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EPITOMIZATION OF BIPHASIC MINI-TABLETS BY USING NATURAL POLYMERS FOR COLON SPECIFIC CHRONOTHERAPEUTIC DRUG DELIVERY

Sandeep Pasunooti[1]*, Rahul Shukla[2] and Venkanna Pasham[3]

[1]Rearch Scholar, Shri Venkateshwara University, Gajraula, Amroha, UP.

[2]School of Pharmaceutical Sciences, Shri Venkateshwara University, Gajaraula, Amroha, UP.

[3]Department of Pharmaceutics, Chaitanya Institute of Pharmaceutical Sciences, Rampur, Warangal, T.S.

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***Corresponding Author**
Sandeep Pasunooti
Rearch Scholar, Shri Venkateshwara University, Gajraula, Amroha, UP.

ABSTRACT

Solid oral tablet dosage forms are one of the most admissible dosages by majority of individuals. In these days increased focus on development of multiple units of single dose effectively compressed into biphasic drug delivery instead of filling into capsules. Propranolol hydrochloride is a medication of the non-selective beta blocker it is suitable drug to formulate as compression coated colon specific biphasic mini-tablets at predetermined release rates, in this fast release mini-tablets gives fast onset of action, delayed release mini-tablets to maintain plasma concentration. Fast, delayed release mini-tablets are prepared direct compression process and coating material prepared by wet granulation method to protect core from upper GI tract by taking different proportions of (F1 to F13) microbial degraded natural (Guar gum, xanthan gum, chitosan) and pH dependent polymers. The results of dissolution studies of formulation containing F13 was shows burst and delayed drug release up to 24hr at targeted region, phosphate buffer containing 4% w/v rat caecal substance and control have clarified the sensitivity of the natural polymers to the colonic enzymatic organism action with subsequent drug release. It follows all the kinetic mechanisms; FT-IR information showed that there is no conceivable between drug and excipients.

KEYWORDS: Propranolol hydrochloride, Compression coated colon specific biphasic mini-tablets, HPMC K 15 M, Guar gum, Xanthan gum, Chitosan.

INTRODUCTION

Oral route has greater importance of patient assistance and compliance, about two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. Truly pharmaceutical companies are planning immediate and repeated dosing of the drugs which may leads to high risk of dose dumping, variances in the dose, local irritation, this emerges the need to outline multiparticulate mini-tablets of biphasic dosage form same as a compressed into single unit larger tablet. Mini-tablets[10,13] are very small tablets whose diameter is equivalent to or littler than 4 mm that can be either put in the sachets or compressed into tablets or filled into a capsule shell for simple administration. They are having more advantages over single unit larger tablets such as exact, reliable drug release, uniform clinical performance and more adaptability during the formulation development and maximum stability on storage. Likewise mini tablets are easier to prepare using direct compression method which includes less number of steps utilizing single simple equipments for their manufacture, standard shape, superb size consistency, subsequently the time and cost can be saved.

Biphasic[2-4] dosage forms release the drug at two diverse discharge rates (or) distinctive time interims that is either fast/delayed or delayed/fast. A fast/delayed system provides an initial bust of drug release followed by a delayed release rate over a defined time period vice versa, these systems are utilized basically when greatest needs to be achieved quickly, trailed by delayed release rate up to 24hr to lessen the dosing frequency, keeping therapeutic concentration of drug for prolonged period of time with minimum local or systemic adverse impacts, so that it could be most valuable to the patient of chronotherapy. Chronotherapeutic[14,15] drug orchestration is concurring with biological rhythms[9] assemble maximal curative of drug in the burst at circadian timings, is accomplished by focusing of drugs to the colon[1,6] which offers steady drug level at the site of action, increased bioavailability of poorly absorbable drugs, decrease in dose of drug, prevents the gastric irritation, diminished dose recurrence, evasion of symptoms, enhanced patient consistence.

Propranolol hydrochloride is a medication of the non-selective beta blocker class, quickly and totally assimilated, with top plasma levels achieved about 1–3 hours after ingestion. It is lipid soluble and also has sodium channel blocking effects, it hinders the activity of epinephrine and norepinephrine at both β1-and β2-adrenergic receptors, used to treat hypertension,

unpredictable pulse, uneasiness, avoid headache migraines and to anticipate promote heart issues in those with angina.

MATERIALS AND METHODS

MATERIALS

Propranolol hydrochloride from Renuka raw pharma, Mumbai., Sodium starch glycolate from FMC bio polymers, HPMC K4M, HPMC K15 M, HPMC K100 M Eudragit-RL100 from Dr.Reddy's labs, Hyd., PVP K30 (PH 102) from Hetero drugs was obtained as a gift samples, Starch, Micro crystalline cellulose, Magnesium stearate, Talc purchased from S.D Fine chemicals Ltd., Guar gum, Xanthan gum, Chitosan purchased from Zeal chemicals.

METHODS

Preformulation studies

a) Determination of absorption maxima

A solution of Propranolol hydrochloride containing the concentration 10µg/ml was set up in the diverse buffer solutions i.e. SGF (pH-1.2), SIF (pH-7.4, pH-6.8) individually, the arrangement was examined in scope of 200 to 400 cm^{-1} by utilizing double beam UV spectrophotometer.

b) Construction of calibration curve

100 mg of Propranolol hydrochloride was precisely weighed and dissolved in 100 ml of methanol containing 100 ml volumetric jar to make(1000 µg/ml) standard stock solution(1). Then 10 ml of stock solution(1) was taken in another 100 ml volumetric jar makeup the mark(100 µg/ml) with various buffer arrangements SGF(pH-1.2), SIF(pH-7.4, pH-6.8) that is standard stock (2), again take 0.4, 0.8, 1.2, 1.6, 2 ml of standard stock (2) was taken in another 10 ml of volumetric jar to get concentration of 4, 8, 12, 16, 20 µg/ml with the same buffer. The absorbance of standard arrangements was resolved utilizing UV spectrophotometer at 290ηm.

Drug-excipient compatability studies

The similarity of the physical blend was contrasted with those of plain drug to investigate the changes in the chemical composition by using IR spectrophotometer (Bruker, India). IR range was recorded from 3500 cm^{-1} to 500 cm^{-1}, resultant range was thought about for any range changes.

Evaluation of Precompression studies

The prepared granules are subjected to various evaluation parameters angle of repose, bulk density, tapped density, compressibility index, hausner ratio.

Formulation of compression coated tablets

Calculation of dose

The stacking, maintenance dose of biphasic drug delivery calculated by following condition

$$Dt = Dose\ (1+0.693\ x\ t/t^{1/2})$$

Where, Dt = Total dose of drug, Dose = Dose of fast release mini-tablets, t = Time (hr), $t^{1/2}$ = Half life of drug (3.79).

$$Dt = 25(1+0.693\ x\ 12/3.79) = 80\ mg$$

Subsequently, formulation contains total dose 80 mg with 25 mg loading dose i.e. Fast release mini-tablets, 55 mg maintenance dose i.e. Delayed release mini-tablets.

