Final weight]/Initial weight) 100

Lag time of coated tablets

The intention of developing the pulsatile tablets was to release the drug at a predetermined time period for suitable therapeutic benefit. Hence, enteric polymers were used for this purpose, which shows variations in lag time with different compositions and the time at which drug release starts is noted as its lag time.

Drug content

For the determination of the content uniformity test, ten tablets were weighed, powdered, and the powder equivalent to 100 mg of tramadol HCl was extracted into methanol. Then, the drug content was estimated by measuring the absorbance value after suitable dilution in methanol. For this determination standard calibration curve of tramadol HCl is used. Then, average drug content is calculated by taking six determinations each [17].

Table 3: Chemical tests for Tamarindus gum

S.No.	Tests	Observation
1	Carbohydrates (Molisch's test)	+
2	Tannins (Ferric Chloride test)	-
3	Proteins (Ninhydrin test)	-
4	Alkaloids (Wagner's test)	+
5	Glycosides (Keller–Killani test)	+
6	Mucilage (Ruthenium red test)	+

+: Present, -: Absent

***In vitro* drug release study of core tablet**

In vitro drug release studies for the prepared compressed coat tablet were studied using USP II apparatus, by taking 900 ml of dissolution medium initially by pH 1.2 HCl for 2 h and then replaced by 900 ml of pH 7.4 phosphate buffer and the shaft is rotated at 50 RPM. At an interval of 1 h, 5 ml aliquots were withdrawn. These are withdrawn from a zone at the midway of dissolution medium and the top of the rotating paddle should not be <2 cm apart from the bottom of the vessel. Suitable sink conditions were maintained throughout the dissolution process. Every time the samples were filtered through Whatman filter paper no 4, the UV absorbance was measured at 271 mm using (UV1700–Shimadzu) spectrometer after diluting with appropriate dissolution medium. The concentrations of tramadol HCl were determined from the standard calibration curves. This *in vitro* dissolution study was performed for a period of up to 12 h [18].

RESULTS AND DISCUSSION

The aim of present work is to formulate compression coated matrix tablet and then enteric coated with Eudragit S 100 and Eudragit L 100 for site-specific delivery of tramadol HCl for timed release. The use of enteric polymer Eudragit S 100 coated matrix tablets makes them able to release the drug at the particular pH of the colonic fluid.

Properties of Tamarindus gum

In this study, Tamarindus gum was extracted as stated above and the flow properties of the gum are reported in Table 1, which were within limits and have shown good flow properties. As it is natural gum, its swelling properties were also studied and they were reported in Table 2, which shows swelling of 1.5 mL in measuring cylinder at the end of 30 min which represents good swelling as well as good mucilage nature of gum. Finally, chemical tests were conducted where the values were represented in Table 3, which shows that the gum is having recognizable quantities of carbohydrates, alkaloids, and glycosides. The gum was proved as mucilage by ruthenium red test, and it was also having pH in the range of 7 to 8. After the identification of gum to optimize the release retarding efficiency of gum, it was combined with HPMC in different percentage proportions (75:25, 50:50, and 25:75).

Pre-formulation studies

FTIR analysis shows that the drug tramadol HCl compatible with the polymers used. There was no drug-excipients interaction in the physical mixture. It also suggests that the drug did not undergo any degradation or interaction through the whole of the coating process.

The method employed for tableting in this study was first focused on direct compression technique for which the powder blend should possess good flow. The optimum value for Carr's index (%) is up to 15%. Values for the angle of repose (θ) ≤25 generally indicate free-flowing material. By means of pilot studies, it was found that pure tramadol HCl exhibited an angle of repose value of 23.21 ± 0.52

