Design and Development of a Colon-Specific Controlled Release System for Tramadol Hydrochloride

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Abstract: ***The study developed matrix tablets using guar gum and chitosan, with an EUDRAGIT L100 coating, for colon-specific delivery of Tramadol hydrochloride.***
FT-IR analysis showed no significant drug-excipient interactions. Powder flow properties and tablet physical characteristics met acceptable standards. In vitro studies indicated that drug release was influenced by guar gum content, with higher levels promoting sustained release. Formulations F1 to F7 achieved better controlled release, while F8 showed increased pH sensitivity due to the absence of guar gum and chitosan. EUDRAGIT L100 coating reduced drug release in the upper GIT, enhancing colon-specific delivery.

Key Words: ***Tramadol hydrochloride, Colon-specific drug delivery, Guar gum, Chitosan, EUDRAGIT L100, Matrix tablets, Controlled release, Polysaccharides.***

INTRODUCTION

Various drug entities based on oral delivery have been successfully commercialized, but many others are not readily available by oral administration, which are incompatible with the physical (or) chemical environments of the upper gastrointestinal tract (GIT) and demonstrate poor uptake in the upper GI tract. Due to the lack of digestive enzymes, colon is considered as suitable site for the absorption of various drugs. Over the past two decades the major challenge for scientist is to target the drugs specifically to the colonic region of GIT. Previously colon was considered as an innocuous organ solely responsible for absorption of water, electrolytes & temporary storage of stools. But now it is accepted as important site for drug delivery.

Colon targeting is used to treat:- Colon-specific drug delivery offers benefits such as targeting treatment for conditions like inflammatory bowel disease and colon cancer, systemic drug absorption, and chronotherapy for circadian-sensitive diseases. The colon's lower digestive enzyme levels reduce drug degradation, aiding absorption of labile substances. Although rectal administration is less convenient, oral formulations for colon delivery must delay release in the upper GI tract and activate upon reaching the colon. This approach improves treatment precision, lowers dosages, and reduces side effects.

MATERIALS AND METHODS

Preparation of standard graph of Tramadol Hydrochloride:

Accurately weighed amount of 100 mg of Tramadol hydrochloride was transferred into a 100 ml volumetric flask. Distilled water was added to dissolve the drug and the primary stock solution was made by adding 100 ml of distilled water. This gives a solution having concentration of 1000 µg/ml, of Tramadol hydrochloride stock solution. From this primary stock 10 ml was transferred in to another volumetric flask and made up to 100 ml with pH 1.2 acetate buffer (100 µg/ml), from this secondary stock 0.4, 0.8, 1.2, 1.6, 2.0, and 2.4 ml, was taken separately and made up to 10 ml with pH 1.2 acetate buffer solution, to produce 4, 8, 12, 16, 20 and 24 µg/ml respectively. The absorbance was measured at 271 nm using a UV spectrophotometer. Standard calibration curve values were shown in Table 11. The standard calibration curve of Tramadol hydrochloride in pH 1.2 was shown in Figure 1. Similarly Tramadol hydrochloride standard graphs were plotted in pH 7.4 and pH 6.8 phosphate buffers by following the above procedure and their calibration curves were shown in Figure 2 and 3.

FT-IR spectroscopy:

The infrared spectra of Tramadol hydrochloride, physical mixture of drug and excipients and placebo were recorded between 400 to 4000 cm^{-1} on FTIR to detect the drug-excipients interactions. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer. The resultant spectra were compared for any possible changes in the peaks of the spectra.

PREPARATION OF COATED TRAMADOL HYDROCHLORIDE TABLETS

1. Preparation of core matrix tablets of Tramadol Hcl:

The core tablets were prepared by direct compression method. The materials were weighed, mixed and passed through a mesh no 60 to ensure complete mixing. The thoroughly mixed materials were then directly compressed into tablets using 6 mm round, flat and plain punches on a single station tablet machine. Tablet quality control tests such as weight variation, hardness, friability, thickness, and dissolution in different media were performed on the core tablets. Different combinations of guar gum and chitosan were given in the table 9.