Preparation of fast release (FR) and Delayed release (DR) core mini-tablets

Fast release, delayed release Propranolol hydrochloride core mini-tablets prepared by joining distinctive extents of super disintegrant (disintegrant time <1 min), enteric polymers as per table 1 and 2, PVP K30 (Binder), MCC (Diluent), Magnesium stearate (Lubricant), Talc (Glidant). The core FR of each mini-tablet excipients was precisely weighed blended and went through the No. #60(250µm) mesh screen to ensure finish blending. Every core DR mini-tablets excipients were precisely weight, taken into a motor and pestle by going through a No. #40 mesh screen, blended physically for 5 min, granulated with starch paste (10%) as a granulating agent then mass was gone through the No. #22 mesh screen, dried in a hot air oven at 50ºC for 2 hr, and dried granules went through the No. #44 mesh screen. At long last talc, magnesium stearate was added to the sieved granules and blend it for about 5 min in a poly pack. Core mini-tablets compressed by direct compression strategy utilizing 4 mm round, flat, plane punches on 16 station tablet punching machine (Cadmach, India).

Table 1: Composition of Propranolol hydrochloride FR core mini tablets.

Formula	Drug	SSG	PVP K30	MCC	Mg stearate	Talc	Total Weight
FR1	25	2.5	2	19	0.50	1	50
FR2	25	5	2	16.5	0.50	1	50
FR3	25	7.5	2	14	0.50	1	50
FR4	25	10	2	11.5	0.50	1	50

Table 2: Composition of Propranolol hydrochloride DR core mini tablets.

Formula	Drug	HPMC K4M	HPMC K100M	Eudragit-RL100	PVP K30	Starh	MCC	Mg stearate	Talc	Total weight
DR1	27.5	2.5	-	-	2	5	11.5	0.50	1	50
DR2	27.5	5	-	-	2	5	9	0.50	1	50
DR3	27.5	7.5	-	-	2	5	6.5	0.50	1	50
DR4	27.5	-	2.5	-	2	5	11.5	0.50	1	50
DR5	27.5	-	5	-	2	5	9	0.50	1	50
DR6	27.5	-	7.5	-	2	5	6.5	0.50	1	50
DR7	27.5	5	-	2.5	2	5	6.5	0.50	1	50
DR8	27.5	5	-	5	2	5	4	0.50	1	50
DR9	27.5	5	-	7.5	2	5	1.5	0.50	1	50

Preparation of compression coated Propranolol hydrochloride mini-tablets

The produced Propranolol hydrochloride core mini-tablets from the past part were subjected to compression coating is shown in table 3. Every ingredients of each coating layer were precisely weight, taken into a motor and pestle by going through a No. #40 mesh screen, blended physically for 5 min. At that point the mix was granulated with starch paste (10%) as a granulating agent then mass was gone through the No. #22 mesh screen, dried in a hot air oven at 50ºC for 2 hr, and dried granules went through the No. #44 mesh screen. At long last talc, magnesium stearate was added to the sieved granules and blend it for about 5 min in a poly pack. Compression coating of tablets was performed by utilizing 9 mm round, flat, plane punches on 16 station tablet punching machine (Cadmach, India). Half sum required for the coat was put in the die then one FR and two DR core mini-tablets are precisely situated in the center of the die and after that the other half was included, the powder were compacted around the core mini-tablets utilizing consistent pressure drive 5kg/cm^2.

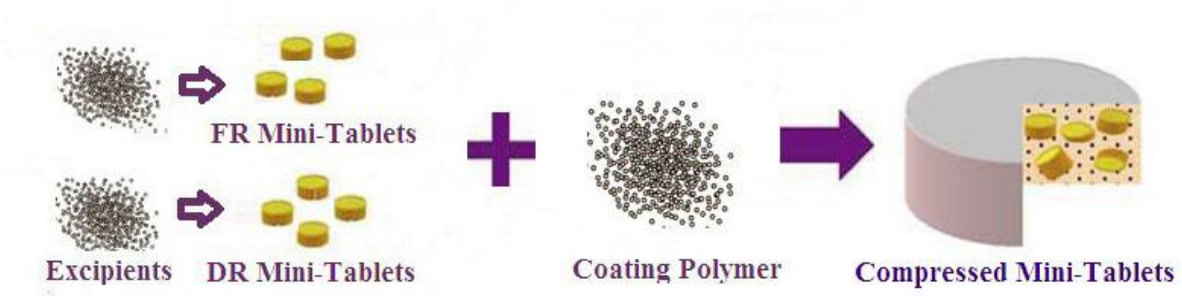


Fig. 1: Epitomization of Biphasic Propranolol hydrochloride mini-tablets.

Table 3: Composition of compression coated Propranolol hydrochloride core mini-tablets.

Formula	Guar gum	Xanthum gum	Chitosan	HPMC K15M	PVP K30	Starh	MCC	Mg stearate	Talc	Coat weight	Core weight	Total weight
F1	150	15	30	-	12	30	54	3	6	300	50	450
F2	150	22.5	22.5	-	12	30	54	3	6	300	50	450
F3	150	30	15	-	12	30	54	3	6	300	50	450
F4	175	17.5	35	-	14	35	63	3.5	7	350	50	500
F5	175	26.25	26.25	-	14	35	63	3.5	7	350	50	500
F6	175	35	17.5	-	14	35	63	3.5	7	350	50	500
F7	200	20	40	-	16	40	72	4	8	400	50	550
F8	200	30	30	-	16	40	72	4	8	400	50	550
F9	200	40	20	-	16	40	72	4	8	400	50	550
F10	200	30	30	8	16	40	64	4	8	400	50	550
F11	200	30	30	16	16	40	56	4	8	400	50	550
F12	200	30	30	24	16	40	48	4	8	400	50	550
F13	200	30	30	32	16	40	40	4	8	400	50	550

Evaluation of Postcompression studies

The prepared compression coated and core mini-tablets were subjected to weight variation, thickness, hardness, friability, drug content and wetting time.

***In vitro* drug release studies**

Drug release studies of Propranolol hydrochloride core mini-tablets

The core mini-tablets containing 80 mg Propranolol hydrochloride of were tested in various buffer solutions SGF (pH-1.2), SIF (pH-7.4, pH-6.8) for their dissolution rates. Dissolution studies were performed utilizing USP dissolution test apparatus (Apparatus II, 50 rpm, 37±0.5 ^{0}C). At different time intervals, a sample of 5 ml was pulled back and supplanted with parallel volume of fresh medium. The samples were analyzed spectrophotometrically at 290 ηm.