Table 4: Formulation of an immediate release core tablet

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Tramadol HCl	100	100	100	100	100	100	100	100	100
SSG	6	-	-	8	-	-	10	-	-
Crospovidone	-	6	-	-	8	-	-	10	-
Pregelatinized starch	-	-	6	-	-	8	-	-	10
Microcrystalline cellulose	41	41	41	39	39	39	37	37	37
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
The total weight (mg)	150	150	150	150	150	150	150	150	150

indicating good flow property. It was further supported by high Carr's index value of 17.24 ± 0.27. All these values are reported in Table 5. The tablet powder blend possessed good flow properties. The flow properties of the powder mixture are helpful in the maintenance of the uniformity of dose in the formulations of tablets. The tablets of different batches showed varied thickness (2.56 ± 0.1–2.70 ± 0.2) and hardness (4.0 ± 0.45 kg/cm^3–6.4 ± 0.29). The friability (0.12%–0.78%) and weight variation (%deviation: 99.5 ± 1.36–101.35 ± 1.63) of different batches of tablets are reported in Table 6 and found within the prescribed limits. The drug content was found to be uniform within the batches, and it is also found that it is above 98% of different tablet formulations. The evaluation of the release profile is recommended as an important tool in the development and optimization of drug formulations. Release studies of core tablet were carried out in pH 7.4 phosphate buffer [17]. Among the core tablets, the formulation containing crospovidone in high concentration as formulation code F8 releases the drug within 30 min and that formulations containing a high concentration of Sodium Starch Glycolate and pregelatinized starch with formulation code F7 and F9 release the maximum drug within 45 min. These data are reported in Table 7 and Fig. 5.

The second part of the formulation focused on the release retarding agents such as HPMC and isolated Tamarindus gum at different ratios which were reported in Table 8 and in the third part, it was focused on the pH-dependent polymeric coating of the tablets. The coating polymers were, Eudragit S-100 and Eudragit L-100, dissolves above pH 7.0 and pH 6, respectively, thereby protecting the drug from releasing from the core before reaching the colonic region. The coating composition and achieved thickness in the form of %TWG values are represented in Tables 9 and 10. Use of Eudragit polymers will be useful in colon targeting of drug or otherwise, it avoids the wastage of drug, and it helps in the chronotropic release of tramadol HCl to treat rheumatoid arthritis. Once the enteric coating dissolves, it is expected that drug release would be by HPMC and a combination of gum.

For this purpose dissolution was carried out in two different media. 6% of Eudragit S 100 and Eudragit L 100 are enteric coated to achieve 5, 10, 15, and 20% weight gain separately. These values are reported in Table 10. The weight variation, hardness, and the drug content of all the formulations were found to be within the official limit. From the dissolution data, it was observed that all the formulations showed little or no significant release at pH 1.2 (i.e., <1% drug release). Release started in pH 7.4 buffer for all the formulations. Beyond this CF1 to CF4 were also studied and their drug release was represented in Fig. 6 This may be attributed to the fact that the threshold pH (pH at which dissolution occurs) of Eudragit L-100 is 6. The lag time for drug release in pH 6.8 buffer was found to be dependent on

Table 5: Characterization of the tablet powder blend

Formulation code	Mean±SD (n=3)				
	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index (%)	Angle of repose (θ)
F1	0.541±0.11	0.691±0.12	1.276±0.45	16.62±0.52	34^0±0.27
F2	0.484±0.13	0.615±0.16	1.271±0.48	14.30±0.48	33^0±0.25
F3	0.710±0.14	0.873±0.14	1.251±0.38	12.714±0.48	31^0±0.21
F4	0.712±0.11	0.870±0.10	1.206±0.32	15.126±0.50	32^0±0.28
F5	0.718±0.16	0.871±0.14	1.223±0.45	14.513±0.46	30^0±0.18
F6	0.410±0.14	0.483±0.16	1.178±0.16	15.113±0.48	32^0±0.24
F7	0.420±0.11	0.462±0.12	1.131±0.24	15.010±0.42	35^0±0.26
F8	0.541±0.12	0.691±0.14	1.276±0.32	11.62±0.46	34^0±0.24
F9	0.450±0.14	0.585±0.12	1.300±0.42	13.07±0.42	31^0±0.27

