AJPRHC

Research Article

DEVELOPMENT AND *IN VITRO* EVALUATION OF GASTRORETENTIVE HIGH DENSITY TABLET OF PROPAFENONE HCL

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This paper is available online at www.jprhc.in

ABSTRACT

A novel Propafenone HCl gastric-resident tablet was developed. A controlled release matrix tablet was prepared by using various controlled release polymers i.e. HPMC E5 and HPMC K100M. Pharmaceutical zinc oxide powder was used as a density-increasing agent. The formulations were evaluated for pharmacopoeial quality control tests and all the physical parameters evaluated were within the acceptable limits. Prepared high density tablet showed density up to 1.63 gm/cm^3 which is higher than the gastric fluid. Also it shows good dimensional stability till the 12 h. In vitro release study shows the good drug release up to the 12 h. Stability studies were carried out on the optimized formulation for period of 3 months at 40^{0}c / 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. Zinc oxide increases the system density, making the system resident in stomach to prolong the drug delivery time in absorption zone.

Keywords: Propafenone HCl, high density tablet, dimensional stability, zinc oxide

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 GRT of a dosage form. Physiological features of the upper gastrointestinal tract shows significant challenge to develop such systems. However, *in vivo* studies of some systems shown promising results. High-density systems are proposed to lodge in the rugae of the stomach withstand the peristaltic activities. Dosage form with a density of 1.3 g/ml or higher are likely to be retained in the lower part of the stomach.

The formulation of heavy pellets is based on the hypothesis that the pellets might be located in the lower part of the antrum because of their higher density shown in Figure 1. Clarke et al. reported that the critical density to delay gastric residence of pellets ranges between 2.4 to 2.8 g/ml. Though, in vivo data do not proved the efficiency of this system, as the most important determining factor of gastric emptying is the state of stomach when it is administered.

Devreux et al reported that the pellets have density of at least 1.5 g/ml have considerably higher GRT both in fed and fasted state.

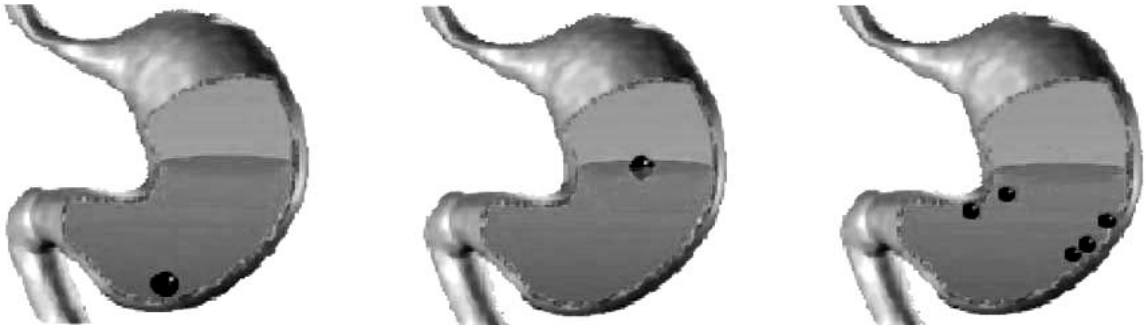

Figure 1: (a) High density system. (b) Low density system.
(c) Mucoadhesive systems.

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, Zinc oxide, Magnesium stearate, Lactose and isopropyl alcohol were purchased from Loba Chemie Pvt. Ltd. Mumbai. PVP K-30 was purchased from Signet Chemical Corporation, Mumbai.

Methods

Preparation of high density Propafenone HCl tablet

The granules were prepared by wet granulation method as per formulae given in the above Table (twenty tablets for each formulation). The drug Propafenone Hydrochloride, hydrophilic polymer (HPMC K100M, HPMC E5), Zinc oxide, 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 high density Tablet (quantities in mg)

Formulation code	H1	H2	H3	H4	H5	H6	H7	H8
Propafenone Hydrochloride	300	300	300	300	300	300	300	300
HPMC E5	100	150	200	-	-	-	150	100
HPMC K100M	-	-	-	100	150	200	100	150
Zinc oxide	35	35	35	35	35	35	35	35
PVP K30	20	20	20	20	20	20	20	20
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	235	185	135	235	185	135	85	85

Table 2: Composition of gastroretentive high density Tablet (quantities in mg)

Formulation code	H9	H10	H11	H12	H13	H14	H15	H16
Propafenone Hydrochloride	300	300	300	300	300	300	300	300
HPMC E5	100	100	150	150	100	150	100	150
HPMC K100M	200	100	150	150	100	100	150	150
Zinc oxide	35	35	35	40	50	50	50	50
PVP K30	20	20	20	20	20	20	20	20
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	35	135	35	30	120	70	70	20

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:

$$\text{Bulk density (g/mL)} = \frac{\text{Weight of sample in grams}}{\text{Volume occupied by the sample}}$$

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:

$$\text{Tapped density (g/mL)} = \frac{\text{Weight of sample in grams}}{}$$

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]

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Carr's index or % compressibility

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

$$\text{Carr's index} = \frac{\text{Tapped density - Bulk density}}{} \times 100$$

Evaluation of high density 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.

$$F = \frac{W1 - W2}{W1} \times 100$$

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]

Tablet density

The density (D) of tablets was calculated from tablet thickness, diameter, and weight by using the following equation:

$$D = \frac{w}{(m/2)^2 \times \pi \times h}$$

Here, m is the diameter of a tablet, π is the circular constant, h is the thickness of a tablet, and w is the weight of a tablet.[14] All measurements were performed in three replicates. The averages and standard deviations were calculated and reported.

