AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Development of Gastroretentive Mucoadhesive Matrix Tablet of Propafenone HCl

Chordiya Mayur Ashok[1]*, Gangurde Hemant Hiraman [2], K. Senthilkumaran [3]

1. Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai, India.
2. Department of Pharmaceutics, NANDHA College of Pharmacy, Erode, Tamil Nadu, India.
3. Department of Pharmaceutics, K.K. College of Pharmacy, Chennai, India.

ABSTRACT

The purpose of this study was to develop a gastroretentive controlled release drug delivery system with mucoadhesive properties of Propafenone HCl. Propafenone HCl has a short elimination half-life, a narrow absorption window and is mainly absorbed in proximal areas of gastro intestinal tract. Tablets were prepared by using controlled release polymers HPMC E5 and HPMC K100M. Mucoadhesive matrix tablet contains sodium carboxy methyl cellulose as a mucoadhesive polymer. The formulations were evaluated for pharmacopoeial quality control tests and all the physical parameters evaluated were within the acceptable limits. All formulations were evaluated for mucoadhesive strength, which showed good detachment force up to 12 h. Mucoadhesion studies via rotating paddle method and *In-vitro* drug release studies were conducted in 0.1 N HCl (pH 1.2) at 37 ± 0.5 ºC. Formulation M11 was proved to be good mucoadhesion, dimensional stability and drug release up to 12 h as compared to the other formulations. Stability studies were carried out on the optimized formulation for period of 3 months at 40^0c/75 %RH. Finally it was observed that there was no change in physiochemical and physical properties as well as in drug release profile even after storage at 45 °C and 75 % for three months.

Keywords: Propafenone HCl, dimensional stability, gastroretentive drug delivery system, mucoadhesive strength.

*Corresponding Author Email: chordiya.mayur@gmail.com
Received 10 August 2013, Accepted 18 August 2013

Please cite this article in press as: Chordiya MA. *et al* Development of Gastroretentive Mucoadhesive Matrix Tablet of Propafenone HCl. American Journal of PharmTech Research 2013.

INTRODUCTION

Oral controlled release drug delivery system has overcome every one of the disadvantages of conventional drug delivery system and for this reason is the mainly ideal route. However, due to a number of physiological difficulties, such as an incapability to restrain and localize the drug delivery system in preferred regions of the GIT and the very much changeable nature of gastric emptying process, predictable and increased bioavailability of drugs cannot be achieved.[1-4]

A variety of systems such as mucoadhesive, swelling, floating system and high density, have been developed to enhance gastric residence time of a dosage form. Physiological features of the upper gastrointestinal tract shows significant challenge to develop such systems.

The mucoadhesive systems are proposed to increase the gastric residence time by adhering them to the gastric mucous membrane. Bioadhesion on soft tissues of certain synthetic or natural polymers has been exploited to control and to extend the gastric retention of the delivery systems. The adhesion of polymers with the mucous membrane may be mediated by bonding, hydration or receptor mediated. Bonding mediated adhesion involves chemical or mechanical bonding. Chemical bonds may involve ionic bonds or covalent or Vander Waals forces between the polymer and the mucous membrane. In hydration mediated adhesion, the hydrophilic polymers converted into sticky and mucoadhesive upon hydration. Receptor mediated adhesion takes place among certain polymers and specific receptors articulated on gastric cells. The polymers could be cationic or anionic or neutral. The utilization of bioadhesive property of certain polymers on tissues in designing gastro retentive dosage forms is unique. Nevertheless, the intrinsic risk of this dosage form is the esophageal adherence resulting in drug induced injuries.

Propafenone HCl is one of the antiarrhythmic agents, which is a Class 1C antiarrhythmic drug with local anesthetic effects, and direct stabilizing action on myocardial membranes. It has less half-life of about 2-10 hours and oral bioavailability very less, i.e. 10 %. Due to this reason it has to be taken frequently, i.e. 150 mg 3 times a day or 300 mg twice a day. To increase the bioavailability of Propafenone, gastroretentive drug delivery system was selected in which the dosage form is retained in the stomach so that it can be released for an extended period of time. The drugs should have following properties to be the ideal candidates for gastroretention, a) narrow absorption window b) less bioavailability c) less plasma half life