Drug release studies of compression coated Propranolol hydrochloride tablets

The release of Propranolol hydrochloride from compression coated mini-tablets was completed utilizing USP basket-type dissolution apparatus (Labindia DS 8000, India) at a turn speed of 100 rpm, temperature of 37±0.5^{0}C. Along these studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the initial 2 hr, as the normal gastric purging time is around 2 hr. At that point the dissolution medium was supplanted with enzyme-free simulated intestinal fluid (SIF, pH 7.4) tried for drug release for 3 hr, as the normal small intestinal travel time is around 3 hr, lastly enzyme-free simulated intestinal fluid (SIF, pH 6.8) was utilized for 19 hr to imitate colonic pH conditions. Drug release was estimated from compression coated Propranolol hydrochloride mini-tablets; a sample of 5 ml was pulled

back and supplanted with measure volume of new medium, analyzed spectrophotometrically at 290 ηm. All dissolution runs were performed in triplicate.

Drug release studies in presence of rat caecal contents

Preparation of rat caecal contents

The sensivity of natural polymer coat to the enzymatic activity of colonic organisms was evaluated by proceeding with the drug release studies in 100 ml of SIF (pH 6.8) containing 4% w/v of rat caecal substance. The caecal substance was gotten from male albino rats after pre-treatment for 7 days with natural polymer dispersion. Presence of 4% w/v rat caecal substance in SIF (pH 6.8) acquired following 7 long periods of pre-treatment of rats with 1 ml of 2% w/v fluid dispersion of natural polymer give the best conditions to in vitro assessment of natural polymer.

Thirty minutes previously the initiation of drug release studies, rats were killed by spinal footing. The belly was opened, the caecal were isolated, ligated at the two finishes, dismembered and instantly moved into SIF (pH 6.8), beforehand bubbled with CO_2. The caecal packs were opened their substance were separately measured, pooled and after that suspended in SIF (pH 6.8) to give a last caecal dilution of 4% w/v. As the caecum is normally anaerobic, every one of these activities was done under CO_2.

Dissolution studies in artificial rat caecal contents

The in-vitro drug release contemplates were completed utilizing USP dissolution rate test apparatus I, 100 rpm, 37^0C with slight alterations. A measuring glass (capacity 250ml) containing 100 ml of 4% rat ceacal substance medium was drenched in the phosphate buffer pH 6.8 kept up in 1000-ml vessel which was in the water bath of the apparatus. The tablet formulation after completing the dissolution studies in 0.1M Hcl (2 hr) and Phosphate buffer pH 7.4 (3 hr) were set in the basket of the apparatus and drenched in the rat ceacal substance medium contained in 250 ml beaker. The drug discharge studies were carried out for 19 hr (common colonic travel time is 20–30 hr) and 1 ml samples were taken at various time intervals without a prefilter and supplanted with 1 ml of fresh SIF (pH 6.8) bubbled with CO_2. To the samples, 1 ml of ethanol was added to guarantee solubility of finely suspended drug particles discharged because of separate of the coat by caecal organisms. The volume was made up to 10 ml with SIF (pH 6.8), centrifuged and the supernatant was filtered through a bacteria- evidence channel and the filtrate was analyzed for propranolol hydrochloride content at 290 ηm, the above investigation was completed on F10, F11, F12 and F13 details.

Control Study: The drug release studies were also conducted without pretreatment of gum in SIF (pH 6.8) by following the same experimental conditions as mentioned above.

***In vivo* X-ray studies**

X-ray imaging method or Roentgenography was utilized to screen the tablet all through GI tract. The inclusion of radio-murky material into the solid dosage form enables it to be envisioned by the use of X-rays. By joining barium sulphate into the pharmaceutical dosage form, it is conceivable to follow the movement, area and integrity of the dosage form after oral administration by setting the subject under a fluoroscope and taking a progression of X-rays at different time focuses.

Three healthy human volunteers, male, with a breaking point of 22-30 years and 50-70 kg body weight, were taken part in *in vivo* studies. They were non-drunkards, non-smokers and have not taken any medications. The motivation behind the examination was completely clarified and volunteers had given their composed assent. Each subject ingested barium sulphate containing natural polymer and HPMC K15 M compression coated (F13 formulation) tablets orally with 200 ml water, after a medium-term fast. The tablets were pictured utilizing X-ray. Stomach radiographs were taken after 30 min, 3, 6, 8 and 24 hr in all subjects. The volunteers were presented with food; 2 hr (breakfast) and 4 hr (lunch) after the administration of the tablet.

Release Rate Kinetics Studies

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi and Korsmeyer-Peppas release model. The correlation coefficient R^2 was used as an indicator of the best fitting for each of the models considered.

Stability studies

The stability studies were carried out according to ICH to assess the changes in the quality of a drug. Optimized formulation was sealed in aluminum packaging laminated with polyethylene. Sample were kept at 40 ^{0}C and 75% RH for 3 months. At the end of the study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics.

RESULTS AND DISCUSSION

The present research was aimed to develop novel colon specific chronotherapeutic drug delivery system of Propranolol hydrochloride for safe and effective therapy by using natural polymers as a compression coat over the core mini-tablets.

Analytical studies

Constructions of calibration curve

The standard graph of Propranolol hydrochloride in SGF (pH 1.2), SIF (pH 7.4) and SIF (pH 6.8) had showed good linearity with R^2 value of 0.999, which suggest that it obeys the "Beer – lambert" law. Standard calibration curve values were shown in table 4, figure 2, 3, and 4.

Table 4: Standard graph of Propranolol hydrochloride in SGF and SIF.

Concentration (µg/ml)	SGF (0.1N Hcl)	SIF (pH 7.4)	SIF (pH 6.8)
0	0	0	0
4	0.261	0.248	0.266
8	0.490	0.503	0.521
12	0.740	0.784	0.751
16	0.960	1.066	1.031
20	1.195	1.332	1.267

SGF = simulated gastric fluid

SIF = simulated intestinal fluid

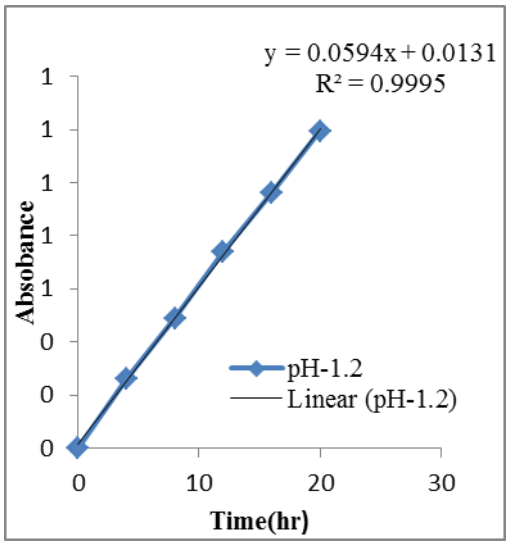


Fig. 2: Standard graph of Propranolol hydrochloride in SGF (0.1N Hcl).

