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Research Article

Optimization of Gastroretentive Delayed-release Drug Delivery using Design of Experiment Approach

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ABSTRACT

Gastroretentive drug delivery with delayed release of propranolol hydrochloride for chronotherapy of hypertension was formulated. The drug delivery in the form of compression coated tablet was developed using Indian pharmacopoeia grade hydroxypropyl methyl cellulose K100M and carbopol 934P as matrix forming polymers and polyvinyl pyrrolidone K30 as a channelling agent. Drug-excipient compatibility study revealed no interaction between drug and excipients. Before drug release, prepared tablets were evaluated for floating lag time, total floating time, and lag time. Drug delivery was optimized by using 3^2 full factorial design. The concentrations of matrix forming polymers were selected as independent variables, whereas lag time before drug release, drug release at 8, 12 and 20 hours were selected as response variables. Tablets of optimized batch F5 containing 25% hydroxypropyl methyl cellulose K100M and 9% polyvinyl pyrrolidone K30 exhibited the maximum similarity with the predicted drug release profile for an ideal formulation with similarity factor of 80.69. The lag time before drug release (5 hour), drug release at 8 hour (27.39%), 12 hours (49.48 %) and 20 hours (86.69 %) of the optimized batch were close to the predicted drug release profile for an ideal formulation. Drug release from optimized batch followed zero order kinetics with super case II transport. Optimized formulation was stable for 1 month at environmental conditions of 40 ± 2°C temperature and 75 ± 5 % relative humidity. Prepared drug delivery of propranolol hydrochloride may be useful to provide sustained drug release for 24 hours at the absorption site for chronotherapy of hypertension.

Introduction

Various diseases like asthma, hypertension, ischemic heart disease and arthritis show circadian variation that demand time-scheduled drug release for effective drug action and are prevalent in early hours of the day.[1] Treating such diseases with immediate release dosage forms may be impractical as the symptoms of the disease are pronounced during the night or early morning. Therapy with modified release dosage forms with zero order drug release theoretically leads to controlled and constant drug levels in plasma throughout the day. To optimize the therapy in terms of safety, patient compliance and efficacy; chronopharmaceutical formulations based upon time-controlled drug delivery systems are considered potential therapeutic options.[2] Epidemiological studies document that the frequency of many cardiovascular diseases, including myocardial infarction and stroke, varies predictably in time over 24 hours as the circadian period.[3] Congestive heart failure and myocardial infarction manifest more frequently at night or early in the morning.[4] Blood pressure, notably just waking up, is usually responsible for such attack.[5] However, for such diseases, conventional drug delivery systems are inappropriate for drug delivery, as they cannot be administered just before the symptoms are worsened because during this time, the patients are asleep.

Delayed and pulsatile oral dosage forms with normal gastric transit are meant to release the drug, usually in the

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large intestine after a lag of 5–6 hours. However, viscous contents of this segment of the gastrointestinal tract (GIT) cause hindrance to drug diffusion along with enzymatic degradation of some drugs, making it an unfavorable site for drug release.[6] Further, highly variable nature of gastric emptying (GE) process may result in an *in-vivo* variability and bioavailability problems. Conversely, gastroretentive drug delivery (GRDDS) resides in the stomach and is not affected by the variability of pH, local environment or GE rate. These delivery systems are specifically advantageous for delivering drugs that are either absorbed from a stomach, having solubility in acidic pH, requiring local delivery in the stomach or degraded in colonic pH. These considerations led to the development of dosage forms possessing gastric retention capabilities.[7,8] The key adopted GRDD approaches comprises of floating, sinking, swelling, effervescence, mucoadhesive and magnetic type.[9] In floating types (lower density systems) system, the GRDD bulk density is kept low than that of the Gastrointestinal (GI) fluid letting the system float in the stomach for an extended period that permits drug release at the desired amount. Based on its buoyancy, these systems may be non-effervescent floating (API mixed with gel-forming polymer) and effervescent floating type that utilizes effervescent agent (s) blended with hydrophilic polymers. Due to the presence of an effervescent agent, the later type system in contact with GI fluid, liberates CO_2 due to chemical reaction. This CO_2 gas is trapped in the hydrocolloid matrix and gives the tablet buoyancy that considerably affects the drug release profiles, while hydrophilic polymers control the drug release rate. Literature survey revealed research articles on gastroretentive drug delivery systems for propranolol using different polymers and approaches [10-17]. However, no research is reported on gastroretentive delayed-release drug delivery system (GRDRDDS) of propranolol hydrochloride (PH) for chronotherapy of hypertension.

Many artificial intelligence techniques today are used in formulation development, such as artificial neural network[18] and experimental design. Of the experimental designs, the most commonly used are fractional factorial design,[19-23] central composite design,[19] mixture experimental design,[20,22] Placket Burman design,[18] Box Behnken experimental design,[24] and full factorial design.[18]

PH is a sympathomimetic agent selectively acting on the β2 -adrenergic receptor. It is used as a bronchodilator to manage hypertension and angina pectoris. It decomposes rapidly at alkaline pH of intestine. The maximum plasma concentration occurs within 2.5 hours and the plasma half-life ranges from 3 to 4 hours. It is given orally at a dose of 40–80 mg, twice a day. The oral bioavailability of PH is ~20% because of extensive first pass metabolism.[25] Thus PH has all the requisite characteristics for developing it into GRDRDDS.