Propafenone HCl an antiarrhythmic agent has a narrow absorption window i.e. it is erratically absorbed through GIT, less bioavailability of about 10 % and hence requires frequent dosing. It

also has less plasma half-life. Drugs having pH dependent solubility i.e. highly soluble at low pH (gastric pH) and poorly soluble at high pH (intestinal pH) are the suitable drug candidates for the gastroretentive drug delivery system. In the treatment of angina, hypertension, cardiac arrhythmias, a loading as well as maintenance dose is required. Thus, Propafenone HCl has all the properties required for gastroretention and hence it was selected as the candidate drug for gastroretentive drug delivery system. [5-7]

MATERIAL AND METHODS

Material

Propafenone Hydrochloride as reference substances were supplied by Glenmark Pharmaceuticals Ltd., Mumbai. HPMC E5, HPMC K100M were used as rate controlled polymers purchased from Loba Chemie Pvt. Ltd. Mumbai. Sodium carboxy methyl cellulose was used as mucoadhesive polymer purchased from Loba Chemie Pvt. Ltd. Mumbai. Magnesium stearate, Lactose and isopropyl alcohol were purchased from Loba Chemie Pvt. Ltd. Mumbai. PVP K-30 was purchased from Signet Chemical Corporation, Mumbai.

Preparation of mucoadhesive matrix tablet of Propafenone HCl

The granules were prepared by wet granulation method as per formulae given in the Table (twenty tablets for each formulation). The drug Propafenone Hydrochloride, hydrophilic polymer (HPMC K100M, HPMC E5), and mucoadhesive polymer sodium carboxy methyl cellulose were passed through sieve 40# separately and blended thoroughly. After proper mixing then slowly add the binding solution containing PVP K-30 in IPA (Iso propyl alcohol) till fine uniform granules were obtained. The wet mass was passed through sieve 16# and dried at 50 °C for 30 minutes to get the moisture content less than one. Then lubricate the dried granules with magnesium stearate which were already passed through sieve 40#. Then lubricated granules were compressed on cadmach tablet punch machine for all formulations.[8] The formulations containing various percentages of polymers were shown in Table 1 and 2.

Table 1: composition of gastroretentive mucoadhesive tablet (all quantities in mg)

Formulation code	M1	M2	M3	M4	M5	M6	M7	M8
Propafenone Hydrochloride	300	300	300	300	300	300	300	300
HPMC E5	150	100	75	-	-	-	75	75
HPMC K100M	-	-	-	150	100	75	75	100
Carboxy Methyl Cellulose	70	70	70	70	70	70	70	70
PVP K30	20	20	20	20	20	20	20	20
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	150	200	250	150	200	250	150	125

Table 2: composition of gastroretentive mucoadhesive tablet (all quantities in mg)

Formulation code	M9	M10	M11	M12	M13	M14	M15	M16
Propafenone Hydrochloride	300	300	300	300	300	300	300	300
HPMC E5	100	100	75	75	75	75	100	100
HPMC K100M	75	100	75	75	75	100	75	100
Carboxy Methyl Cellulose	70	70	105	119	140	140	140	140
PVP K30	20	20	20	20	20	20	20	20
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	125	100	115	101	80	55	55	30

Evaluation of granules

Angle of repose

Granules flowability was determined by calculating angle of repose by funnel technique. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm above the platform. About 20 g of granules was slowly passed along the wall of funnel till the tip of the pile produced and touches the stem of the funnel. A rough circle was drawn about the pile base and the radius of the sample cone was measured.[9] Angle of repose was calculated from average radius using formula:

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = angle of repose

h = height of the pile

r = average radius of the powder cone.

Bulk Density

Apparent bulk density of granules was determined by the graduated cylinder and measuring the volume and weight "as it is".[10] Bulk density was calculated by using following formula:

Bulk density (g/mL) = Weight of sample in grams /Volume occupied by the sample

Tapped Density

Tapped density was determined with the aid of tapped density tester apparatus. In this method 20 gm of sample was poured gently through a glass funnel in to a 100mL graduated cylinder. The cylinder was then placed in the apparatus and parameters were set to carry out the test. [10] Volume occupied by the sample after tapping were recorded and tapped density was calculated by following formula:

Tapped density (g/mL) = Weight of sample in grams/After tapping volume occupied by the sample

Hausner ratio

It provides an indication of the degree of densification which could result from vibration of the feed hopper. Hausner ratio closer of less than 1.25 indicates good flow, while greater than 1.5 indicates poor flow materials.[11]

Hausner ratio = Tapped density /Bulk density

Carr's index or % compressibility

Carr's index or % compressibility [11] was calculated by using following equations:

Carr's index = Tapped density - Bulk density /Tapped density × 100

Evaluation of mucoadhesive matrix tablets

Tablet thickness and diameter

Tablet Thickness and diameter were accurately measured by using digital vernier caliper in mm. [12] Results were expressed as mean values ± SD.

