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Formulation Design and Optimization of Expandable Gastro Retensive Film for Controlled Release of Propranolol Hydrochloride

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Abstract: The gastroretentive drug delivery system is site-specific and allows the ig to remain in the stomach for a prolonged period of time so that it can be eased in a controlled manner in the gastrointestinal tract. The purpose of the earch work is to formulate and optimize the gastro retensive film (GRF) ntaining Propranolol hydrochloride in order to prolong the release time and prove the bioavailability. Five basic gastroretensive films were developed by lvent casting method for preliminary trial . The best formulation was subjected for o factor two level design approach. Independent variables selected were ncentrations of Eudragit S 100 (X1) and Eudrajit RL 100 (X2) and dependent riables were Folding Endurance (Y1) Tensile strength (Y2) Elongation at break 3) and in vitro drug release (Y4). The results of the study indicate optimized mulation (P2) exhibit folding endurance 114, tensile strength 1.3 kg mm², ongation at break 22% and in vitro release 46.5 % for 12h. The in vitro release data re well fit into Higuchi and Korsmeyer-Peppas model and followed non-Fickian fusion mechanism. The gastro retensive formulations can be used in diseases here an extended release of propranolol is required.

Keywords: Propranolol hydrochloride,Gastroretensive expandable film, Dptimization.

INTRODUCTION

Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug wastage, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestine.

Several approaches have been attempted in the preparation of gastroretentive drug delivery system as floating, swellable and expandable, high density, bioadhesive, altered shape, gel forming solution or suspension system and sachet systems [1-3]

Propranolol is a nonselective beta-adrenergic receptor blocking agent, which is well established efficiency in treating hypertension and in the treatment of migraine [4-6]. The half life of the drug is 4h. So to obtain desired therapeutic drug plasma level requires frequent administration leading to poor patient compliance. The drug is relatively stable at acidic pH (1.2) of the stomach, and as it moves towards regions of higher pH along the GIT, the drug shows instability due to degradation reactions. Moreover, the drug lies in the Class I of BCS classification showing high aqueous solubility as well as high intestinal permeability leading to better absorption of the drug via the gastrointestinal tract [7-9]. Considering all the factors the study aimed to develop and optimize novel expandable gastro retensive delivery system to the improved oral bioavailability and patient compliance of the drug.

MATERIALS AND METHODS

Propranolol hydrochloride (Yarrowchem products,Mumbai) HPMC, Eudragit RS100 and Eudragit RL100 (Nice chemical, Cochin). All other chemicals used were of analytical grade.

Formulation Design

The drug containing polymeric film was prepared by solvent casting method. A polymeric dispersion of HPMC, eudragit S100 and eudragit RL100 was prepared by dissolving polymers in ethanol and dichloromethane with the ration of 1:1 Then the measured quantity of Propranolol hydrochloride was dissolved and added to the clear polymeric mixture. Finally required quantity PEG 400 and Dibutylphthalate was added to the dispersion as a plasticizer. The dispersion was

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stirred vigorously in mechanical stirrer at 200 rpm for 15 minutes. The resulting dispersion was poured into a petri dish and allowed to dry at room temperature for 24 hours. The film obtained as a result of solvent evaporation was carefully removed and cut into $4\text{cm} \times 2\text{cm} (8\text{cm}^2)$ rectangle units. The prepared film was folded into zigzag pattern and then inserted into hard gelatin capsule shell [10-13]. Totally five formulations were designed with various compositions of polymers for preliminary trial (Table-1).

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectral data were taken for the determination of potential molecular interactions between the drug and excipients by the KBr disc method using FTIR spectroscopy (IR affinity-1, Shimadzu Corporation, Japan). The sample disc was scanned from 4000 to 400 cm-1 at a resolution of 4 cm-1.

Physical Evaluation

The appearance of each integrated device was determined by visual inspection for each trial. The thickness range was determined for all films of the batch by using vernier caliper and determined the average thickness and standard deviation for the same to ensure the thickness of the prepared film [15]. Weight Three different films of same formulations were separately weighed by using digital balance and the mean of three patches were recorded .

Folding endurance

A strip of specific area was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance [14].

Drug content determination

The film is cut into pieces of suitable size (2x2) and placed in 100 ml of dissolution medium pH 1.2, stirred continuously using a mechanical stirrer and the sample is withdrawn at the end of three hours and the drug content is determined spectrophotometrically at 294 nm^[15].