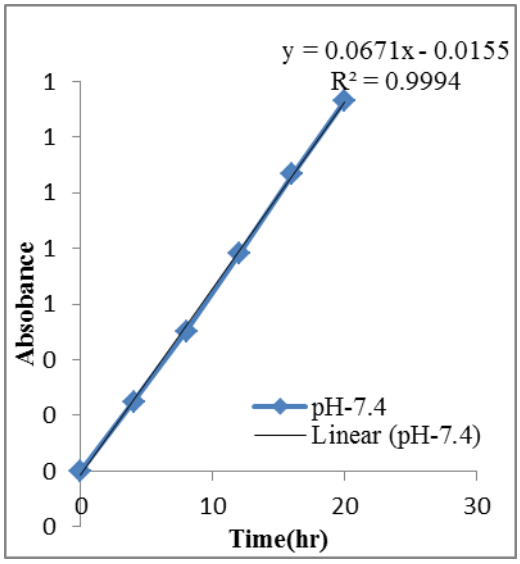


Fig. 3: Standard graph of Propranolol hydrochloride in SIF (pH 7.4).

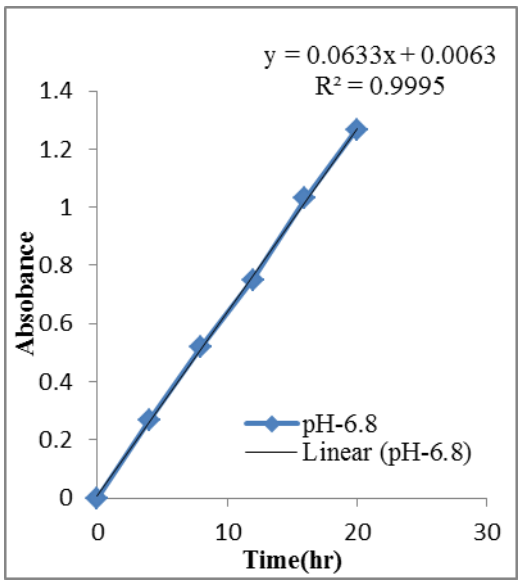


Fig. 4: Standard graph of Propranolol hydrochloride in SIF (pH 6.8).

Evaluation of Precompression studies

The powder mixtures of different formulations were evaluated for angle of repose, bulk density, compressibility index, Hausners Ratio and their values were shown in Table 5.

Table 5: Characterization of FR and DR powder mixture.

Formulation code	Angle of Repose(degrees)	Bulk density	Tapped density	Compressibility Index (%)	Hausners Ratio
FR1	26.25±1.22	0.432	0.471	8.28	1.09
FR2	26.14±1.52	0.434	0.473	8.25	1.09
FR3	26.14±1.19	0.437	0.474	7.81	1.08
FR4	27.17±1.33	0.441	0.476	7.35	1.08
DR1	24.24±1.26	0.429	0.480	10.63	1.12
DR2	25.29±1.22	0.431	0.475	9.21	1.10
DR3	25.14±1.35	0.435	0.475	8.42	1.09
DR4	26.36±1.21	0.444	0.475	6.53	1.07
DR5	26.45±1.42	0.443	0.474	6.54	1.07
DR6	26.31±1.42	0.442	0.474	6.75	1.07
DR7	25.56±1.54	0.444	0.479	7.31	1.08
DR8	25.47±1.54	0.448	0.476	5.88	1.06
DR9	26.15±1.82	0.446	0.476	6.30	1.07

Table 6: Characterization of compression coated powder mixture.

Formulation code	Angle of Repose(degrees)	Bulk density	Tapped density	Compressibility Index (%)	Hausners Ratio
F1	26.55±1.41	0.429	0.469	8.53	1.09
F2	26.15±1.32	0.434	0.477	9.01	1.10
F3	26.58±1.69	0.439	0.476	7.77	1.08
F4	25.85±1.65	0.44	0.468	5.98	1.06
F5	26.24±1.35	0.431	0.472	8.69	1.10
F6	26.54±1.69	0.435	0.467	6.85	1.07
F7	26.65±1.85	0.436	0.474	8.02	1.09
F8	26.55±1.89	0.439	0.476	7.77	1.08
F9	27.19±1.22	0.433	0.469	7.68	1.08
F10	26.44±1.56	0.434	0.465	6.67	1.07
F11	27.54±1.55	0.436	0.475	8.21	1.09
F12	26.34±1.57	0.44	0.469	6.18	1.07
F13	26.88±1.40	0.441	0.466	5.36	1.06

The results of angle of repose (<35), compressibility index (<15) and Hausner ratio (<1.25) indicates good flow properties of the powder mixture.

Evaluation of Postcompression studies

Physical characterization of Propranolol hydrochloride core mini-tablets

The core mini-tablets formulations were prepared according to the formula table 2; different formulations were subjected to various evaluation tests such as uniformity of weight, drug content, hardness, friability and *in vitro* dissolution.

Table 7: Physical properties of FR and DR core tablets.

Formulation Code	Hardness (Kg/cm^2)	Deviation in Weight variation (mg)	Thickness (mm)	Friability (%)	Drug Content (%)
FR1	4.62±0.14	50.42±0.47	3.54±0.56	0.40	98.64
FR2	4.64±0.26	51.60±0.24	3.58±0.21	0.57	100.24
FR3	4.49±0.35	50.85±0.29	3.60±0.41	0.56	99.84
FR4	4.52±0.69	50.58±0.35	3.53±0.42	0.60	97.65
DR1	5.12±0.65	50.12±0.25	3.23±0.54	0.42	97.56
DR2	5.17±0.56	50.20±0.87	3.38±0.25	0.46	98.95
DR3	5.22±0.26	50.45±0.24	3.45±0.62	0.42	101.1
DR4	5.45±0.15	51.41±0.48	3.33±0.56	0.49	96.99
DR5	5.37±0.62	50.52±0.89	3.64±0.36	0.58	98.59
DR6	5.25±0.56	50.58±0.78	3.28±0.22	0.53	100.21
DR7	5.74±0.19	51.22±0.56	3.38±0.41	0.51	100.32
DR8	5.86±0.18	50.54±0.77	3.58±0.42	0.56	99.45
DR9	5.65±0.39	50.41±0.55	3.63±0.88	0.56	98.23

Data represents mean ± SD, n = 3

The physical parameters for the core mini-tablet formulations were within the limits. Hardness 4.49±0.35 to 5.86±0.18 kg/cm2, thickness 3.53±0.42mm to 3.64±0.36, friability (<1) and showed 100% of labeled amount of drug indicating uniformity of drug content, disintegrates within 58sec showing the required fast disintegration characteristics, wetting time for all the tablets was found in the range of 11.34 ± 0.26 (FR2) sec.