Hardness and Friability

Hardness of tablet was determined by Monsanto hardness tester. Friability test was done by Roche friabilator. Ten tablets were weighed and were subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at distance of 6 in. with each revolution. Operated for 100 revolutions, the tablets were de dusted and reweighed. [13] The percentage friability was calculated.

F = W1 −W2/ W1× 100

Where F represents the percentage weight loss, and W1 and W2 are the initial and final tablet weights, respectively.

Weight variation

Twenty tablets were selected at random and average weight was determined. Then individual tablets were compared with the average weight. [13]

***In vitro* mucoadhesive strength determination**

The *in vitro* mucoadhesive strength of tablet was measured with goat stomach mucosa, using a modified physical balance. On one side of the balance, a rubber closure tied with thread was attached and on other side empty polythene bag was attached. Goat stomach mucosa was obtained from a local slaughter house and stored in a phosphate buffer pH 6.8 upon collection. The experiments were performed within 3 h of collection of stomach mucosa which has been separated from sheep stomach. The goat stomach mucosa was fixed to the opening of the glass vial with thread and then placed in a beaker, well packed. Phosphate buffer pH 6.8 was added into the beaker upto the upper surface of the buccal mucosa to maintained stomach mucosal viability during the experiment. The tablet was sticked to the rubber closure with cyanoacrylate

glue, then the beaker was raised slowly until contact between goat stomach mucosa and tablet was established. A preload of 5 gm was placed on the clamp for 5 min (preload time) to establish adhesion bonding between tablet and goat stomach mucosa. The preload time were kept constant for all the formulations. After completion of the preload time, preload was removed from the clamp and water was then added in the polythene bag by pipette in drop-wise manner, at a constant rate. The weight of water required to detach tablet from stomach mucosa was noted as in vitro mucoadhesive strength, and these experiments were repeated with fresh mucosa in an identical manner. The modified physical balance for *in vitro* mucoadhesive strength determination consisting of polythene bag (on one side) and rubber closure for attachment of tablet (on other side).[14] The mucoadhesive force, expressed as the detachment stress in dyne/cm^2 was determined using following equation:

Detachment stress (dyne/cm^2) = mg/A

Where, m = Weight of water added to polythene bag in grams;

G = Acceleration due to gravity taken as 980 cm/sec^2;

A = Area of the tissue exposed and is equal to πr^2

Mucoadhesion studies via rotating paddle

The mucoadhesive properties of the formulations were examined using a second system called the rotating paddle method. Tablets were attached to freshly excised goat stomach mucosa which was provided from the local slaughter house and fixed to the paddle with cyanoacrylate glue. After that, the paddle was displaced into the dissolution apparatus and completely immersed into the simulated gastric fluid, pH 1.2 at 37°C. Then the paddle was agitated at a speed of 100 rpm. The detachment of the test tablets was determined visually in every 30 min during an observation time of 12 h. [15]

Drug content

For determination of drug content, Weighed and powder 5 tablets, then weighed accurately a quantity of the powder equivalent to about 100 mg of Propafenone HCl, transfer to a 100ml volumetric flask and dissolved in 100 ml of methanol. The resultant solution was analyzed spectrophotometrically at 250 nm. [16]

Dimensional stability

The dimensional stability of the formulations was studied by using USP dissolution Apparatus II. The dissolution medium was 0.1N HCL and the volume being 900mL, the temperature was maintained at 37 °C. The rotation speed was 100 rpm. The dimensional stability of gastroretentive mucoadhesive tablet was observed visually. [17]

Drug release study

Three tablets of each formulation were used in the release experiment. The release rates of Propafenone HCl were determined using USP apparatus I (basket apparatus) at 37 °C in 900 ml of 0.1N HCl solution (pH, 1.2) with the rotation speed of 100 rpm. At appropriate time intervals 0.25. 0.5, 1, 2, 3, 4, 6, 8, 10, 12 h, 5ml of sample was withdrawn and an equal volume of medium was added to keep the volume constant. Samples were analyzed spectrophotometrically at 250 nm.[17]