Ingredients	Quantity (mg) present in the formulation							
	F1	F2	F3	F4	F5	F6	F7	F8
Tramadol hydrochloride	100	100	100	100	100	100	100	100
Guargum	100	-	25	35	50	65	75	-
Chitosan	-	100	75	65	50	35	25	-
Lactose	50	50	50	50	50	50	50	100
Magnesium stearate	3	3	3	3	3	3	3	3
Microcrystalline cellulose	50	50	50	50	50	50	50	100
Talc	2	2	2	2	2	2	2	2

Table 1: Composition of guar gum & chitosan (100 mg) used in core tablets

2. Coating of the tablets:

Tablet coating was done by dipping method. Coating solution was prepared with Eudragit L 100 by dissolving it in Isopropyl Alcohol (12.5%). Poly Ethylene Glycol 400 was used as plasticizer (1.25%). Coating was done by dipping the core tablet in coating solution and drying the tablets in hot air oven at 40ºC for 30 min and coating thickness was measured.

In vitro drug release studies:

1. Drug release studies of Tramadol hydrochloride Core tablets: The core tablets containing 100 mg of Tramadol hydrochloride were tested in pH 1.2, pH 7.4 and pH 6.8 solutions for their dissolution rates. Dissolution studies were performed using USP dissolution test apparatus (Apparatus 2, 50 rpm, 37±0.5 °C). At various time intervals, a sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically.

2. Drug release studies of Coated Tramadol hydrochloride tablets: The release of Tramadol hydrochloride from coated tablets was carried out using USP basket-type dissolution at a rotation speed of 100 rpm, and a temperature of 37±0.5 °C. For tablets, gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in gastric fluid without pepsin, pH 1.2 for the first 2 hrs as the average gastric emptying time is about 2 hrs. Then, the dissolution medium was replaced with enzyme-free intestinal fluid, pH 7.4 and tested for drug release for 3 hrs, as the average small intestinal transit time is about 3 hrs, and finally colonic fluid, pH 6.8 was used for 15 hrs to mimic colonic pH conditions. Drug release was measured from coated Tramadol hydrochloride tablets, added to 900 ml of dissolution medium. Samples withdrawn at various time intervals were analyzed spectrophotometrically.

RESULTS AND DISCUSSION

Standard graph of Tramadol hydrochloride:

The standard graph of Tramadol hydrochloride in pH 1.2 showed good linearity with R^2 value of 0.999, which suggest that it obeys the "Beer – Lambert" law. The standard graphs in pH 7.4 and pH 6.8 had R^2 values of 0.999 and 0.996 respectively. Standard calibration curve values were shown in Table 11. Calibration curves were shown in Figures (1, 2 & 3).

Table 2: Standard graph of Tramadol hydrochloride Absorbance (nm)

Concentration (µg/ml)	pH 1.2	pH 7.4	pH 6.8
0	0	0	0
4	0.022	0.024	0.023
8	0.040	0.044	0.042
12	0.060	0.064	0.061
16	0.080	0.083	0.081
20	0.098	0.106	0.105
24	0.115	0.124	0.116