Hence, in the present research; GRDRDD of propranolol hydrochloride intended for bedtime dosing to deliver the drug after a lag time of 7 hours at an absorption site in the stomach with controlled drug release for 17 hours after a lag time was formulated. The drug delivery was developed by compression coating of an outer polymeric layer on the inner core tablet containing the drug. The developed drug delivery was optimized using 3^2 full factorial design.

Materials and Methods

Materials

Propranolol hydrochloride IP (PH) was procured from Yarrow Chem Products, Mumbai, India. Indian Pharmacopoeial grade hydroxypropyl methyl cellulose K100M (HPMC K100M), carbopol 934P, polyvinyl pyrrolidone K30 (PVP K30), microcrystalline cellulose (MCC), lactose monohydrate and talc were purchased from SD Fine Chem. Ltd., Mumbai, India. Methanol, hydrochloric acid (HCl) and other reagents used were of analytical grade.

Methods

Analysis of Propranolol hydrochloride

Accurately weighed 100 mg of PH was transferred into 100 mL volumetric flask. It was dissolved in 10 mL ethanol and further diluted with 0.1 N HCl, and the volume was made up to 100 mL with 0.1 N HCl to get the stock solution of 1000 µg/mL. The stock solution was diluted with 0.1 N HCl and scanned for UV spectrum by using Shimadzu 1800 UV-Visible double beam spectrophotometer. The solution exhibited maximum absorption at a wavelength of 289 nm. Serial dilutions in the range of 5–40 µg/mL in 0.1 N HCl were prepared from the stock solution. The absorbance of taken concentrations was measured in triplicate using 0.1 N HCl as a blank. The average absorbance values obtained against taken concentrations were plotted to generate calibration curve and an equation for the line obtained was: Absorbance (Y) = 0.020 x Concentration (X) - 0.000 with correlation coefficient of 0.999. This calibration curve equation was used to calculate the concentration of an unknown solution based on absorbance.

Calculation of Drug Dose Required in Gastroretentive Delayed-Release Drug Delivery

Total dose of PH for GRDRDD was calculated using available pharmacokinetic data of the drug for one compartment model with the simultaneous release of loading dose and a zero order release maintenance dose, as described by Robison and Eriksen.[26] Required dose calculation revealed that the drug delivery with a total dose of 120 mg should release 40 mg (33.33%) drug at 8 hours after a predetermined lag time of 7 hours as loading dose to attain minimum effective concentration then followed by 5 mg (4.167 %) per hour up to 24 hours. Accordingly, the

predicted drug release profile for an ideal formulation was generated using above values and is shown in Fig. 1.

Drug-excipient Compatibility Study

The drug-excipient compatibility study was carried out by using Fourier Transform Infrared (FT-IR) spectroscopy. DSC of pure PH was carried out using DSC 60 instrument (Shimadzu, Kyoto, Japan). In this process, samples (5 mg) were weighed into aluminum pans and heated at a rate of 10°C/min under nitrogen from 5 to 350°C. Fetal Tissue Transplantation Research (FTTR) spectra were recorded using KBr mixing method in the range of 400 to 4000 cm^{-1} on FTTR instrument (FTTR- 1700, Shimadzu, Kyoto, Japan) available at the central instrument laboratory of the institute.

Preparation and Evaluation of Inner Core Tablets Containing Drug

Inner core tablets, each containing PH, lactose monohydrate, magnesium stearate and talc were prepared by direct compression technique using composition shown in Table 1A. All the ingredients were accurately weighed, passed through 60 sieve (250 µm) of 12-inch diameter and mixed well by using cone blender for 5 min. Then the powder was compressed directly in to tablets using 8 mm diameter die on rotary tablet compression machine (Rimek Minipress, Karnavati Engineering, Kadi, India) to produce tablet weighing 150 mg.

The prepared inner core tablets were evaluated for diameter, thickness, hardness, weight variation, content uniformity and disintegration test. The average thickness and diameter were measured by taking 10 tablets using a micrometre screw gauge. A hardness test was conducted for 5 tablets using monsanto hardness tester and average values were calculated. For friability determination, pre weighed tablet sample (20 tablets) was placed in the friabilator (Electrolab, Mumbai, India), which is then operated for 100 revolutions. The tablets were de-dusted and reweighed. For weight variation test, 20 tablets were weighed by random selection and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 7.5%. For content uniformity,[27] twenty tablets were weighed and powdered in a glass mortar. Quantity of powder