SD: Standard deviation

Table 6: Characterization of compressed core tablet

Formulation code	Mean±SD		Friability (%)	Mean±SD		
	Weight variation (n=3)	Hardness (kg/cm^2) (n=3)		Thickness (mm) (n=3)	Content uniformity (n=3)	Disintegration time (min) (n=3)
F1	101±1.12	6.4±0.32	0.72	2.6±0.21	99.28±1.36	3.1±0.24
F2	97±1.16	6.3±0.24	0.68	2.6±0.24	97.16±1.24	2.6±0.26
F3	98±1.14	5.8±0.24	0.69	2.7±0.26	101.1±1.28	2.4±0.18
F4	99±1.11	5.6±0.26	0.66	2.75±0.24	97.68±1.16	2.7±0.22
F5	98±1.20	5.7±0.32	0.68	2.6±0.12	99.41±1.36	2.3±0.16
F6	99±1.12	6.4±0.28	0.65	2.62±0.16	98.19±1.28	1.4±0.12
F7	97±1.13	4.0±0.32	0.12	2.6±0.12	102.6±1.12	19.0±0.24
F8	100±1.12	4.5±0.26	0.78	2.56±0.12	99.5±1.24	17.2±0.24
F9	98±1.16	6.4±0.24	0.70	2.59±0.16	99.6±1.28	21.3±0.26

SD: Standard deviation

Table 7: Percentage drug release studies of core tablets

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	26.8±1.22	28.5±1.40	28.5±1.4	32.8±1.22	34.5±1.40	34.8±1.25	36.8±1.22	38.5±1.40	38.8±1.25
10	47.96±1.43	52.23±1.58	35.6±1.61	50.96±1.43	54.23±1.58	47.6±1.30	53.96±1.43	56.23±1.58	57.6±1.30
15	68.13±1.58	70.43±1.24	55.6±1.20	70.13±1.58	73.43±1.24	58.3±1.34	72.13±1.58	76.43±1.24	75.3±1.34
30	81.6±1.48	86.4±1.58	78.2±1.46	84.6±1.48	88.4±1.58	80.7±1.48	86.6±1.48	99.8±1.58	89.7±1.48
45	92.6±1.58	98.6±1.52	87.8±1.36	96.6±1.58	99.6±1.52	90.21±1.47	99.6±1.58	-	99.21±1.47
60	101.4±1.80	-	92.65±1.56	-	-	98.2±1.48	-	-	-

Values are expressed as mean±SD (n=3) for all the samples. SD: Standard deviation

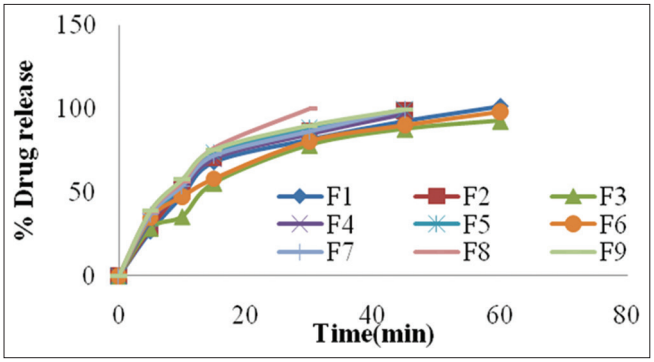

Fig. 5: %Drug release of F1 to F9

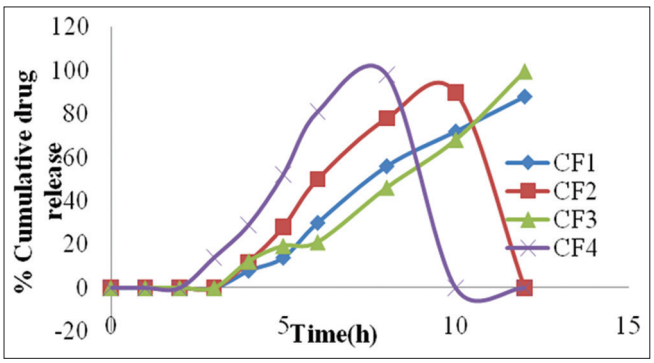

Fig. 6: % Drug release of CF1 to CF4

Table 8: Formulation development of compression coated tablet

S.No	Ingredients	CF1	CF2	CF3	CF4
1	HPMC	400	300	200	100
2	Tamarindus gum	0	100	200	300