Physical characterization of Propranolol hydrochloride compression coated Tablets

The compression-coated tablet formulations were prepared according to the formula table 3; different formulations were subjected to various evaluation tests such as uniformity of weight, drug content, hardness, friability and *in vitro* dissolution.

Table 8: Physical characterization of Propranolol Hydrochloride compression coated tablets.

Formulation code	Hardness (Kg/cm^2)	Deviation in Weight variation (mg)	Thickness (mm)	Friability (%)	Drug Content (%)
F1	5.41±0.39	452.42±0.44	4.49±0.14	0.56	99.94
F2	5.54±0.12	451.22±0.14	4.60±0.17	0.59	98.26
F3	5.49±0.56	450.23±0.85	4.58±0.25	0.50	100.2
F4	6.11±0.14	501.21±0.47	5.08±0.21	0.55	98.58
F5	6.17±0.24	499.07±0.14	5.12±0.14	0.62	99.45
F6	6.21±0.08	500.22±0.25	5.17±0.09	0.57	100.01
F7	6.55±0.12	550.45±0.21	5.28±0.17	0.50	99.98
F8	6.49±0.24	550.24±0.08	5.31±0.11	0.52	100.04
F9	6.48±0.21	552.16±0.51	5.27±0.12	0.47	99.98

F10	6.54±0.11	550.25±0.70	5.30±0.14	0.45	98.25
F11	6.41±0.41	550.54±0.65	5.27±0.15	0.49	99.17
F12	6.50±0.04	550.68±0.32	5.31±0.04	0.46	101.23
F13	6.45±0.15	550.23±0.22	5.36±0.06	0.48	100.11

Data represents mean ± SD, n = 3

The physical properties of compression coated tablets are given in Table 8. Weight variation was found to be 450.23±0.85 to 552.16±0.51, mean thickness 4.08±0.11 to 4.39±0.27, friability lose less than 1%, hardness 4.49±0.14 to 5.36±0.06 kg/cm^2. It was found that crushing strength of compression coated tablets was dependent on amount of guar gum, xanthan gum, chitosan, HPMC polymers, when HPMC in polymer mixture increased the crushing strength of coated tablets increased (India Pharmacopoeia, 1996).

In-vitro drug release studies

Drug release studies of FR and DR core mini-tablets

The in-vitro dissolution studies of FR and DR mini-tablets indicated that the optimized FR2 formulation released 98% of the drug in 45 min and DR7 formulation released drug in the delayed release up to 12hr to maintain plasma drug level shown in Fig 6.

Table 9: Cumulative percentage drug release of F1-F9 with different concentrations of enteric polymers.

Time (hr)	DR1	DR2	DR3	DR4	DR5	DR6	DR7	DR8	DR9
0	0	0	0	0	0	0	0	0	0
1	14.38	9.64	9.82	8.48	6.70	5.18	4.82	7.77	6.16
2	27.41	19.46	19.11	17.77	15.36	11.34	10.65	18.75	15.54
3	35.98	30.71	27.05	24.11	22.14	17.23	19.55	25.63	20.18
4	48.21	41.16	30.98	28.93	26.96	22.68	27.95	31.43	27.41
5	61.34	51.61	38.21	32.68	30.09	26.43	33.48	37.77	34.20
6	75.89	61.43	47.41	38.66	35.27	31.88	41.52	45.36	38.13
8	83.66	74.82	56.25	44.38	40.80	37.95	49.91	54.02	46.61
10	99.73	86.79	63.04	49.64	45.45	42.32	61.25	59.11	55.18
12	100.00	97.95	69.55	55.27	51.88	47.68	70.27	64.91	62.32
14	100.09	99.38	74.29	63.13	60.54	55.09	80.98	71.61	68.48
16	99.38	100.27	79.46	68.39	65.54	63.39	89.46	77.68	74.20
18	98.84	100.00	84.55	73.66	69.38	68.39	99.91	84.64	78.84
20	99.29	99.38	87.68	77.59	74.02	72.59	99.29	88.04	83.48
24	98.84	98.84	93.13	81.61	79.91	76.61	98.30	93.57	89.02

Data represents mean ± SD, n = 3

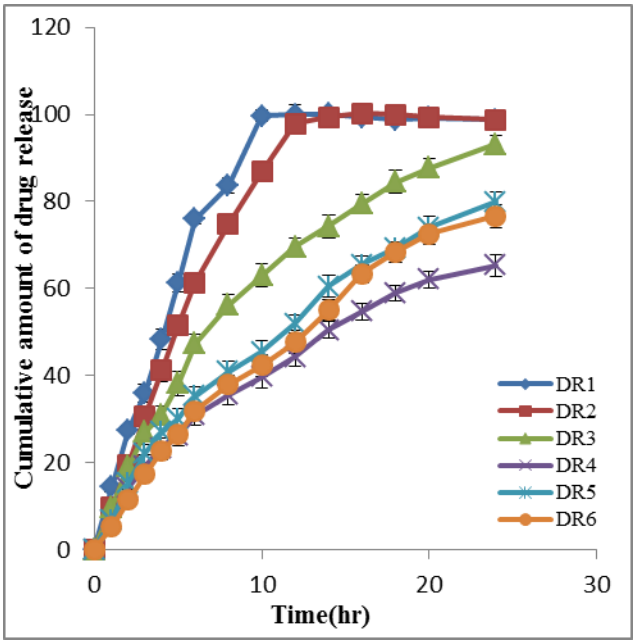


Fig. 5: Dissolution profiles of DR1-DR6 core mini-tablets.

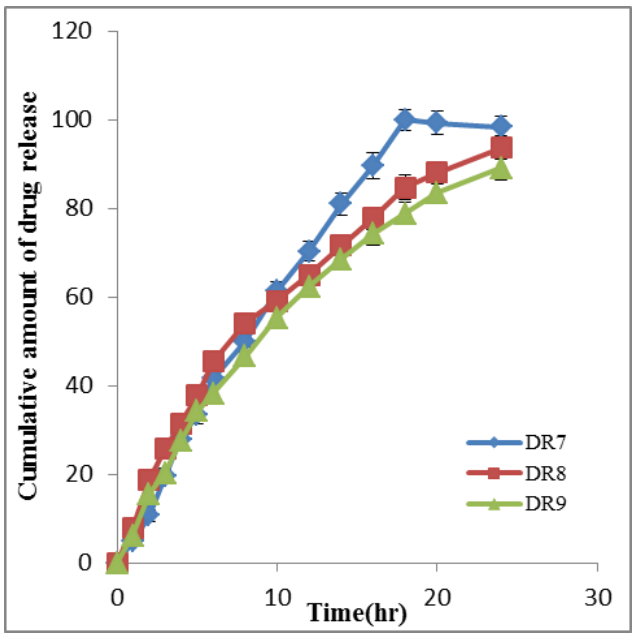


Fig. 6: Dissolution profiles of DR7-DR9 core mini-tablets.