Tensile strength

The instrument used to measure the tensile strength designed in our laboratory especially for this research work. The modification of chemical balance is used in which One pan of the balance was replaced with one metallic plate having a hook for attaching the film. The equilibrium of the balance was adjusted by adding weight to the right pan of balance. The instrument was modified in such a way that the film can be fixed up between two hooks of the horizontal beams to hold the test film. A film of 2.5cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan [16].

Tensile strength, $T = \frac{m \times g}{b \times t}$ Dynes/cm² T=Force at break/initial cross sectional area of sample

Where,

m= mass in grams

g=acceleration due to gravity,b= breadth of the specimen (cm) t=thickness of the sample (cm)

Elongation at break

Stress conditions would be stated as stretching the film/patch to the point till it breaks down and measuring the largest length of the intact patch before breaking. Percent Elongation at break was calculated by using the following equation [17].

Elongation at break (%) = Increase in length/Original length \times 100

In-vitro Drug release study

The *in vitro* release of Propranolol from the capsule filled expandable film was conducted using USP type II paddle dissolution apparatus. The dissolution medium used was 900 ml of 0.1N HCl at the rotation speed of 50 rpm, kept at $37^{\circ} \pm 0.5^{\circ}$ C. At the predetermined time intervals samples were withdrawn, and replaced with the fresh dissolution medium. The samples were analyzed spectrophotometrically at 290 nm 18].

Drug release kinetics

The obtained dissolution data was fitted to zero order, first order, Higuchi-Crowell and Korsmeyer-Peppas equations to understand the rate of drug release from the prepared formulations [19]. The correlation coefficient values were calculated and used to find the fitness of the data.

Statistical optimization

A 2 factor 2 level central composite design was used to derive a polynomial quadratic model and construct contour plots to predict responses. The independent variables selected were concentration of Eudragit S 100 (X1) concentration of Eudragit RL 100 (X2) and response variables were folding endurance (Y1) percentage drug release (Y2), Tensile strength (Y3) Elongation at break (Y4) The results are shown in Table-3.

RESULTS AND DISCUSSION

Fourier Transform Infrared Spectroscopy

Compatability studies were performed using FT-IR spectrophotometer. The results of the study reveals that the FT-IR spectrum of Drug and excipients did not differed with major peaks of Propranolol hydrochloride ,all the major peaks of the drug appeared on the blend reveals that there is no possible interaction between drug and excipients

Physiochemical characterization

The prepared gastro retensive films of Propranolol hydrochloride was observed visually and were found to be opaque with number of air bubbles which were flexible in nature. Thickness of formulations ranged between 1.18 ± 0.2 to 0.149 ± 0.3 mm, weight variations of the film was found to be uniform which ranges from 0.236 ± 0.01 to 0.277 ± 0.021 g.it is observed that the weight of the film was increases with increase in film thickness. Folding endurance for all the prepared film was from 98-140 which indicate good flexibility and integrity. The drug contnt ranges from 95.66 to 98.45%.

Tensile strength of the formulations was in the range of 0.96 to 1.6 indicated that as concentration of eudragit S 100 increases and concentration of eudragit RL 100 decreases tensile strength increases. All formulations have shown 0 % constriction of the film. No amount of constriction in the formulated GR Film ensured their 100% flatness. Elongation at break ranges from 10.59% to 21.45%. Tenilestrength and elongation at break is interconnected. As the tensile strength increases elongation at break also increases.

The tested formulations showed sustained release pattern of drug over 12h with varying cumulative percentage release. When the GR films were exposed to dissolution medium, the medium penetrated into the free spaces between macromolecular chains of the polymer. The result of dissolution studies of all the formulations was evaluated. Formulation containing high concentration of eudragit S100 and decreased concentration of Eudragit RL100 (F1)shows controlled release as compared to others. The results of physiochemical chearacterization of the film was found tobe satisfactory.

Ingredients	F1	F2	F3	F4	F5
Propranolol IP	40.0	40.0	40.0	40.0	40.0
HPMC	350	350	350	350	350
Eudragit S100	800	600	500	400	200
Eudragit RL100	200	400	500	600	800
DCM/Ethanol	20.0	20.0	20.0	20.0	20.0
Dibutyl Phthalate	0.25	0.25	0.25	0.25	0.25
PEG 400	0.50	0.50	0.50	0.50	0.50

Table-1: Composition of Propranolol HCl GR Film for Preliminary trial

Note: 1.Quantities are expressed in mg / ml 2.Area of the film- 4x2 cm, Dose of drug per film 40mg