HPMC: Hydroxypropyl methylcellulose

Table 9: Composition of coating solution

Ingredient	Amount/100 mL
Eudragit L 100/S 100 (g)	6
Triethyl citrate (mL)	2
Isopropyl alcohol (mL)	100
Talc (g)	2

Table 10: Percentage composition of coating solution with formulation code

Eudragit L 100		Eudragit S 100	
Percentage TWG	Formulation code	Percentage TWG	Formulation code
5	EL a	5	ES a
10	EL b	10	ES b
15	EL c	15	ES c
20	EL d	20	ES d

the level of coating 5%, 10%, 15%, and 20% (coating level in TWG) corresponding to batches EL a, EL b, EL c, and EL d, respectively, showed significant drug release (i.e., >20%) after a lag time of 5 h. Formulations coated with ES-100 TWG 15% and 20% showed no release in pH 7.4 buffer (i.e., <1% drug release). However, the release for formulations coated with ES 100 TWG 5%, 10% started in 7.4 buffer. Furthermore, the lag time for drug release in pH 6.8–7.4 buffer

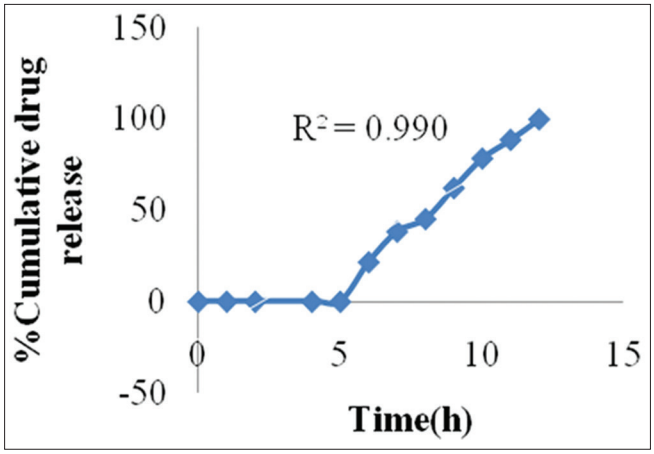

Fig. 7: Zero-order release of CF3 with ESc coat

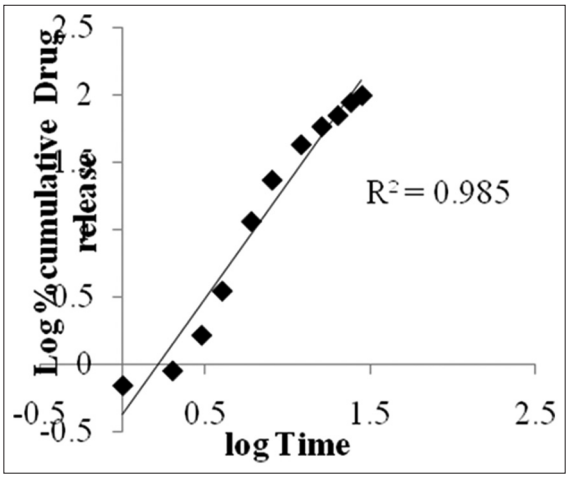

Fig. 8: Korsmeyer's Peppas plot of CF3 with Esc coat

was found to be dependent on the level of coating. 5, 10, 15, and 20% (coating level in TWG) corresponding to batches ES a, ES b, ES c, and ES d showed significant drug release (i.e., < 25%) after a lag time of 5 h (in pH 7.4 medium). Drug release in pH 7.4 buffer is > 90% for ES a, ES b in 10 h, >90% for ES c in 12 h, and <90% for EL d in 10 h. Formulation ES c coated with 15% TWG of Eudragit S-100 showed the most desirable properties. These values are reported in Table 11. Hence, ES c was considered as the optimized formulation for colonic drug delivery. Taking into account the dissolution profile of tramadol HCl compressed coated tablets, the CF3 was an optimized formulation as its dissolution profile was according to the expected requirements of the study [19].