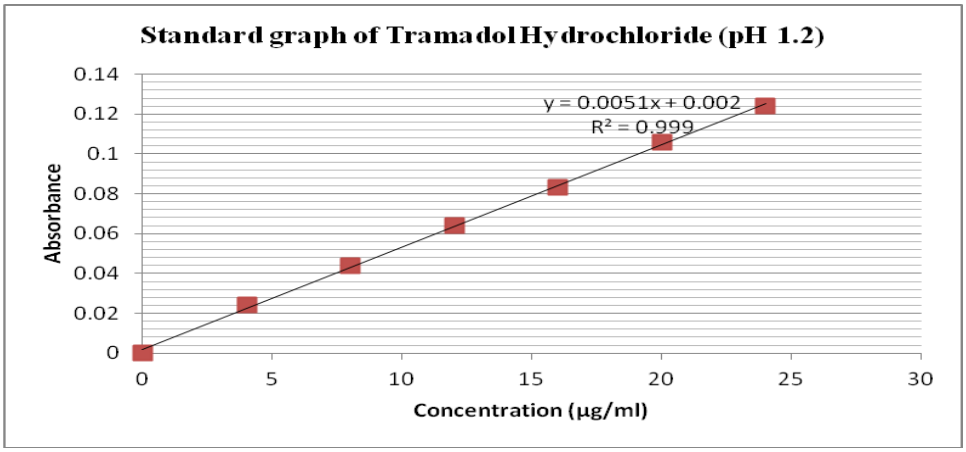

Figure 1: Standard graph of Tramadol HCl in pH 1.2

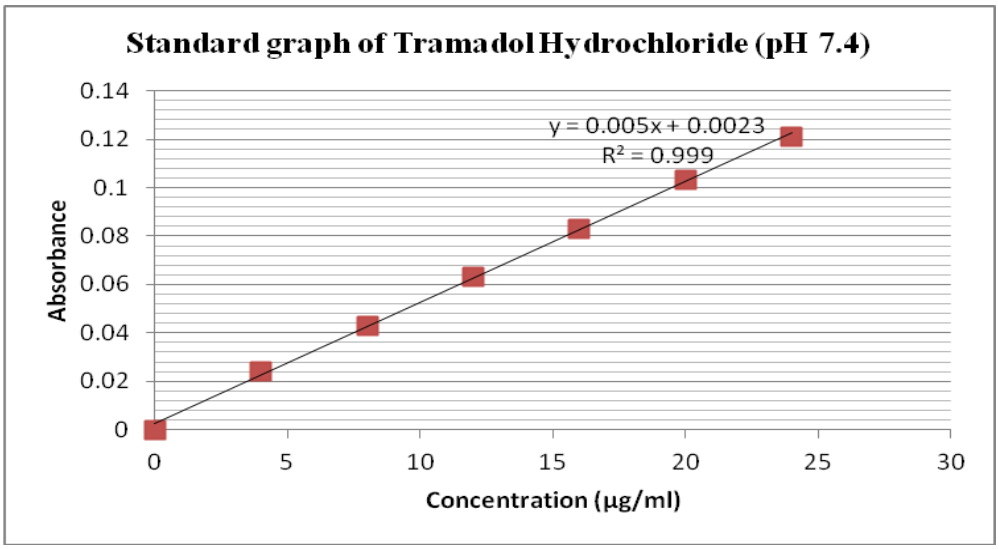

Figure 2: Standard graph of Tramadol HCl in pH 7.4

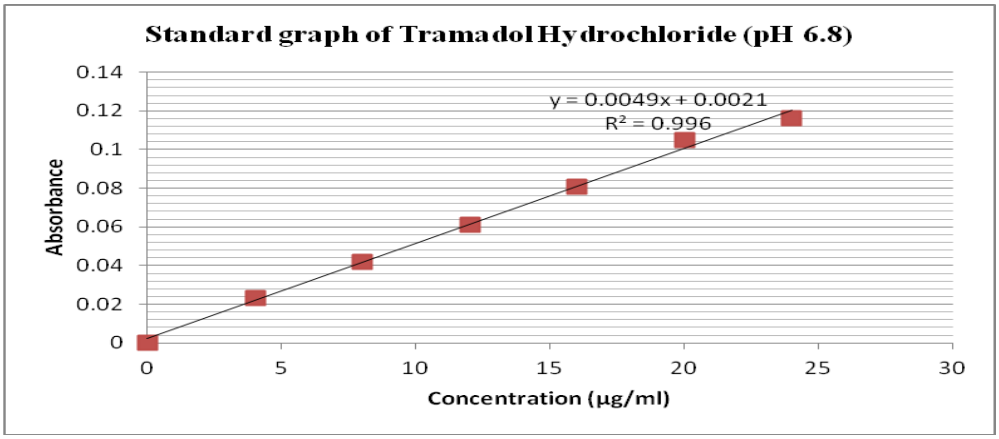

Figure 3: Standard graph of Tramadol HCl in pH 6.8

FT-IR spectroscopy:

In the FTIR spectrum of Tramadol Hydrochloride, the characteristics of aromatic CH stretching vibration about 3050 cm^{-1}, OH shoulders at 3300cm^{-1}, aliphatic CH stretching vibrations about 2900 cm^{-1} and aromatic ring stretching vibration about 1600 cm^{-1} are observed. It is evident that only slight shift in some of the groups characteristics of drug, took place with overlapping and broadening of similar peaks. No new bands were detected in the spectra of tablet formulation. Therefore, the drug was chemically stable after the formulation.