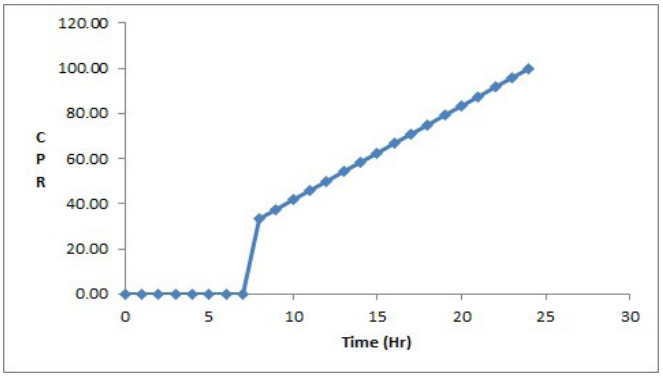

Fig. 1: Predicted drug release profile for an ideal formulation

Table 1: Layout for composition of formulations

A: Composition of inner core tablet												
Ingredients	***Quantity per tablet (mg)***											
Propranolol hydrochloride	120											
Lactose monohydrate	25											
Magnesium stearate	2											
Talc	3											
Weight of core tablet (mg)	150											
B: Composition of Outer Coating Layer												
	Quantity (%)											
Ingredients/Batch	***P1***	***P2***	***P3***	***P4***	***P5***	***P6***	***P7***	***P8***	***P9***	***P10***	***P11***	***P12***
HPMC K100M	30	30	35	35	40	40	20	20	25	25	30	30
Carbopol 934P	5	5	5	5	5	5	5	5	5	5	5	5
Sodium bicarbonate	10	10	10	10	10	10	10	10	10	10	10	10
Lactose	52	52	52	52	52	52	52	52	52	52	52	52
Talc*	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate*	1	1	1	1	1	1	1	1	1	1	1	1
C: Composition of Compression Coated GRDRDDS												
Inner core tablet (mg)	150	150	150	150	150	150	150	150	150	150	150	150
Outer coating layer (mg)	400	450	400	450	400	450	300	350	300	350	300	350
Weight of final tablet (mg)	550	600	550	600	550	600	450	500	450	500	450	500

*Indicates extra granular addition

equivalent to 120 mg of PH was accurately weighed and transferred in a 100 mL volumetric flask containing 20 mL of distilled water. The flask was shaken for 10 min and 50 mLof methanol was added. The flask was shaken for an additional 10 min and the final volume was made up to 100 mL with methanol add the resulting solution was filtered through Whattman filter paper. The filtrate was collected and suitably diluted with methanol to produce final solution of 40 mcg/mL concentration and the absorbance of the solution was measured by UV-Visible Spectrophotometer (UV-1800, Shimadzu, Kyoto, Japan) at 290 nm. The content of PH was calculated taking a value of 206 as a specific absorbance at 290 nm.

Disintegration test was carried out for 6 tablets using USP disintegration test apparatus (Electro lab, Mumbai, India). The medium used was 0.1 N HCl maintained at 37°C. The time taken for complete disintegration was noted and average disintegration time was calculated.

Preparation and evaluation of granules for outer polymeric coating layer

Granules for outer polymeric coating layer was prepared using varying concentration of HPMC K1OOM with a fixed concentration of other excipients as shown in Table 1B (Batches P1 to P12). All the ingredients were accurately weighed and passed through 60 sieve (250 µm) of 12-inches diameter. Then it was mixed properly by using cone blender for 5 min. The resultant powder was granulated by using isopropyl alcohol (IPA) and passed through 40 sieve (400 µm) of 12-inches diameter. The prepared granules were dried in pre-heated oven at 50°C for 10 min. The granules were mixed with the ingredients to be added extra granularly, such as talc and magnesium stearate. The prepared granules were stored in zip lock plastic bag away from moisture till further use.

The prepared granules were evaluated for preformulation parameters like bulk density (BD), tapped density (TD), Carr's Index (CI), Hausner's ratio (HR) and angle of repose (AOR).[28-31] Accurately weighed 25 g of granules, which were previously passed through 20 sieve (841 µm) of 12-inches diameter were transferred in 100 mL graduated cylinder. Granules were carefully leveled without compacting, and unsettled apparent volume (Vb) was noted. The apparent BD in g/mL was calculated by the following formula:

Bulk density = Weight of powder/Bulk volume (Vb).

The cylinder containing the sample was mechanically tapped by raising it and allowing it to drop under its own weight using a mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per min. The cylinder was tapped for 500 times and measured the tapped volume (Vt) to the nearest graduated units. The tapped BD in g/mL was calculated by the following formula: Tapped Density = Weight of powder/ Tapped volume (Vt). The CI of the granules blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a granules and the rate at which it packed down. The formula used for calculating Carr's index was: Carr's Index (%) = [(TD-BD) x100]/TD. The HR is a number that is correlated to the flowability of a granular material. HR = TD/BD.

The AOR of granules was determined by the funnel method. The accurately weighed granules were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the granules cone was measured and the AOR was calculated using an equation: tan ɵ = h/r, where, h and r are the height and radius of the granules cone, respectively.

Preparation of GRDRDDS by Compression Coating of Outer Polymeric Layer on Inner Core Tablet

The GRDRDDS was developed by compression coating of outer polymeric layer on inner core tablet at different coating levels as shown in Table 1C. The quantity of granules required for outer polymeric coating was accurately weighed. Half of the granules were manually filled in the die cavity and leveled properly. Then the inner core tablet was placed on granule bed exactly in the centre, and the remaining half of the granules were filled in the die cavity. After proper leveling the granules were compressed using Rotary tablet compression machine (Rimek Minipress, Karnavati Engineering, Kadi, India) by 12 mm flat punch to produce compression coated GRDRDDS.

Evaluation of Compression Coated GRDRDDS to Select Prototype Formulation

The prepared GRDRDDS was evaluated for diameter, thickness, hardness, friability, weight variation and content uniformity as per the procedure described earlier. he GRDRDDS was evaluated for *in vitro* floating studies.[32] *In vitro* floating studies were determined by floating lag time (FLT), total floating time (TFT) and matrix integrity. Floating lag time test was performed to check the floating behavior. The GRDRDDS was dropped in the dissolution medium, i.e, 0.1 N HCl maintained at 37°C and stirred at 50 rpm. The time taken by the GRDRDDS to come to the surface of the dissolution medium was reported as FLT. Matrix integrity was observed throughout *in vitro* dissolution studies. The swollen mass of the GRDRDDS remained intact or not was checked. The TFT was determined by visual inspection of the GRDRDDS placed in the dissolution medium maintained at 37°C and stirred at 50 rpm.