Accelerated stability study of optimized formulations

Accelerated stability study was carried out for optimized formulations, to assess its stability as per ICH guidelines. The optimized formulation were wrapped in the laminated aluminum foils and was placed in the accelerated stability chamber (6CHM-GMP, Remi Instrument Ltd., Mumbai) at elevated temperature and humidity conditions of 40^0C/ 75% RH and a control sample was placed at an ambient condition for a period of three months. Sampling was done at a predetermined time of initial 0, 1, 2 and 3 months interval respectively. At the end of study, samples were analyzed for the drug content, *in vitro* drug release profile and other physicochemical parameters.[18-20]

RESULTS AND DISCUSSION

Granules evaluation

The physical characteristics of the granules (M1 to M16) such as bulk density, tapped density, carr's index, husners ratio, angle of repose were determined. The results are given in Table 3. The bulk densities were ranged from 0.609-0.780 gm/ml. The tapped densities were ranged from 0.711-0.801 gm/ml. The carr's compressibility index were ranged from 2.62-18.03%. The housners rations were found to be in the limit 1.02-1.22. The angles of repose of all formulation were found to be between the limit 20.69°-28.61°. All the formulation shows excellent flow properties. So, the granule passes the evaluated tests and subjected to next stage of work compression.

Table 3: Evaluation and characterization of granules

Formulation	Bulk density gm/ml	Tapped density gm/ml	Carr's index (%)	Hausner's ratio	Angle of repose (°)
M1	0.780±0.02	0.801±0.06	2.62±0.10	1.02±0.05	22.68±1.26
M2	0.667±0.05	0.720±0.02	7.36±0.15	1.07±0.03	21.30±2.30
M3	0.678±0.01	0.711±0.06	4.64±0.21	1.04±0.04	24.68±1.73
M4	0.670±0.03	0.729±0.01	8.09±0.26	1.08±0.03	25.68±1.44
M5	0.667±0.07	0.771±0.07	13.48±0.22	1.15±0.02	27.34±0.98
M6	0.690±0.02	0.768±0.04	10.15±0.18	1.11±0.04	23.68±1.36

M7	0.685±0.05	0.799±0.03	14.26±0.09	1.16±0.05	20.69±1.05
M8	0.681±0.06	0.725±0.09	6.06±0.08	1.06±0.01	28.61±2.57
M9	0.609±0.04	0.743±0.02	18.03±0.13	1.22±0.01	26.53±1.33
M10	0.681±0.09	0.721±0.04	5.54±0.07	1.05±0.06	22.61±1.85
M11	0.685±0.04	0.719±0.08	4.72±0.03	1.04±0.05	25.68±1.54
M12	0.672±0.05	0.723±0.01	7.05±0.04	1.07±0.03	23.47±1.79
M13	0.684±0.02	0.781±0.03	12.41±0.15	1.14±0.03	24.71±1.52
M14	0.690±0.07	0.764±0.02	9.68±0.06	1.10±0.05	24.49±1.35
M15	0.687±0.03	0.794±0.05	13.47±0.11	1.15±0.02	23.96±1.69
M16	0.682±0.02	0.763±0.03	10.61±0.09	1.11±0.07	23.04±1.57

x= mean; ± SD; n= 3

Tablet thickness and diameter

The thickness of the tablets range from 4.46-5.65 mm respectively. The diameter of the tablet in the range of 12.98-13.03mm.There is no variation in tablet thickness and diameter between the formulations. The results are given in Table 4.

Hardness, friability and weight uniformity of tablets

The hardness of the tablet was within the range and optimum for controlled release, and ranging from 7.8-8.2 Kg/cm^2 for all M1-M16 formulations. The friability of all formulations was ranging from 0.089-0.198 % w/w and passes as per IP limit should not be more than 1 % w/w. The weight uniformity of tablet in all formulation was observed to be within the IP limit 10 %. All formulations were complying with the official test. The values were mentioned in Table 4.