Tab	Table-2: Characterization of Propranolol HCl GR Films for preliminary traial						
	Parameters	F1	F2	F3	F4	F5	
	Visual appearance	Opaque	Opaque	Opaque	Opaque	Opaque	
	Thickness(mm)	0.15	0.13	0.13	0.12	0.15	
	Film Weight (mg)	0.28	0.26	0.25	0.24	0.28	
	Folding endurance	154	131	122	109	98.0	
	Drug content (%)	98.5	96.3	98.1	95.7	97.2	
	Tensilestrength	10	1.2	1.2	1.3	1.6	
	Elongation at break	10.50	12.86	17.5	20	21.45	
	Drug release (%)	49.42	58.25	60.21	62.15	71.11	l

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Table-3: Layout of 2 Full Factorial Design						
Independent variables			Dependent variables			
Code	X ₁	\mathbf{X}_{2}	Y1	Y2 (%)	$Y3(kg/mm^2)$	Y4(%)
f1	-1	-1	98	42.229	1.04	20
f2	-1	+1	114	46.58	1.3	22
f3	-1	-1	126	40.08	1.16	27.7
f4	+1	+1	110	43.89	0.99	30

Table-3: Layout of 2² Full Factorial Design

Note: all the values are average of three such determinations X1(Eudragit S100):-1(150mg),+1(250mg) X2(Eudragit RL100):-1(750mg),+1(850mg) Y1folding endurance Y2 In vitro release study(%) Y3 tensile strength(kg/mm²) Y4 elongation at break(%)



Fig-1: FTIR study of (A) Propranolol Hydrochloride (B) Drug and Excipients mixture



Fig-2: Comparative in vitro drug release profile (F1-F5)

Statistical optimization

A 2^2 central composite full factorial design was used to optimize the best preliminary trial batch (F1 batch). The study result of polynomial equations given below.

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1 X_2 + b_{22} X_2 X_2$$

Where,

Y= Dependent variable

 b_0 =Arithmetic mean response of 8 runs

 b_1, b_2 are estimated regression coefficient for factor X_1 .

Effect on folding endurance

Folding endurance =115.60 + 4.33 X_1 - 2.50 X_2 + 0.95 X_1 * X_1 - 1.05 X_2 * X_2 - 3.00 X_1 * X_2

The values for Folding endurance of the film Y1 ranges between 98-126 and were significantly influenced (P = <0.05) by factors (X_1, X_2). A positive correlation was observed for both X1 and X2 in folding endurance. However when combine effect of X_1 and X_2 decrease the folding endurance.

Effect on in vitro release

Drug release (%) = 44.17 - 2.04 X_1 + 0.62 X_2 - 0.57 X_1 * X_1 + 1.63 X_2 * X_2 + 1.87 X_1 * X_2

The influence factor X_1 negatively influences the *invitro* release pattern. X_2 factor (eudragit RL 100) significantly increases the amount of drug relese over the time. Combined effect of X_1 and X_2 rapidly release of drug.

Effect of Tensile strength

Tensile strength = $1.1920 + 0.0126 X_1 - 0.0600 X_2 0.0779 X_1 X_1 + 0.0346 X_2 X_2 + 0.0350 X_1 X_2$

The percentage of tensile strength ranges from 0.99-1.3 kg/mm². When concentration of X_1/X_2 increases the tensile strengthe also increased.

Effect of elongation at break

Elongation at break = $23.98 + 0.56 X_1 + 1.54 X_2 + 3.06 X_1 * X_1 - 1.37 X_2 * X_2 - 1.92 X_1 * X_2$

Elongation at break interconnected with tensile strength and it ranges from 20 to30%. The application of ANOVA using the provisions of Design expert software revealed statistically significant (p < 0.05). When both X_1 and X_2 increases decrease the film breaking. Effect of independent variables X1 and X2 on response variables were shown in response surface plot and counter plot.



Fig-3: Surface and Contour plots for folding endurance (Y1)drug release (Y2),tensile strength(Y30 elongation at break(Y4)

Drug release kinetics for optimized batch

The *in vitro* drug release data obtained were extrapolated by zero order, first order, Higuchi, Hixson, Korsmeyer peppas in order to define the permeation profiles. In this study, the *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation, (r^2 from 0.95 to 0.99). The mechanism of drug release was non–Fickian (Anomalous transport).

CONCLUSION

In the current research work an attempt was carried out to develop gastroretensive film of propranolol hydrochloride by solvent casting method and to statistically optimize the formulation variables. Based on the study results Eudragit S100 (150 mg) and Eudragit RL 100 (750 mg) suitable for formation of good quality gastroretensive film.

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