The *in-vitro* dissolution study of GRDRDDS was performed using USP apparatus type II (model TDT-08T, Electro lab, Mumbai, India) fitted with paddle (50 rpm) at 37 ± 0.5°C using 0.1 N HCL (pH 1.2; 900 mL) as a dissolution medium. At the predetermined time intervals, 10 mL samples were withdrawn and replaced with equal volume of fresh

dissolution medium maintained at same temperature**.** The samples were filtered and suitably diluted**.** Absorbance of these solutions was recorded at 289 nm wavelength using Shimadzu UV-1800 double**-**beam spectrophotometer (Shimadzu, Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve**.** All the studies were carried out in triplicate**.**

Water permeability test[33] was used to evaluate the extent of water penetration into GRDRDDS. GRDRDDS containing 2 mg of amaranth (water soluble dye) in the core tablet was prepared and used to aid easy recognition of water penetration. Each tablet was separately immersed in 900 mL 0.1N HCl kept at 37 ± 0.5°C. The tablets were removed from the medium at an interval of 1, 2, 4, 6 and 10 hours and observed for color change. The spreading of dye in the swollen mass indicated the time for complete wetting of core tablet by 0.1 N HCl. Visual observation of the color change and the core condition were used to evaluate the extent of water penetration.

Table 2: Formulations with varying filler and channelling agent in outer coating layer

Ingredients/Batch	*Quantity per tablet (%)*					
	PF1	*PF2*	*PF3*	*PC1*	*PC2*	*PC3*
HPMC K100M	25	25	25	25	25	25
Carbopol 934P	5	5	5	5	5	5
Sodium bicarbonate	10	10	10	10	10	10
Lactose	57	-	28.5	52	52	52
MCC	-	57	28.5	-	-	-
PVP K30*	-	-	-	5	-	-
NaCl*	-	-	-	-	5	-
PEG 4000*	-	-	-	-	-	5
Talc*	2	2	2	2	2	2
Magnesium stearate*	1	1	1	1	1	1
Coating level in mg/tablet	300	300	300	300	300	300

*Indicates extra granular addition; MCC: microcrystalline cellulose; PVP: polyvinyl pyrrolidone; NaCl: Sodium chloride; PEG: polyethylene glycol

Study on Variables in Outer Coating Layer of Compression Coated GRDRDDS

Based on the evaluation results of batches P1 to P12, batch P9 was selected as prototype formulation for further development. The outer coating layer containing a fixed concentration of HPMC K100M and carbopol 934P with varying filler type and concentration (Table 2, formulations PF1 to PF3) was used to study filler's effect on drug release and matrix integrity. These formulations were subjected to *in-vitro* floating and dissolution studies. Based on evaluation results of formulations PF1 to PF3, further formulations were developed using three different channelling agents to study their effect on drug release rate (Table 2, formulations PC1 to PC3). These formulations were subjected to *in-vitro* floating and dissolution studies.

Optimization of variables using Design of Experiment

A 3^2 randomized full factorial design was used as DoE tool for optimization in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The concentration of polymer HPMC K100M (X_1) and the concentration of channelling agent PVP K 30 (X2) were independent variables. Lag time before drug release (LT), Q_8, Q_{12}, Q_{20} (%drug release at 8, 12, 20 hours, respectively) were taken as dependent variables. The formulation layout for the factorial design batches (F1-F9) is shown in Table 3. Selection of optimum batch by comparison of dissolution profiles.

The similarity factor (f2) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profiles. The dissolution profiles are similar when f2 is between 50 and 100. The similarity factor was calculated using the formula:

Table 3: Composition of factorial batches

Ingredients	*Formulation code*								
	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
HPMC K100M (X_1)	20	20	20	25	25	25	30	30	30
Carbopol 934P	5	5	5	5	5	5	5	5	5
Sodium bicarbonate	10	10	10	10	10	10	10	10	10
PVP K30* (X_2)	6	9	12	6	9	12	6	9	12
Talc*	2	2	2	2	2	2	2	2	2
Magnesium stearate*	1	1	1	1	1	1	1	1	1
Lactose q.s. to	100	100	100	100	100	100	100	100	100
Coating level (mg/tablet)	300	300	300	300	300	300	300	300	300
Independent variables	*Coded values*					*Actual values (mg)*			
Amount of HPMC K 100 M	-1	0		+1		60	75	90	
Amount of PVP K30	-1	0		+1		18	27	36	

#Indicates percentage; *Indicates extra granular addition; PVP: polyvinyl pyrrolidone

$$f_2 = 50 \text{ X } \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} w_t \left(R_t - T_t \right)^2 \right]^{-0.5} \text{ X } 100 \right\}$$

Where, n is the dissolution time and R_t and T_t are the reference (here this is the predicted drug release profile for an ideal formulation) and test dissolution value at time t.

Kinetic Modelling of Dissolution Data

The dissolution profile of all batches was fitted to various models such as zero order, first order, Higuchi,[34] Hixon-Crowell,[35] Korsemeyer and Peppas[36] to ascertain the kinetic of drug release. The method described by Korsemeyer and Peppas was used to describe mechanism of drug release.

Short-term Stability Study

The stability studies were carried out on the optimized formulation (Batch F5) as per ICH guidelines Q1C. The stability studies were performed at 40 ± 2°C / 75 ± 5 % RH conditions. At the end of 1 mo., samples were analyzed for the drug content, hardness, *in-vitro* floating and dissolution studies.

RESULTS

Drug-excipient Compatibility

DSC thermogram of PH is shown Fig. 2.

It is evident from the DSC thermogram that the sharp endothermic peak obtained in pure PH was corresponds to its melting point showing its purity.