Drug release studies of compression coated Propranolol hydrochloride mini-tablets

The prepared Propranolol hydrochloride compression coated mini-tablets were subjected to in-vitro dissolution testing to recognize a reasonable formulation which immediately release Propranolol hydrochloride after slack time (<10%) if least 5hr. In this way, we prepared nine formulations of compression coated mini-tablets of various coat weights (300, 350, 400 mg) with different ratios of natural polymers (Guar gum 50%, Xanthan gum: Chitosan-5:10, 7.5:7.5, 10:5%) as appeared in the table 3. F1 to F6 (300, 350 mg coat) neglect to protect the

drug release in the upper regions of gastro intestinal tract (Figure 7), Cumulative amount of drug released from 400mg coat weight contains F7, F8, F9 was observed to be 4% in SGF (2hr), 5 to 13% in SIF (5hr), 25 to 30% in SIF (24hr) as appeared in the table 10. It was found that as the convergence of gum polymer was increasing, the release rate of Propranolol hydrochloride from compression coated mini-tablets was diminishing. This is because of hydrophilic nature of gum polymer and its rate of hydration has increased by the rise its concentration resulting in decreased dissolution rate. After that we prepared from the optimized formulation (F8) of F10, F11, F12 and F13 with time dependent polymer (HPMC K15M) in the different ratios 2%, 4%, 6%, 8% of four formulations additionally impede the drug release. Cumulative percent of drug release from the above formulations was found to vary from 0% in SGF (2hr), 3 to 5% in SIF (5hr), 17 to 20% in SIF (24hr) respectively.

In this way the F1 to F9 were not examined further in rat caecal contents. Despite the fact that F10, F11, F12 and F13 formulation releasing little amount of drug after 24 hr study, it was additionally studied in 4% caecal substance to know the impact of coat thickness (400 mg coat weight) compared with 2% caecal substance.

Table 10: Cumulative percentage drug release of F1-F13 with different coat weights.

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	9.15	7.82	7.44	6.96	6.39	5.43	3.15	0	0	0	0	0	0
2	11.44	10.58	9.15	8.20	7.53	6.67	5.53	5.24	0	0	0	0	0
3	15.95	15.62	14.02	14.52	13.77	12.68	6.88	5.88	2.94	0	0	0	0
4	16.96	16.20	15.20	14.94	14.78	15.28	10.33	8.48	4.70	3.78	2.77	0	0
5	20.57	19.81	19.06	16.88	16.04	16.54	12.09	12.34	6.97	5.04	4.37	3.69	3.95
6	26.25	24.64	24.38	19.64	22.23	19.64	20.09	19.91	11.61	9.38	6.38	5.00	4.64
8	30.45	29.64	27.59	25.27	24.91	23.48	24.02	23.04	16.25	10.71	10.09	6.34	6.52
10	33.75	32.59	32.59	27.41	26.96	25.36	26.52	26.52	18.30	12.41	11.16	8.93	8.57
12	37.86	36.07	35.18	28.75	27.05	26.70	28.04	27.50	20.80	14.29	12.32	10.54	10.18
14	39.82	38.30	36.79	31.52	28.30	28.75	29.11	28.66	22.77	15.80	14.55	12.23	11.70
16	42.23	40.09	37.68	34.73	30.18	31.16	30.89	29.46	24.82	17.86	15.98	14.20	12.86
18	44.55	41.88	38.30	37.68	33.57	34.29	31.96	30.27	26.52	19.11	17.50	15.27	14.38
20	46.25	43.93	40.27	39.29	36.34	35.80	33.30	31.96	27.14	21.07	19.07	16.88	15.89
24	48.57	45.80	41.88	41.43	39.64	36.96	35.54	33.48	28.84	22.41	20.45	18.63	17.05

Data represents mean ± SD, n = 3

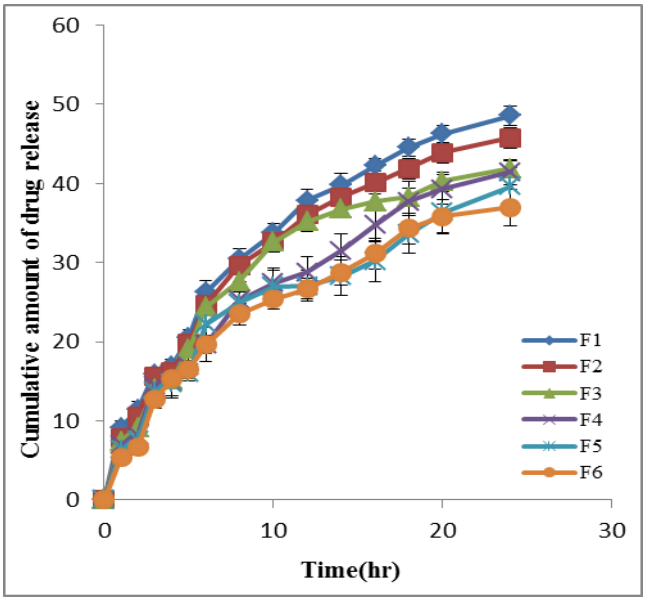


Fig. 7: Dissolution profiles of F1-F6 formulations containing 300, 350mg coat weight.

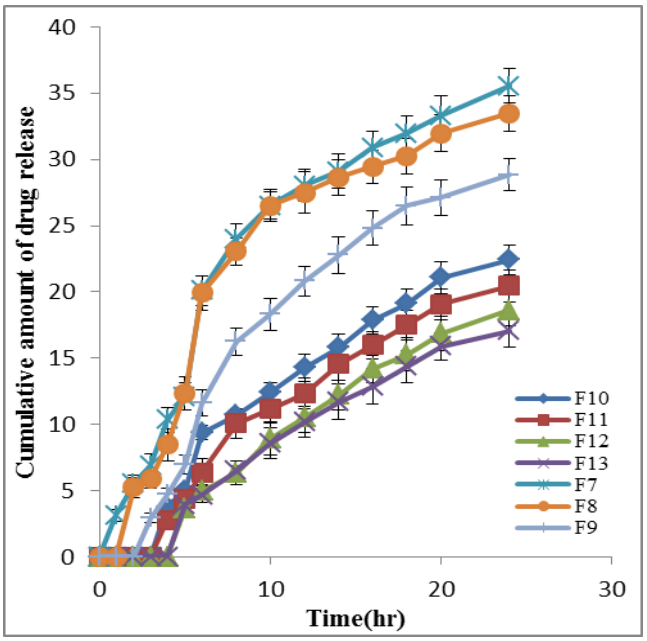


Fig. 8: Dissolution profiles of F7-F13 formulations containing 400 mg coat weight.