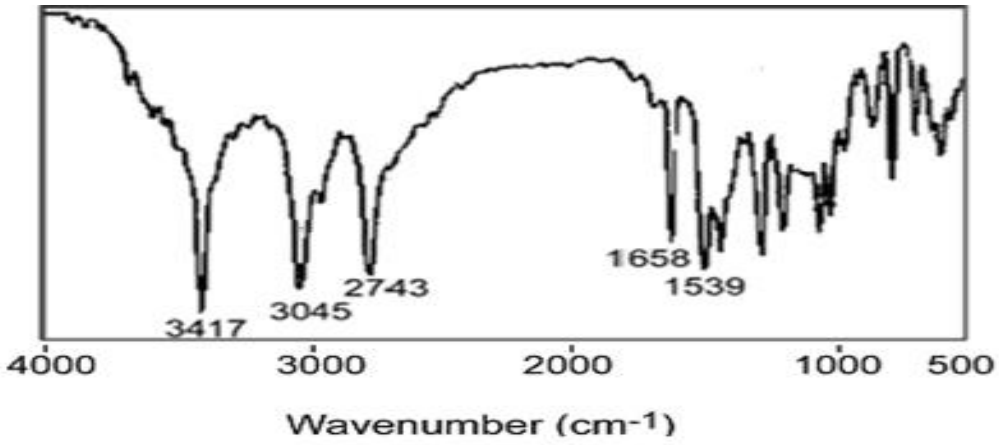

Figure 4: FTIR graph of Pure Tramadol HCl

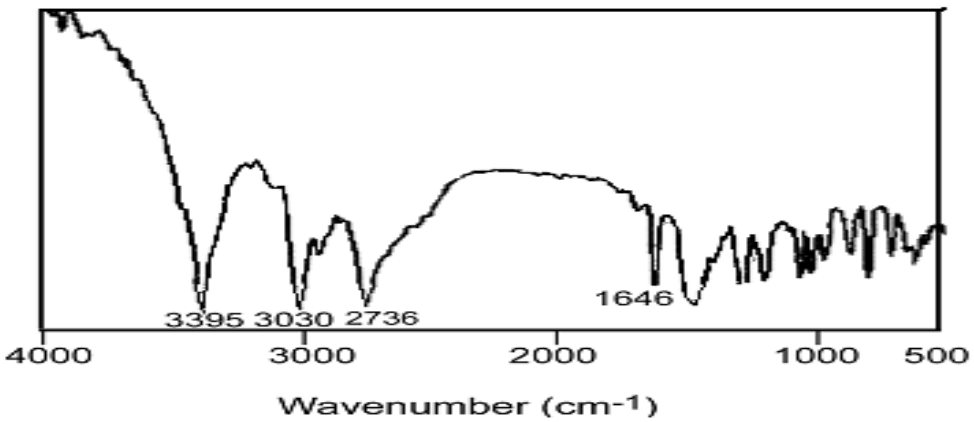

Figure 5: FTIR graph of optimized formulation

Powder characterization: The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped), and compressibility index and their values were shown in Table 3.

Formulation code	Angle of Repose (θ)	Bulk density (g/ml)	Tapped Bulk density (g/ml)	% Carr's Index	Hausner's ratio
F1	29.12±1.24	0.321	0.402	20.149	1.252
F2	31.23±1.32	0.332	0.412	19.417	1.241
F3	30.35±1.35	0.312	0.386	19.170	1.237
F4	29.56±1.46	0.323	0.398	18.844	1.232
F5	27.12±1.13	0.325	0.405	19.753	1.246
F6	30.35±1.35	0.365	0.469	22.174	1.285
F7	32.12±1.84	0.344	0.436	21.100	1.267
F8	30.65±1.35	0.332	0.412	19.417	1.241

Table 3: Characterization of powder mixture of different formulations

The apparent Bulk density and Tapped bulk density values ranged from 0.312 to 0.365 g/ml and 0.386 to 0.469 g/ml respectively. The results of Angle of repose and Carr's index (compressibility index (%) ranged from 27.12±1.13 to 31.23±1.32 and 19.417 to 22.174% respectively. The results of angle of repose (<35) and Carr's index (compressibility index) (<23) indicates fair to passable flow properties of the powder mixture and Hausner's ratio results ranged from 1.232 to 1.285 and these are (>1.232) indicates coarse to fine flow properties of the powder.