Table 4: Evaluation of Propafenone HCl mucoadhesive tablet

Formulation	Thickness mm	Diameter mm	Hardness Kg/cm^2	Friability ^{x}% w/w	Weight variation mg
M1	4.53±0.01	12.99±0.04	7.8±0.07	0.120±0.03	704.16±1.37
M2	4.55±0.01	13.00±0.02	7.9±0.09	0.128±0.05	702.86±1.48
M3	4.60±0.03	13.02±0.01	7.8±0.10	0.198±0.02	698.77±3.55
M4	4.65±0.02	12.98±0.02	8.2±0.03	0.098±0.01	695.32±2.74
M5	4.51±0.02	12.99±0.03	8.0±0.11	0.114±0.03	700.94±1.96
M6	4.58±0.03	13.01±0.02	8.1±0.05	0.105±0.06	695.37±2.54
M7	4.49±0.03	13.02±0.01	8.0±0.07	0.118±0.05	695.68±2.60
M8	4.62±0.02	13.01±0.01	8.2±0.04	0.089±0.03	703.62±3.41
M9	4.60±0.01	13.03±0.03	7.9±0.12	0.131±0.09	696.40±2.58
M10	4.54±0.01	13.01±0.04	8.0±0.08	0.124±0.03	698.54±2.53
M11	4.53±0.01	13.11±0.02	8.1±0.10	0.108±0.10	706.90±1.47
M12	4.46±0.01	12.99±0.01	7.9±0.02	0.135±0.04	697.49±1.40
M13	4.62±0.02	12.98±0.02	8.0±0.05	0.120±0.06	705.78±3.57
M14	4.51±0.02	12.99±0.02	8.1±0.08	0.104±0.02	703.42±1.83
M15	4.59±0.01	13.02±0.01	8.1±0.04	0.109±0.03	701.59±3.61
M16	4.60±0.03	13.00±0.02	8.0±0.06	0.114±0.08	705.21±2.35

x= mean; ± SD; n= 3

***In vitro* mucoadhesive strength determination**

From the results it was found that as the concentration of sodium carboxy methyl cellulose increases the mucoadhesive strength increases and decreases the drug release. But formulation M11 shows the optimum mucoadhesive strength with good drug release when compared to all other formulations subjected in this test. Hence the mucoadhesive property of the formulation M11 could assist the tablet to stay in the upper part of gastro intestinal tract and enhance the gastroretention. The values were mentioned in Table 5.

Mucoadhesion studies via rotating paddle

This was supported by the visual observations made in rotating paddle method of mucoadhesion testing shown in Figure 1. Formulations M11-M16 tablets were found to remain attached to the mucosa for 12 h along with maintaining tablet integrity. While formulation M1-M10 tablets doesn't showed good mucoadhesion with mucosa till 12 h. The values were mentioned in Table 5.

After 1st h **After 12th h**

Figure 1: Mucoadhesive study of formulation M11 by rotating paddle method

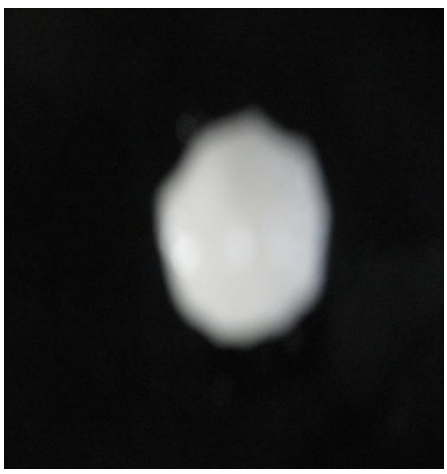
Drug content

The assays of all formulation from H1-H16 were found to be between 99.19-99.79 %. The result shows that all formulation containing drug were within the limit (99-101 %). The values were mentioned in Table 5.

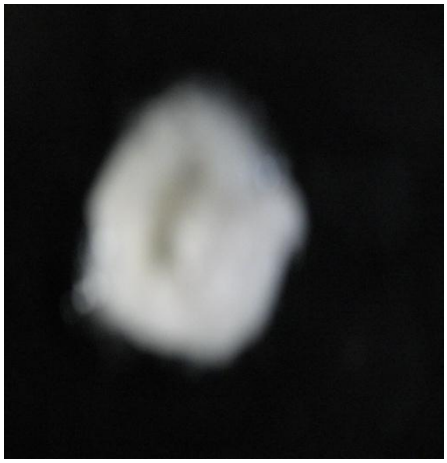
Dimensional Stability

It is important to maintain the physical integrity of the tablet up to 12 h in case of once daily formulations. In all formulations the concentration of polymers also acts as release retardant was increased in ascending order to achieve the *in vitro* release. So increasing concentrations the dimensional integrity of tablet also increased respectively. The dimensional integrity of