Drug release studies in artificial rat caecal substance

The presence of rat caecal substance in the dissolution medium brought about enhanced drug release after 5hr when compared to control. The percent drug released after 24h of testing was 70% with 2%w/v caecal substance though it was just 60% without caecal substance demonstrating that polysaccharide are available in the caecal matter that metabolize polymers was shown in Figure 9. As total drug release was not accomplished with 2%w/v. Hence, the level of caecal matter in the dissolution medium was increased to 4%w/v and the percent drug released after 24h of testing was observed to be 99.73%.

In-vitro drug release studies and in-vivo studies using the formulation F13 clearly indicated that the mix of natural polymers as a coat material applied over core mini-tablets was capable of protecting the drug from being released in the physiological condition of stomach, small intestine and vulnerable to colonic bacterial enzymatic activity with resultant drug release in the colon. Thus, the study clearly demonstrated that the blend of natural polymers was a potential colon specific drug delivery carrier.

Table 11: Cumulative percentage drug release of F10, F11, F12 and F13 formulations in presence of 2%, 4% rat caecal contents and control.

Time (hr)	2% Rat caecal contents				4% Rat Caecal Contents				Control			
	F10	F11	F12	F13	F10	F11	F12	F13	F10	F11	F12	F13
0	0	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	6.13	5.71	5.54	4.45	5.04	5.46	4.37	4.11	6.55	5.29	5.21	4.87
6	25.98	26.11	24.93	21.41	33.21	31.25	28.30	26.16	24.73	21.88	19.91	18.21
8	30.63	33.67	35.18	36.94	41.88	40.98	39.73	35.36	32.95	29.91	26.79	29.11
10	35.45	38.04	39.73	41.43	55.18	52.95	51.88	47.23	35.63	37.23	36.07	39.02
12	39.46	41.07	44.20	47.23	70.45	68.84	62.77	60.45	39.20	40.80	41.96	45.36
14	46.07	48.66	50.63	53.66	84.20	80.45	74.02	71.79	43.84	45.45	48.93	52.50
16	52.14	54.55	56.07	61.79	99.55	95.80	83.75	80.63	48.04	50.00	54.02	56.70
18	57.86	59.91	61.25	66.70	99.20	99.55	96.70	91.61	51.96	54.38	58.57	63.21
20	63.21	65.80	67.86	70.54	98.57	98.75	99.38	96.61	55.89	58.21	62.95	68.13
24	65.80	68.75	73.75	76.43	97.50	97.68	98.66	99.73	60.54	63.04	67.05	72.05

Data represents mean ± SD, n = 3

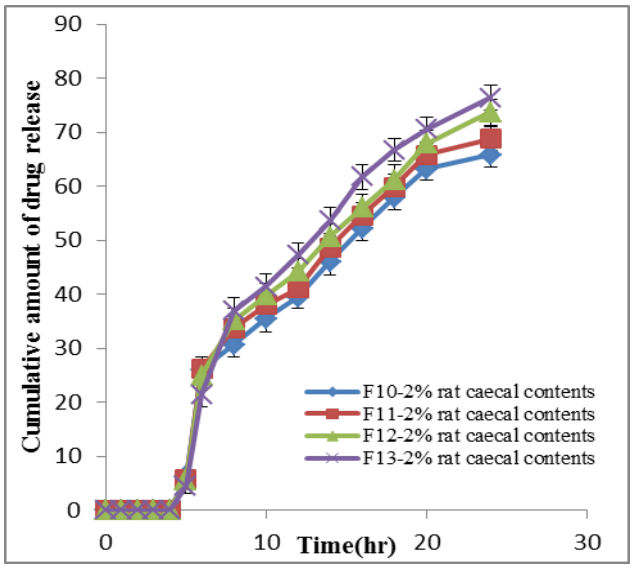


Fig. 9: Dissolution profiles of F10, F11, F12 and F13 formulations in presence of 2%rat caecal contents.

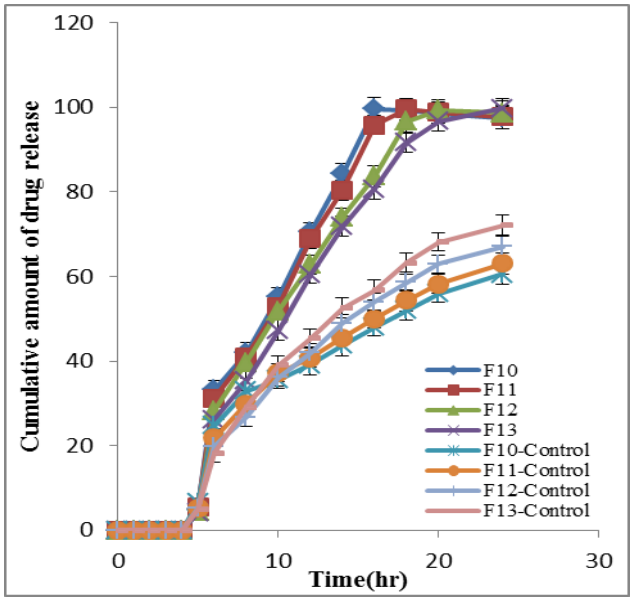
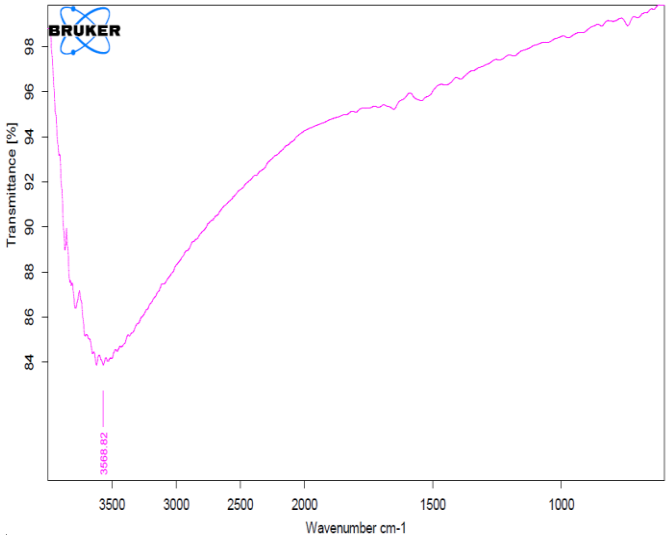