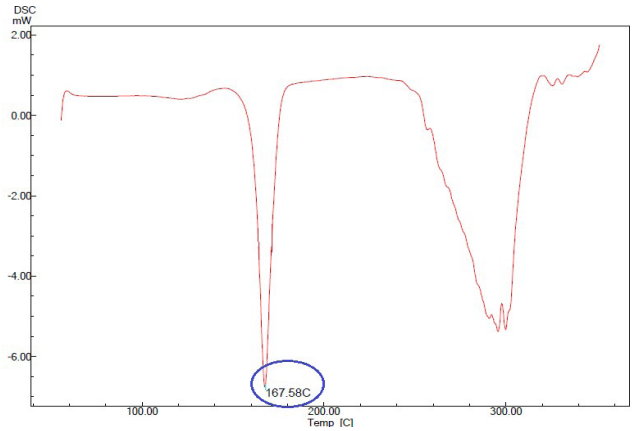

Fig. 2: DSC thermogram of propranolol HCL

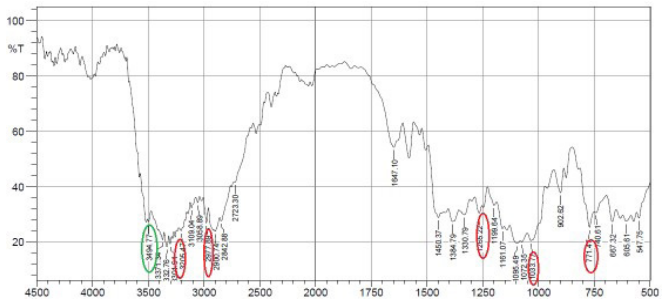

Fig. 3: FT-IR spectra of propranolol HCL

FTTR spectra of PH and composite mixture of PH with other excipients are shown in Fig. 3 and 4, respectively.

The prominent peaks observed for different functional groups in FT-IR spectra for pure PH and the composite mixture are shown in the Table 4.

There was no major change in the peaks corresponding to the functional groups, indicating no chemical interaction of PH with the excipients used in the tablet formulation.

Evaluation of Inner Core Tablets

The prepared inner core tablets were evaluated for diameter, thickness, hardness, weight variation, content uniformity and disintegration test. The results of evaluation are shown in Table 5. All the parameters were within the acceptable limit for the inner core tablets.

Evaluation of Granules for Outer Coating Layer

The granules for outer coating layer were evaluated for micromeritic properties and preformulation parameters.

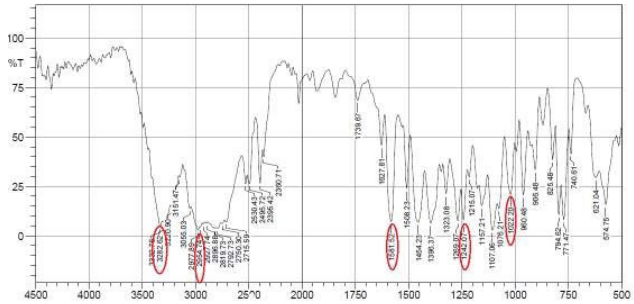

Fig. 4: FT-IR spectra of propranolol HCL with other excipients

Table 4: FT-IR data for drug and physical mixture

Functional group	*Drug Peak (cm^{-1})*	*Physical Mixture Peak (cm^{-1})*
NH stretch	3282.62	3286.47
C-H stretch	2954.74	2977.89
Aryl C=C stretch	1581.52	1581.52
Aryl -O–CH2 symmetric stretch	1242.07	1265.22
Aryl-O–CH2 symmetric stretch	1022.20	1033.77
Peak due to alpha-substituted naphthalene	794.62	771.47

Table 5: Results of evaluation parameters of inner core tablet

Evaluation Parameter	*Result (Mean ± SD)*
Diameter (mm)	7.5 ± 0.25
Thickness (mm)	2.1 ± 0.1
Hardness (kg/cm^2)	3.6 ± 0.15
Average weight of tablet (mg)	150.89 ± 1.25
Drug content (%)	99.89 ± 1.02
Disintegration time (sec)	65 ± 5

SD: Standard deviation for 3 determinations

Results for evaluation are shown in Table 6. Results showed that the granules had accepted flowability and compressibility.

Selection of Prototype GRDRDDS from Batches P1 to P12

The results of evaluated batches prepared for preliminary screening of polymer concentration and coating level are shown in Table 7.

From the results of preliminary trials (batches P1 to P6) it was observed that increasing the polymer concentration decreased the drug release and drug release at 8 hours was < 5% in most batches. Hence, it was decided to use lower concentration of polymer and lower coating level (batches P7 to P12) to get the required lag time before drug release. Tablets with 20% polymer concentration were intact for 6 hours, broken after 6 hours and exhibited burst release at both coating levels. Tablets with 25% and 30% polymer concentration at each coating level were intact but exhibited lower than required drug release at 8 hours. In water permeability test, the spreading of dye in batch containing 30% HPMC K100M was slower than batch containing 25% HPMC K100M due to higher diffusional resistance to water penetration offered by high polymer concentration. From this study, it can be concluded that tablets with higher polymer concentration have a longer time for water penetration than tablets with lower polymer concentration. The results follow lesser drug release observed when using higher polymer concentration.