Evaluation of tablets:

1. Physical characteristics of Tramadol hydrochloride Core tablets:

Tramadol HCl and other excipients were compressed directly into a core tablet by using direct compression vehicle such as microcrystalline cellulose. The mean percent drug content of the Tramadol HCl core tablets was found to be ranging between 91.9 and 107.2% of the labeled amount indicating uniformity of drug content in the formulation (Table 13). The hardness of the core tablets of Tramadol HCl was 4.4±0.58 to5.4±0.64 kg/cm^2. The core tablets of Tramadol HCl were also found to comply with the friability test since the weight loss was found to be 0.05 to 0.64% and Weight was deviated between 224±2 to 308±2 mg and Thickness was between 2.80 ± 0.005 and 3.82 ± 0.014 mm. All the results were under the standards.

Formulation Code	Hardness (Kg/cm^2)	Deviation in Weight variation (mg)	Friability (%)	Drug Content (%)
F1	5.0±0.61	304±3	0.05	98.6
F2	5.2±0.35	306±3	0.33	94.4
F3	5.1±0.42	302±2	0.17	98.6
F4	5.0±0.25	308±2	0.34	102.9
F5	5.4±0.64	305±1	0.26	98.6
F6	4.6±0.70	305±2	0.64	107.2
F7	4.4±0.58	304±1	0.54	94.4
F8	4.8±0.46	224±2	0.15	91.9

Table 4: Physical properties of Tramadol hydrochloride Core tablets for different formulations

2. Physical characteristics of Eudragit L100 Coated tablets:

The coated tablets of Tramadol HCl were evaluated for physical characteristics like hardness, weight variation and drug content. Hardness of the tablets was ranging between 4.6±0.57 and 5.4±0.63 Kg/cm^2. Weight was deviated between 276.7±2.15 to 358.0±2.67 mg and drug content was between 95.6 and 99.9% and Thickness was between 3.64 ±0.039 and 5.75±0.022 mm. Friability values for coated tablets were almost 0% for all formulations. These values indicating that the coating of polymer was complete and uniform throughout all the formulation and they have given tremendous strength to these tablets. All the results were under the standards.

Formulation Code	Hardness (Kg/cm^2)	Deviation in Weight variation (mg)	Friability (%)	Drug Content (%)
F1	5.2±0.62	354.2±3.55	0	95.9
F2	5.3±0.34	356.4±3.11	0	95.8
F3	5.2±0.41	352.6±2.53	0	98.2
F4	5.1±0.24	358.0±2.67	0	96.6
F5	5.4±0.63	355.3±1.85	0	99.0
F6	4.8±0.75	355.2±2.44	0	95.6
F7	4.6±0.57	354.5±1.62	0	97.2
F8	4.7±0.45	276.7±2.15	0	99.9

Table 5: Physical properties of Tramadol hydrochloride Coated tablets for different formulations

3. Thickness of Core and Coated tablets:

Formulation Code	Thickness of Core Tablets (mm)	Thickness of Coated Tablets (mm)
F1	3.81 ± 0.011	5.74±0.023
F2	3.82 ± 0.014	5.73±0.021
F3	3.81 ± 0.012	5.74±0.024
F4	3.79 ± 0.010	5.69±0.022
F5	3.82 ± 0.012	5.75±0.022
F6	3.80 ± 0.013	5.73±0.024
F7	3.79 ± 0.012	5.72±0.023
F8	2.80 ± 0.005	3.64 ±0.039

Table 6: Thickness of Core and Coated tablets of different formulations

4. Dissolution results of Core Tramadol HCl tablets:

The tablet formulations containing various proportions of guar gum and chitosan were prepared. Drug release studies were performed in three types of fluids. In presence of pH 1.2 the drug release was below 5% for formulations F1-F7 by the end of 2hrs. This shows the integrity of the formulation in presence of stomach fluid and F8 releases 96.78% drug because of absence of guargum and chitosan. Further studies shows at the end of 6th hr drug release ranges below 25%. A further study in presence of pH 6.8 produces the drug release ranging F1 (70.24%) – F2 (98.35%). The increase of drug release is due to the susceptibility for degradation of guar gum and chitosan to colonic enzymes. The drug release was dependent on composition of guargum. Drug release decreases upon increase of guar gum composition in the formulation.