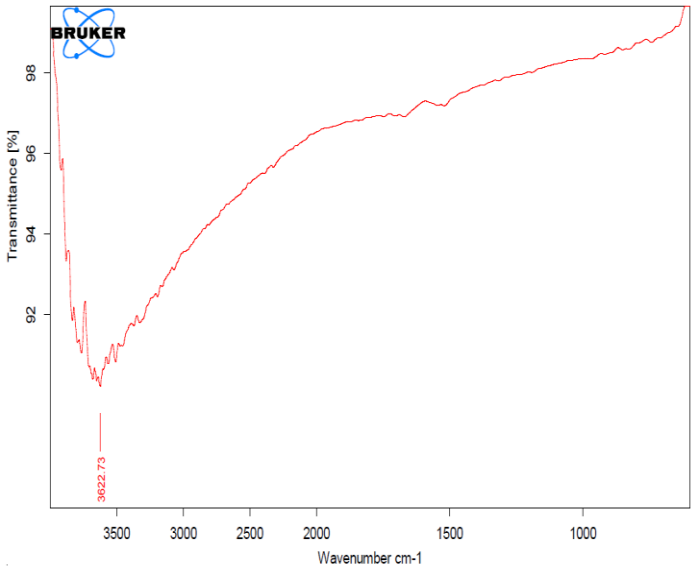
Fig. 10: Dissolution profiles of F10, F11, F12 and F13 formulations in presence of 4%rat caecal contents vs control.

Fourier Transforms Spectroscopy Studies

The FT-IR spectrum of Propranolol hydrochloride pure drug and the physical blend of formulation F13 demonstrated the characteristic absorption peaks in the IR region with negligible variation in the band position of different functional groups and various bonds in comparison to FT-IR of pure drug. As there was no much variation in the nature of IR range, it was concluded that there was no interaction of the drug with the excipients used for the study and the drug held its identity without experiencing any type of interaction with the excipients. The FT-IR ranges are given in Figure 11.



a) Propranolol hydrochloride pure drug.



b) Physical mixture of optimized formulation (F13).

Fig. 11: FT-IR Spectra's of Propranolol hydrochloride pure drug and physical mixture optimized formulation (F13).

***In vivo* X-ray studies**

X-ray studies were completed on the F13 formulation tablets, in order to see the compression coated tablets throughout the GI system. The situation of the tablets in the body was checked at various time focuses is shown in Table 7 and the X-ray pictures of tablet all through the GI system are shown in Figure 12.

The in-vivo results demonstrated that the tablets (F13 formulation) reached the colon without disintegrating in the upper region of the GI system in all subjects; tablets entered the colon varying between 5-6 h for all volunteers after tablet administration, tablets gradually broke down all through the colon after reaching it**.**

Table 12: The position of the tablets throughout the GI tract at various time points.

Subjects	30 min	3h	6h	8h	24h
1	Stomach	Caecum	Ascending colon	Ascending colon	Not observed

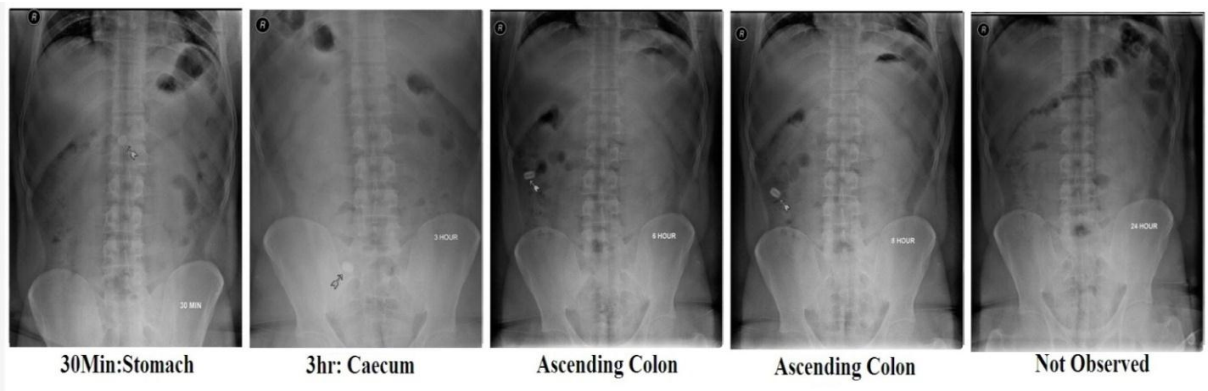


Fig 12: The localization of the tablet in the gastrointestinal tract in subject.

Release Rate Kinetics Studies

The mechanism and kinetics of drug release of Propranolol hydrochloride is determined by the application of korsmeyer-peppas model, higuchi's model, zero order and first order kinetics as shown in Table 13. Since they fitted well with Korsmeyer–Peppas models as their R^2 values in the range of 0.779 – 0.956with n value above 1.

Table 13: Drug release kinetics.

Formulation code	Zero order	First order	Higuchi	Korsmeyer & Peppas	Peppas (n)
F12	$R^2 = 0.956$	$R^2 = 0.779$	$R^2 = 0.879$	$R^2 = 0.862$	1.203

Stability studies

The stability studies indicated that after storing the optimized formulation (F13) for 3 months at 40ºc and 75% RH, the percent degradation of the drug was 1 to 2%, indicating steadiness of the formulation.

CONCLUSION

A biphasic compression coated mini-tablets for chronotherapeutic drug delivery system was effectively arranged by blend of natural polymers (Guar gum, xanthan gum, chitosan) and HPMC K15M as a coating material, this framework might be accomplished by initial fast followed by a time of deferred relating to the drug release of mini-tablets. The in-vitro drug release ponders demonstrates that contrasted with artificial ceacal substance (4%) and control less than 4% of drug in the physiological environment of upper GI tract and released 100% of the drug in the target area i.e. physiological environment of colon, in-vivo x-ray studies indicated that formulation F13 was a promising system to provide targeting of Propranolol hydrochloride to the colon and release pattern above details was best fitted to all the

conceivable kinetic models. The presence of blend of natural polymers in the coat lessens the underlying swelling of HPMC K15M which impedes the drug release in physiological environment of upper part of gastrointestinal tract and ensures complete arrival of drug in the colon because of its microbial corruption. FT-IR examinations demonstrated that there is no collaboration between the drug and the excipients. In this manner the tablets containing ideal extent of natural polymers and HPMC K15M is well on the way to target Propranolol hydrochloride to the colon without being discharged altogether in stomach and small digestive system.

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