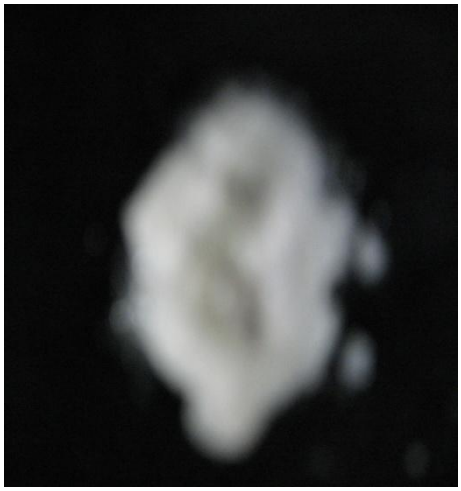
formulations was represented with code along with picture representation in Table 5 and Figure 2. The formulation M1-M16 shows excellent dimensional stability, except formulation M3 and M6 shows very good dimensional stability.



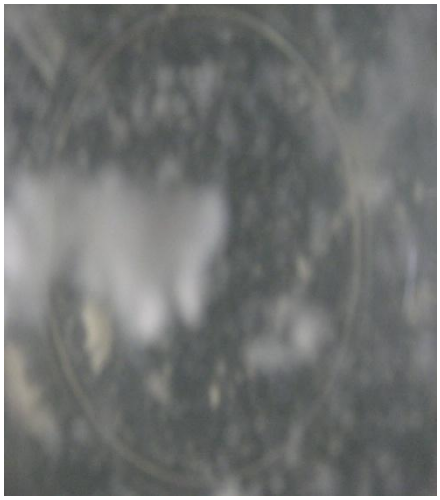
Excellent



Very good



Good



Poor

Figure 2: Picture representation for dimensional stability

Table 5: Evaluation parameters for Propafenone HCl mucoadhesive matrix tablet

Formulation	Detachment force (dyne/cm^2)	Adhesion retention period Hr	Drug content^x (%)	Dimensional stability
M1	1398.29	10	99.63±0.06	excellent
M2	1255.79	9.5	99.79±0.03	excellent
M3	1131.01	9	99.44±0.05	very good
M4	1480.52	10.5	99.37±0.10	excellent
M5	1420.68	10	99.19±0.11	excellent
M6	1377.25	10	99.66±0.13	very good
M7	1352.78	10.5	99.47±0.09	excellent
M8	1443.58	11	99.34±0.10	excellent
M9	1369.96	11.25	99.52±0.09	excellent

M10	1584.99	11.5	99.29±0.06	excellent
M11	1510.85	>12	99.46±0.13	excellent
M12	1625.40	>12	99.39±0.09	excellent
M13	1831.47	>12	99.28±0.06	excellent
M14	1613.48	>12	99.45±0.16	excellent
M15	1583.73	>12	99.67±0.15	excellent
M16	1673.49	>12	99.49±0.11	excellent

x= mean; ± SD; n= 3

***In vitro* drug release study**

In our work, we have shown the effect of polymers on *in vitro* drug release studies of Propafenone HCl. Formulation batch M1-M6 releases drug up to 80-85% only. In the later batches M7-M16 use of combination of polymers in that case it exhibits good drug release up to the 12 h. Formulation M11 shows maximum drug release up to 92.88% with controlled manner which also exhibits excellent mucoadhesive strength. Cumulative % drug release of formulation M1-M16 showed in Table 6 and 7.