Therefore, to get the required drug release at 8 hours

Table 6: Results of evaluation parameters for granules

Parameter	*Result*
Angle of repose (^{o})	28
Bulk density (g/mL)	0.731
Tapped density (g/mL)	0.819
Hausner's ratio	1.12
Carr's index (%)	10.74

Table 7: Selection of polymer concentration and coating level

Parameter	*Preliminary Batches*											
	P1	*P2*	*P3*	*P4*	*P5*	*P6*	*P7*	*P8*	*P9*	*P10*	*P11*	*P12*
*FLT (s)	45 (5)	75 (8)	56 (6)	90 (4)	60 (3)	102 (8)	10 (4)	10 (2)	35 (5)	35 (2)	42 (4)	40 (5)
TFT (h)	>24	>24	>24	>24	>24	>24	10	10	>24	>24	>24	>24
Matrix Integrity (h)	24	24	24	24	24	24	8	8	24	24	24	24
Lag time for drug release (h)	8	10	10	>12	12	>12	5	6	6	7	7	8
*CPR at 8 hours	4.8 (0.1)	1.4 (0.1)	3.1 (0.1)	1.1 (0.1)	1.0 (0.1)	0.9 (0.1)	4.8 (0.1)	84.8 (1.7)	13.1 (0.8)	11.2 (0.7)	9.2 (0.3)	8.1 (0.3)
*CPR at 12 hours	13.5 (0.5)	10.5 (0.5)	10.8 (0.4)	7.0 (0.3)	8.4 (0.3)	6.8 (0.2)	84.4 (0.6)	98.4 (1.8)	38.8 (1.3)	35.0 (1.2)	20.4 (0.6)	69.5 (1.4)
*CPR at 20 hours	45.8 (1.4)	41.2 (1.1)	36.5 (1.0)	31.3 (1.2)	18.1 (0.8)	15.4 (0.7)	100 (1.3)	100 (2.8)	75.2 (2.2)	65.6 (1.3)	69.4 (1.8)	65.1 (1.1)

*Values in parenthesis indicate standard deviation for thee determinations; FLT: floating lag time; TFT: total floating time; CPR: cumulative percentage drug release

Table 8: Results of evaluation parameters of factorial batches

Parameter	*Batch Code*								
	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
Weight Variation (mg)	452.2 (2.3)	451.2 (1.8)	449.4 (1.1)	450.4 (1.5)	451.0 (2.1)	448.2 (1.6)	452.2 (1.9)	451.0 (1.8)	450.8 (1.3)
Hardness (kg/cm^2)	7.3 (0.2)	6.7 (0.2)	7.0 (0.1)	7.4 (0.1)	6.6 (0.2)	7.0 (0.3)	7.5 (0.2)	6.5 (0.1)	6.9 (0.3)
Thickness (mm)	3.81 (0.01)	3.86 (0.01)	3.80 (0.02)	3.66 (0.02)	3.77 (0.02)	3.89 (0.01)	3.65 (0.02)	3.72 (0.01)	3.63 (0.01)
Diameter (mm)	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Friability (%)	0.04	0.52	0.42	0.05	0.57	0.46	0.05	0.58	0.32
Drug content (%)	100.7 (0.9)	99.4 (1.2)	101. 1 (0.7)	99.5 (2.1)	101.6 (1.65)	101.3 (2.1)	99.8 (3.0)	99.7 (2.2)	100.1 (1.8)
Floating lag time (s)	25 (8)	56 (5)	69 (4)	72 (5)	85 (4)	88 (5)	85 (6)	105 (5)	100 (4)
Total floating time (h)	9	8	8	>24	>24	>24	>24	>24	>24
Matrix Integrity (h)	8	7	7	>24	>24	>24	>24	>24	>24

reduction in coating level would not be advisable as core: coat ratio should at least be 1:2. So, it was decided to use lower polymer concentration. From the prepared batches, batch P9 with 25 % HPMC K100M concentration and 300 mg coating level was selected as prototype formulation for further development.

Effect of Filler and Channelling Agent in Outer Coating Layer

Compression-coated tablets were prepared with different types of fillers. The evaluation results for *in-vitro* floating and dissolution studies revealed that lactose was the most suitable filler. Compression-coated tablets were formulated using thee different channelling agents to increase drug release rate. The evaluation results for *in -vitro* floating and dissolution studies revealed that PVP K 30 was the most suitable channeling agent.

Evaluation of Factorial Batches

Tablets of factorial batches were evaluated for physicomechanical properties, *in-vitro* floating and dissolution studies. The results are summarized in Table B. The comparative *in-vitro* dissolution profiles of factorial batches are shown in Fig. 5.

The results of the *in-vitro* drug release study concluded that as the concentration of polymer increases, the drug release decreases due to increased diffusional resistance at higher concentration of polymer. Adding a channelling agent increases the drug release but a higher concentration of a channelling agent causes rupture of tablet matrix and such effect is typically observed at lower concentration of polymer. Drug release increases proportionately with an increase in the concentration of the channelling agent.

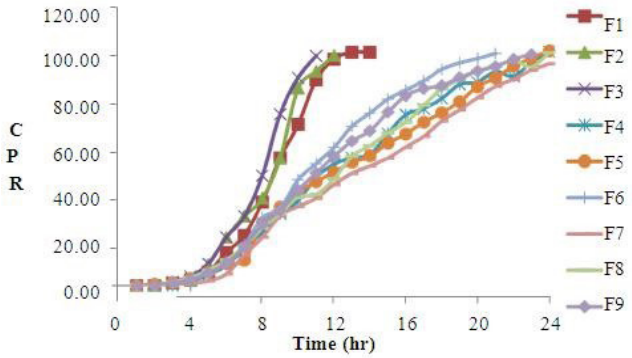

Fig. 5: *In-vitro* dissolution profiles of factorial batches

Statistical Analysis of DoE

A statistical model: $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$, incorporating interactive and polynomial terms was used to evaluate the responses. Where, Y is the dependent variable, b0 is the arithmetic mean response of the 9 runs, and bi is the estimated coefficient for the factor Xi. The main effects (X_1 and X_2) represent the average result of changing one factor from low to high values at a time. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. All independent and dependent variables are shown in Table 9. The *in-vitro* release profile for 9 batches showed a variation i.e. cumulative drug release at 8 hours (Q_8), cumulative drug release at 12 hours (Q_{12}), cumulative drug release at 20 hours (Q_{20}) and lag time (LT). The data indicate that the release profile of the drug is strongly dependent on the selected independent variables.