The release mechanism is influenced by porosity and tortuosity of the matrix. Release kinetics was further fitted with different kinetic models, zero-order, first-order, Higuchi, or Korsmeyer–Peppas. Among these zero-order and Peppas plots are represented in Figs. 7 and 8. The drug release kinetics data was reported in Table 12 According to the observed values, ES c formulation was best fitted with a zero-order model indicating their release kinetics is not dependent on the concentration of the drug. The drug release data were fitted to the Korsmeyer–Peppas equation. In this study, the tramadol HCl release, in neutral medium, from Tamarindus gum tablets showed a good fit into the Korsmeyer–Peppas equation, indicating the combined effect of diffusion and erosion mechanisms for drug release. It exhibited a correlation coefficient (r^2) >0.98. If the values are, 0.45< n corresponds to a Fickian diffusion mechanism, and n = 0.89 indicates a purely relaxed controlled delivery which is referred to as Case II transport. Intermediate values 0.45< n < 0.89, which indicate

Table 11: Percentage drug release studies of compression coated CF3 with an enteric coat

pH	Time (h)	EL a	EL b	EL c	EL d	ES a	ES b	ES c	ES d
1.2	0	0	0	0	0	0	0	0	0
	1	0.5±0.01	0.09±0.01	0.07±0.01	0.07±0.01	0.7±0.05	0.3±0.07	0.7±0.08	0.3±0.02
	2	0.8±0.01	0.6±0.07	0.6±0.07	0.3±0.1	1.6±0.1	1±0.07	0.9±0.043	0.5±0.01
7.4	3	15.96±1.08	12.1±0.7	9.3±0.08	4.31±0.07	2.7±0.07	4.96±0.08	1.65±0.05	1.25±0.05
	4	24.58±1.26	21.7±1.41	17.27±0.5	18.46±0.4	3.5±0.4	4.7±0.5	3.5±0.26	2.46±0.08
	5	33.58±1.04	28.3±0.81	21.29±0.88	22.9±0.825	12.7±0.825	23.6±0.9	4.9±0.1	24.3±0.1
	6	64.68±1.06	36±1.05	29.57±0.88	53.05±0.955	24.06±0.955	49.01±0.88	21.6±1.48	57.6±0.1
	8	99.47±1.14	92.6±1.04	38.6±1.5	71.41±0.799	38.6±0.799	60.17±1.5	45.6±1.58	73.96±0.23
	10			98.88±1.4	97.5±1.37	49.14±1.37	98.28±1.4	68.4±1.80	94.43±0.4
	12							99.4±1.68	

Values are expressed as mean±SD (n=3) for all the samples. SD: Standard deviation

Table 12: Drug release kinetics

Formulation code	Zero-order	First-order	Higuchi	Korsmeyer–Peppas	Peppas (n)
CF3 with ES c (R^2)	0.9901	0.8231	0.8957	0.9851	0.981

an anomalous behavior (Non-Fickian kinetics with the mechanism of coupled diffusion/polymer relaxation). The values of n > 0.89 have been observed, which has been regarded as Super Case II kinetics. The mechanisms of drug release are (super case-II) since they fitted well with Korsmeyer–Peppas models as their r^2 values in the range of 0.999 with n value above 1. This indicates that the drug release depends on swelling, relaxation, and erosion of polymer and also follows zero-order release kinetics [20].

CONCLUSION

A successful chronotropic drug delivery requires that the suitable release mechanism in the delivery system only respond to the biological conditions such as variation in pH particular to the colon. Due to the lack of discontinuity in physiological parameters along the GI tract, few mechanisms can be incorporated into a delivery system to effect in this type of drug release, among them site-specific drug delivery was selected. Here, the use of Tamarindus gum as release retardant has special benefits in combination with HPMC in case of rheumatoid arthritis treatment to obtain desired lag time. A modified oral chronotropic system for timed release of tramadol HCl was made possible with the compressed coated tablets CF3 which shows better drug release followed by enteric coating with Es c coat fulfilled our objective of work.

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AUTHORS' CONTRIBUTIONS

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

CONFLICTS OF INTEREST

No conflicts of interest associated with this work.

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