Table 6: Cumulative % drug release of formulated mucoadhesive tablet

Time	Cumulative % drug release [x]							
(h)	M1	M2	M3	M4	M5	M6	M7	M8
0.25	3.01±0.07	3.84±0.41	5.11±0.05	3.91±0.55	4.30±0.38	6.72±0.51	9.31±0.78	7.57±o.62
0.5	5.18±0.65	10.74±1.01	8.52±0.75	5.24±0.91	7.73±0.55	11.76±1.31	14.82±1.31	12.14±1.04
1	11.62±1.06	13.76±1.29	14.46±1.53	10.32±1.03	12.43±1.04	16.40±1.48	19.93±1.53	17.52±1.62
2	17.35±1.98	22.21±2.48	22.04±2.81	15.65±1.37	23.78±2.12	29.36±1.89	21.4±1.46	19.47±1.83
3	24.90±2.48	31.02±2.39	35.13±2.90	21.53±2.92	33.44±2.73	37.61±2.72	32.18±1.76	25.62±2.91
4	34.37±2.55	40.88±3.73	44.43±3.94	34.35±2.78	40.79±2.40	48.38±3.55	44.82±2.98	36.67±2.50
6	48.02±3.71	56.06±3.61	60.13±3.61	44.66±2.47	52.72±3.85	58.73±3.81	59.36±3.04	53.89±3.81
8	57.63±3.37	64.76±3.72	65.62±3.50	65.39±2.93	61.29±3.09	67.19±3.42	73.44±3.87	68.38±3.57
10	64.32±3.43	64.08±2.86	75.82±2.89	72.98±2.38	70.73±3.27	74.06±2.02	80.86±2.70	83.31±2.94
12	80.36±2.94	83.82±2.18	85.71±1.96	81.63±2.43	83.31±2.83	85.51±2.38	93.45±1.08	90.31±0.96

x= mean; ± SD; n= 3

Table 7: Cumulative % drug release of formulated mucoadhesive matrix tablet

Time	Cumulative % drug release [x]							
(h)	M9	M10	M11	M12	M13	M14	M15	M16
0.25	6.24±0.45	2.98±0.22	5.31±0.44	4.83±1.03	5.62±0.68	4.16±0.52	3.43±0.99	2.93±0.32
0.5	9.15±0.78	6.02±1.16	8.67±1.28	9.46±1.28	10.03±1.25	8.32±0.98	7.15±1.31	5.02±0.46
1	14.81±1.31	11.78±1.86	14.56±1.73	13.78±1.75	14.63±1.09	19.92±1.72	11.93±1.42	8.95±1.28
2	21.23±2.37	18.38±2.34	19.94±1.90	16.43±2.63	20.75±2.77	22.17±1.97	20.42±1.79	16.84±1.96
3	31.42±2.64	26.32±2.93	28.18±1.12	23.10±2.69	29.53±2.74	30.21±2.83	29.47±2.33	25.53±2.30
4	38.71±2.85	31.63±2.05	39.36±2.64	34.52±3.31	35.68±2.52	34.40±2.41	34.97±2.62	31.01±2.46
6	50.92±3.81	43.78±3.25	54.61±3.30	52.34±3.74	53.61±3.74	47.36±3.13	52.88±2.80	43.83±2.63
8	63.47±3.06	55.83±3.81	71.85±3.15	68.96±3.78	63.43±3.69	57.43±4.67	64.63±2.73	57.87±3.49
10	79.64±2.17	73.29±3.27	86.27±2.79	80.25±3.82	67.58±3.83	72.08±3.81	75.46±3.82	71.30±3.25
12	90.57±1.83	80.25±3.65	92.88±1.48	89.94±2.15	80.32±2.84	88.36±2.70	89.03±2.15	83.98±3.59

x= mean; ± SD; n= 3

Accelerated stability study

Propafenone HCl optimized formulation M11 was found to be stable during accelerated stability studies for drug content 99.46, 99.36, 99.32 and 99.27% at 0, 1, 2 and 3 months respectively at 40^0c/75% RH. *In vitro* drug release studied for 12 h was found to be 92.88, 92.28, 91.98 and 91.82% at 0, 1, 2 and 3 months respectively at 40^0c/75% RH. It also observed that, there was no significant change in mucoadhesive strength. Results obtained were shown in Table 8. Finally it was observed that there was no change in physiochemical and physical properties as well as in drug release profile even after storage at 45 °C and 75 % for three months. It may be inferred that there was no degradation of physical properties and change in the matrix system of the formulation.

Table 8: Results of Accelerated stability study of optimized formulations

	Optimized formulation (M11)		
	Drug content(%)	**% drug release**	**Detachment force (dyne/cm^2)**
Initial	99.46	92.88	1510.85
One month			
Ambient	99.45	92.79	1504.47
40^0c / 75%RH	99.36	92.28	1501.31
Two month			
Ambient	99.35	92.47	1490.89
40^0c / 75%RH	99.32	91.98	1485.93
Three month			
Ambient	99.29	92.38	1488.62
40^0c / 75%RH	99.27	91.82	1482.64

CONCLUSION

The present study concludes that the mucoadhesive matrix tablet of Propafenone HCl could be successful option for the gastroretentive drug delivery system for the treatment cardiac arrhythmias. Loading and maintenance dose was maintained with the proper selection of controlled release polymers such as, HPMC E5 and HPMC K100M. Sodium carboxy methyl cellulose exhibits excellent mucoadhesive strength. Thus, the designed formulation can be considered as one of the promising formulation techniques for preparing Propafenone HCl mucoadhesive matrix tablet for the gastroretentive drug delivery system in management of cardiac arrhythmias and other diseases.