The coefficients for fitted equations (full and reduced) relating the responses to the transformed factor are shown in the Table 10.

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive). Table 11 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Data were analysed using Microsoft Excel.

R^2 value for LT, Q_8, Q_{12} and Q_{20} are 0.794, 0.9791, 0.9915 and

Table 9: Factors in 3^2 full factorial design

Batch Code	*Variable Levels in Coded Form*		*FLT (h)*	Q_8 (%)	Q_{12} (%)	Q_{20} (%)	f_2
	X_1	X_2					
F1	-1	-1	5	36.39	98.77	101.69	27.84
F2	-1	0	4	38.02	100.42	100.42	27.77
F3	-1	1	4	47.98	100.18	100.18	21.88
F4	0	-1	5	23.26	52.85	88.63	61.47
F5	0	0	5	27.39	49.48	86.69	80.69
F6	0	1	5	29.45	60.20	99.02	44.97
F7	1	-1	6	20.97	43.96	81.92	58.95
F8	1	0	5	24.99	46.51	93.61	57.62
F9	1	1	5	26.64	56.36	93.47	50.61

All batches contained 120 mg of Propranolol HCl, 10% sodium bicarbonate, 2% talc and 1 % magnesium stearate; X1 indicates concentration of HPMC K100M; X2 indicates concentration of PVP K30; Q8, Q12 and Q20 indicate percentage drug released after 8, 12 and 20 hours, respectively; LT indicates lag time before drug release.

Table 10: Summary of results of regression analysis

For Lag time (LT)						
Response (LT)	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	4.86	0.53	-0.37	-0.53	-0.13	0.21
RM	-	-	-	-	-	-
For Q_8						
Response(Q8)	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	25.82	-8.08	3.69	-1.81	6.02	1.32
RM	26.70	-8.29	3.90	-	5.79	-
For Q_{12}						
Response(Q12)	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	52.45	-24.26	3.82	1.00	19.90	2.60
RM	54.17	-24.26	4.26	-	19.46	-
For Q_{20}						
Response(Q20)	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	90.48	-5.35	3.12	2.97	4.05	1.45
RM	-	-	-	-	-	-

FM: Full model; RM: Reduced model

0.8378; respectively indicating good correlation between dependent and independent variables. The reduced models were developed for response variables by omitting the insignificant terms with $p > 0.05$. The terms with $p < 0.05$ were statistically significant and retained in the reduced model. The coefficients for full and reduced models for response variables are shown in Table 10.

The significance levels of the coefficients b_{12} and b_{22} were p= 0.196 and 0.472, respectively. So they were omitted from the full model to generate a reduced model. The results of statistical analysis are shown in Table 10. The coefficients b_1, b_2 and b_{11} were significant at $p < 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{12} and b_{22} contribute significance information to the prediction of Q_8. The results of model testing are shown in Table 11. The critical value of F for $\alpha = 0.05$ equals 5.79 (DF=2, 5). Since the calculated value (F=1.39) is less than critical value (F=5.79), it may be concluded that the interaction term b_{12} and b_{22} do not contribute significantly to the prediction of Q_8 and can be omitted from the full model to generate the reduced model. Equation for full model is: $Q8 = 25.82\text{-}8.08\ X_1 + 3.69X_2 - 1.81X_{12} + 6.02X_{11} + 1.32X_{22}$ and for reduced model is: $Q8 = 26.70\text{-}8.29X_1 + 3.90X_2 + 5.79X_{11}$.

The significance levels of the coefficients b_{12} and b_{22} were p= 0.641 and 0.430, respectively. So they were omitted from the full model to generate a reduced model. The results of statistical analysis are shown in Table 11. The coefficients b_1, b_2 and b_{11} were found to be significant at $p < 0.05$; hence they were retained in the reduced model. The reduced model was tested in proportion to determine whether the coefficient b_{12} and b_{22} contribute significance

Table 11: Calculation for testing the model in portions

For Lag Time						
	DF	*SS*	*MS*	*F*	R^2	
Regression						
FM	5	2.29	0.46	2.31	0.794	
RM	-	-	-	-	-	
Error						
FM	3	0.696	0.198			
RM	-	-	-			
For Q8						
	DF	*SS*	*MS*	*F*	R^2	
Regression						
FM	5	583.60	116.72	28.20	0.9791	Fcal=1.39 Ftab=5.79 DF=(2,5)
RM	3	572.06	190.69	39.80	0.9597	
Error						
FM	3	12.42	4.14			
RM	5	23.96	4.79			
For Q12						
	DF	*SS*	*MS*	*F*	R^2	
Regression						
FM	5	4545.69	909.13	70.14	0.9915	Fcal=0.83 Ftab=5.79 DF=(2,5)
RM	3	4524.12	1508.04	124.72	0.9868	
Error						
FM	3	38.89	12.96			
RM	5	60.45	12.09			
For Q20						
	DF	*SS*	*MS*	*F*	R^2	
Regression						
FM	5	332.30	66.46	3.10	0.8378	
RM	-	-	-	-	-	
Error						
FM	3	64.30	21.43			
RM	-	-	-			