	Time	Cumulative % Drug release of Core Formulations							
	(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8
	0	0	0	0	0	0	0	0	0

pH 1.2	1	2.85	3.26	3.14	2.54	1.12	1.35	1.6	20.92
	2	4.31	4.91	4.82	3.82	2.08	2.46	3.12	62.65
pH 7.4	3	6.72	7.85	7.19	6.17	3.12	4.31	4.53	96.78
	4	9.13	10.80	9.56	8.55	9.54	6.71	6.78	-
	5	11.67	13.74	11.92	10.87	12.67	9.12	9.03	-
	6	12.18	22.04	24.38	20.04	19.96	14.51	17.38	-
pH 6.8	7	28.69	30.77	36.52	29.21	15.27	19.84	21.77	-
	8	37.20	39.51	45.36	38.38	20.54	28.17	32.27	-
	9	44.70	48.23	53.68	47.55	26.35	36.5	39.75	-
	10	50.25	56.86	62.08	53.72	35.48	44.83	49.24	-
	11	55.68	65.69	70.46	62.48	45.27	53.16	58.64	-
	12	60.35	75.42	78.58	75.06	56.53	61.49	67.54	-
	13	65.56	84.13	86.32	84.23	69.36	65.32	76.03	-
	14	70.24	98.35	95.65	93.45	75.24	69.82	83.52	-
	15	70.24	98.35	95.65	93.45	89.64	78.78	87.72	-

Table 7: Cumulative % Drug release of Tramadol HCl of Core tablet Formulations in pH 1.2, pH 7.4 and pH 6.8

5. Dissolution results of Coated Tramadol Hcl tablets: For the tablets coated with Eudragit L 100 drug release was found to be zero for first 2 hrs in presence of pH 1.2 shows no drug release due to insolubility of coat. At the end of 6 hrs the drug release was below 5% for formulations F1 to F7 and for F8 drug releases 94.35%. Further studies shows at the end of 8th hr drug release was 20.23%. The coating was able to resist the drug release. A Further drug release study in presence of pH 6.8 produces the drug release ranging 63.67% - 92.74% in which F1 which is having 100 mg of guar gum shows 63.67% drug release and F2 which is not having guar gum shows a maximum of 92.74% drug release. Moreover the drug release profiles increases with decrease of guar gum concentration. When we compare F8 with remaining formulations, they avoid the premature drug release. It occurs with F8 due to pH variations in the GIT.

	Time (Hrs)	Cumulative % Drug release of Coated Formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
pH 1.2	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	0	0
	2	0	0	0	0	0	0	0	0
pH 7.4	3	1.18	1.23	1.57	1.43	1.05	1.33	1.63	1.89
	4	2.41	3.43	2.23	3.46	1.89	2.59	2.46	2.75
	5	3.62	4.24	3.87	5.49	2.74	3.85	3.55	10.12
	6	4.54	6.37	4.43	6.54	3.59	5.12	4.51	20.23
pH 6.8	7	12.11	15.10	15.14	15.71	13.80	8.45	12.53	64.21
	8	19.68	23.83	20.75	26.88	20.01	16.78	20.49	94.35
	9	27.25	32.56	31.36	37.05	31.22	25.11	28.87	-
	10	32.82	41.29	39.97	46.22	42.43	35.44	37.47	-
	11	39.39	50.02	48.58	53.39	51.64	43.77	45.96	-
	12	48.86	58.75	57.19	63.56	60.06	50.15	54.45	-
	13	54.53	67.38	65.80	72.73	69.06	59.43	62.94	-
	14	59.12	76.10	74.41	79.92	76.16	66.76	71.43	-
	15	63.67	92.74	89.02	87.65	83.37	72.09	81.92	-

Table 8: Cumulative % Drug release of Tramadol HCl of Coated tablet Formulations in pH 1.2, pH 7.4 and pH 6.8

SUMMARY AND CONCLUSION

Matrix tablets of guar gum and chitosan, coated with EUDRAGIT L100, effectively protect Tramadol

hydrochloride from release in the upper GIT. FT-IR confirmed no drug-excipient interactions, and tablet properties met standards. In vitro studies showed that drug release depended on guar gum content, with sustained release achieved by higher levels. EUDRAGIT L100-coated tablets minimized upper GIT release, making this approach suitable for colon-specific delivery.

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