REFERENCES

1. Narendra C, Srinath M, Ganesh B. Optimization of bilayer floating tablets containing metoprolol tartrate as a model drug for gastric retention. AAPS Pharm Sci.Tech. 2006; 7: E1-E7.

2. Karande A, Dhoke S, Yeole P. Formulation and evaluation of bilayer tablet with antihypertensive drugs having different release pattern. Indian drugs. 2005; 43(1): 44-50.
3. Amidon LG, Lobenberg R, Kim JS. Pharmacokinetics of an immediate release, a controlled release and a two pulse dosage form in dogs. Eur J Pharm Biopharm. 2005; 60: 17-23.
4. Rekhi GS, Nellore RV, Hussain AS, Tillman LG. Development of metoprolol tartrate extended release matrix tablet. J Control Release. 1998; 50: 247-256.
5. Ch'ng HS, Park H, Kelly P, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery. II. Synthesis and evaluation of some swelling, water insoluble polymers. J Pharm Sci. 1985; 74(4): 399-405.
6. Longer MA, Ch'ng HS, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery. III. Oral delivery of Chlorothiazide using bioadhesive polymers. J Pharm Sci. 1985; 74(4): 406-411.
7. Park K, Robinson J. Bioadhesive polymers as platform for oral-controlled drug delivery: method to study bioadhesion. Int J Pharm. 1984; 19(1): 107-127.
8. Lachman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed. Bombay; Varghese publishing house; 1987;294-342.
9. Fiese EF, Hagen TA. Preformulation In: The Theory and Practice of Industrial Pharmacy. Lachman L, Lieberman HA, Kanig JL. 3rd Ed. Varghese Publishing House. 1990; p. 183-84
10. Wells JI, Aulton ME. Pharmaceutical Preformulation, In: Aulton's Pharmaceutics, Churchill Livingstone Elsevier., 3rd Ed, p. 355-56.
11. Hausner H. H. Friction condition in a mass of metal powders. Int J Powder Metall. 1967; 3: 713.
12. Khan FN, Dehghan MH. Enhanced bioavailability of atorvastatin calcium from stabilized gastric resident formulation. AAPS Pharm Sci Tech. 2011; 12(4): 1077-1086.
13. Veerareddy PR, Nama M, Gonugunta CR. Formulation and evaluation of gastroretentive dosage forms of clarithromycin. AAPS Pharm Sci Tech. 2008; 9(1): 231-237.
14. Vaghani SS, Patel SG, Jivani RR, Jivani NP, Patel MM, Borda R. Design and optimization of a stomach-specific drug delivery system of repaglinide: Application of simplex lattice design. Pharm Dev Tech. 2012; 17(1): 55-65.
15. Senyigit ZA, Vetter A, Guneri T, Schnurch AB. A comprehensive in vitro and in vivo evaluation of thiolated matrix tablets as a gastroretentive delivery system. Drug Del.

2011; 18(6): 405-414.

16. Gowda DV, Ram AS, Gupta VK, Ahmad A. Formulation and evaluation of Propafenone hydrochloride matrix pellets for controlled release. Inventi Impact: NDDS. 2012; 2: 124-129.
17. Chavanpatil M, Jain P, Chaudhari S, Shear R, Vavia P. Development of sustained release gastroretentive drug delivery system for ofloxacin: *In vitro* and *in vivo* evaluation. Int J Pharm. 2005; 304: 178-184.
18. Kanvide SA, Kulkarni MS. Stability of oral solid dosage form-A global perspective. Phama Times. 2005; 37: 9-16.
19. Banker GS, Rhodes CT. Modern Pharmaceutics. Marcel Dekker; 1979; p. 203.
20. Schellekens RCA, Stuurman FE, Van der Weert FHJ, Kosterink JGW, Frijlink HW. A novel dissolution method relevant to intestinal behavior and its application in the evaluation of modified release mesalazine products. Eur J Pharm Sci. 2007; 30:15-20.