DF indicates degree of freedom; SS, sum of squares; MS, mean of squares; R2, regression coefficient; FM, Full model; RM, Reduced model

information to the prediction of Q_{12}. The results of model testing are shown in Table 11. The critical value of F for $\alpha = 0.05$ is equal to 5.79 (DF=2, 5). Since the calculated value (F=0.83) is less than critical value (F=5.79), it may be concluded that the interaction term b_{12} and b_{22} do not contribute significantly to the prediction of Q_{12} and can be omitted from the full model to generate the reduced model. Equation of for full model is: $Q_{12} = 52.45\text{-}24.26X_1 + 3.82X_2 + 1.00X_{12} + 19.90X_{11} + 2.60X_{22}$ and for reduced model

is: Q_{12}= 54.17-24.26X_1 +4.26X_2+19.46X_{11}.

The significance levels of the coefficients b_1, b_2, b_{12}, b_{11} and b_{22} were found to be 0.074, 0.214, 0.319, 0.310, and 0.719, respectively. Coefficients b_1, b_2, b_{12}, b_{11} and b_{22} do not contribute significantly to predicting %drug release at 20 hours. So, the generation of reduced model from the full model is not possible. The results of statistical analysis are shown in Table 11. Equation of for full model is: Q_{20}= 90.48-5.35X_1 +3.12X_2 +2.97X_{12} +4.05X_{11} +1.45X_{22}.

The significance levels of the coefficients b_1, b_2, b_{12}, b_{11} and b_{22} were found to be 0.068, 0.19, 0.840, 0.709 and 0.594, respectively. Coefficients b_1, b_2, b_{12}, b_{11} and b_{22} do not contribute significantly to the prediction of lag time. So, generation of reduced model from the full model is not possible. The results of statistical analysis are shown in Table 11. Equation of for full model is: LT= 4.86+0.53X_1-0.37X_2 -0.53X_{12} -0.13X_{11} +0.21X_{22}.

Table 12: Results of validation of proposed model

Batch	*Response*	*Experimental value*	*Predicted value*	*% Prediction error*
	LT (h)	4.0	4.01	0.25
CB1	Q_8 (%)	35.55	33.99	4.3
	Q_{12} (%)	72.50	71.86	0.88
	Q_{20} (%)	96.37	95.35	1.05
	LT (h)	5.00	5.08	1.6
CB2	Q_8 (%)	24.37	25.24	3.56
	Q_{12} (%)	49.84	49.55	0.58
	Q_{20} (%)	87.14	86.99	0.17

LT: lag time before drug release; Q_8, Q_{12}, Q_{20}: % drug release at 8, 12 and 20 hours, respectively

Validation of Proposed Model by Check Point Batches

The proposed model was validated by preparing randomly selected check point batches with X_1=-0.5 (22.5%), X_2=+0.5 (10.5%) and X_1=0 (25%), X_2=-0.7 (7.7%) along with all other excipients in the same amount as used in factorial design batches. The response variables were determined and compared with predicted values as shown in Table 12.

The results obtained with check point batches are very close to predicted values. Thus, we can conclude that the statistical model is mathematically valid.

Selection of Optimum Batch

The similarity factor (f_2) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profiles. Dissolution data of all batches was subjected to find similarity factor for selecting the optimum batch. The predicted drug release profile for an ideal formulation was taken as a reference. Batch F5 showed maximum similarity (f_2=80.69) compared with other batches (Table 9). Hence formulation F5 was selected as optimized based on highest similarity with predicted

Table 13: Kinetic treatment of dissolution data

Batch	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
Zero order									
B	17.444	19.678	17.241	4.775	4.619	5.709	4.685	4.973	5.466
A	-102.7	-118.6	-85.42	-7.92	-7.04	-10.33	-13.33	-10.27	-11.55
R^2	0.9985	0.97702	0.9757	0.9859	0.9987	0.9795	0.9980	0.9771	0.9818
First order									
B	0.127	0.136	0.104	0.035	0.032	0.039	0.036	0.035	0.040
A	0.563	0.513	0.887	1.242	1.273	1.259	1.163	1.230	1.216
R^2	0.9884	0.97016	0.9507	0.9433	0.9787	0.9398	0.9712	0.9463	0.9455
Higuchi									
B	107.16	121.20	106.48	37.529	35.965	43.049	36.464	39.074	41.169
A	-266.7	-304.6	-249.2	-79.78	-75.21	-89.80	-82.52	-85.05	-87.47
R^2	0.9982	0.9792	0.9806	0.9936	0.9971	0.9898	0.9968	0.9843	0.9911
Hixson Crowell									
B	-0.379	-0.412	-0.331	-0.103	-0.098	-0.119	-0.106	-0.107	-0.119
A	4.313	4.528	3.540	2.271	2.208	2.258	2.246	2.312	2.351
R^2	-0.994	-0.973	-0.959	-0.962	-0.985	-0.955	-0.985	-0.959	-0.960
Korsemeyer and Peppas									
A	-2.935	-3.095	-2.356	-1.670	-1.551	-1.642	-1.772	-1.698	-1.702
n	2.782	2.978	2.292	1.245	1.140	1.288	1..291	1.272	1.314
R^2	0.9939	0.9784	0.9641	0.9799	0.9960	0.9756	0.9929	0.9787	0.9797

B= Slope, A=Intercept, R^2= Correlation coefficient, n= Diffusion exponent