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 301 nm.[15]

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 high density tablet was observed visually.[16]

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 301 nm.[16]

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.[17-19]

RESULT AND DISCUSSION

Granules evaluation

The physical characteristics of the granules (H1 to H16) 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 0.963-1.060 gm/ml. The tapped densities were ranged from 1.104-1.220 gm/ml. The carr's compressibility index were ranged from 10.77-20.61%. The housners rations were found to be in the limit 1.12-1.25. The angles of repose of all formulation were found to be between the limit 22.19°-26.61°. 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 code	Bulk density ^{x} gm/ml	Tapped density ^{x} gm/ml	Carr's index ^{x} (%)	Hausner's ratio ^{x}	Angle of repose ^{x} (°)
H1	0.970±0.05	1.131±0.02	14.23±0.19	1.17±0.06	23.68±0.99
H2	0.966±0.07	1.124±0.01	14.05±0.11	1.16±0.03	23.30±2.04
H3	0.971±0.02	1.115±0.04	12.91±0.13	1.14±0.05	25.15±2.65
H4	1.060±0.01	1.220±0.03	13.11±0.10	1.15±0.03	24.68±2.17
H5	0.976±0.05	1.185±0.04	17.63±0.21	1.23±0.02	26.39±1.49
H6	0.963±0.06	1.185±0.04	18.73±0.26	1.24±0.04	23.16±1.38
H7	0.985±0.07	1.104±0.02	10.77±0.15	1.12±0.04	22.19±2.76
H8	0.981±0.03	1.111±0.01	11.70±0.09	1.13±0.03	26.61±2.09
H9	0.909±0.02	1.145±0.06	20.61±0.18	1.25±0.01	25.43±2.44
H10	0.981±0.06	1.117±0.03	12.17±0.08	1.13±0.07	22.61±2.27
H11	0.985±0.03	1.146±0.04	14.04±0.09	1.16±0.03	23.68±1.97
H12	0.978±0.06	1.115±0.02	12.28±0.09	1.14±0.07	25.72±1.44
H13	0.988±0.01	1.136±0.02	13.02±0.06	1.15±0.02	24.14±2.89
H14	0.969±0.04	1.116±0.05	13.17±0.10	1.15±0.08	23.71±2.68
H15	0.973±0.06	1.113±0.01	12.57±0.11	1.14±0.06	24.05±2.63
H16	0.983±0.02	1.121±0.03	12.31±0.15	1.14±0.09	23.18±2.79

x= mean; ± SD; n= 3

Tablet thickness and diameter

The thickness of the tablets range from 3.24-3.98 mm respectively. The diameter of the tablet in the range of 12.95-13.01mm.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 were within the range and optimum for controlled release, and ranging from 7.4-8.2 Kg/cm^2 for all H1-H16 formulations. The friability of all formulations was ranging from 0.084-0.219 % 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 high density tablet

Formulation	Thickness ^{x} mm	Diameter ^{x} mm	Hardness ^{x} Kg/cm^2	Friability ^{x} % w/w	Weight variation ^{x} mg
H1	3.98±0.02	13.00±0.03	7.6±0.11	0.120±0.02	699.04±2.14
H2	3.86±0.03	13.01±0.04	7.4±0.09	0.138±0.05	705.41±1.91
H3	3.75±0.02	12.99±0.03	7.7±0.08	0.098±0.01	703.43±1.66
H4	3.81±0.01	12.98±0.02	7.5±0.15	0.219±0.06	695.78±1.43
H5	3.61±0.03	12.98±0.03	7.9±0.10	0.154±0.03	703.65±2.74
H6	3.58±0.03	13.01±0.01	7.5±0.09	0.135±0.02	698.09±2.37
H7	3.67±0.01	13.01±0.02	8.0±0.03	0.103±0.03	695.56±2.81
H8	3.60±0.03	12.98±0.02	7.8±0.16	0.189±0.07	697.90±2.90
H9	3.61±0.02	12.95±0.03	7.4±0.06	0.141±0.10	704.58±3.01
H10	3.74±0.02	13.01±0.03	7.9±0.10	0.084±0.09	706.32±1.16
H11	3.53±0.03	12.98±0.03	7.8±0.13	0.093±0.13	707.13±1.08
H12	3.39±0.01	12.99±0.01	7.9±0.05	0.128±0.12	698.61±1.78
H13	3.32±0.01	12.98±0.02	8.1±0.12	0.138±0.09	706.13±2.35
H14	3.29±0.01	12.98±0.02	8.2±0.09	0.098±0.11	701.18±2.38
H15	3.24±0.03	12.99±0.02	8.0±0.18	0.104±0.14	698.88±3.82
H16	3.24±0.02	12.98±0.03	7.9±0.06	0.219±0.12	696.93±1.68

x= mean; ± SD; n= 3

Tablet density

The tablet densities of all the formulation were in the range of 1.32-1.63 gm/cm^3, which was the greater than the gastric fluid and optimum for the gastroretentive high density system.

Drug content

The assays of all formulation from H1-H16 were found to be between 99.19-99.71 %. The result shows that all formulation containing drug were within the limit (99-101 %).

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 concentrations of polymers also act 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 (+++) excellent, (++) very good, (+) good, (-) lack of integrity, along with picture representation in Table 5 and Figure 2.

The formulation H2-H16 shows excellent dimensional stability, except formulation H1 shows the good dimensional stability.

(+++) **(++)**

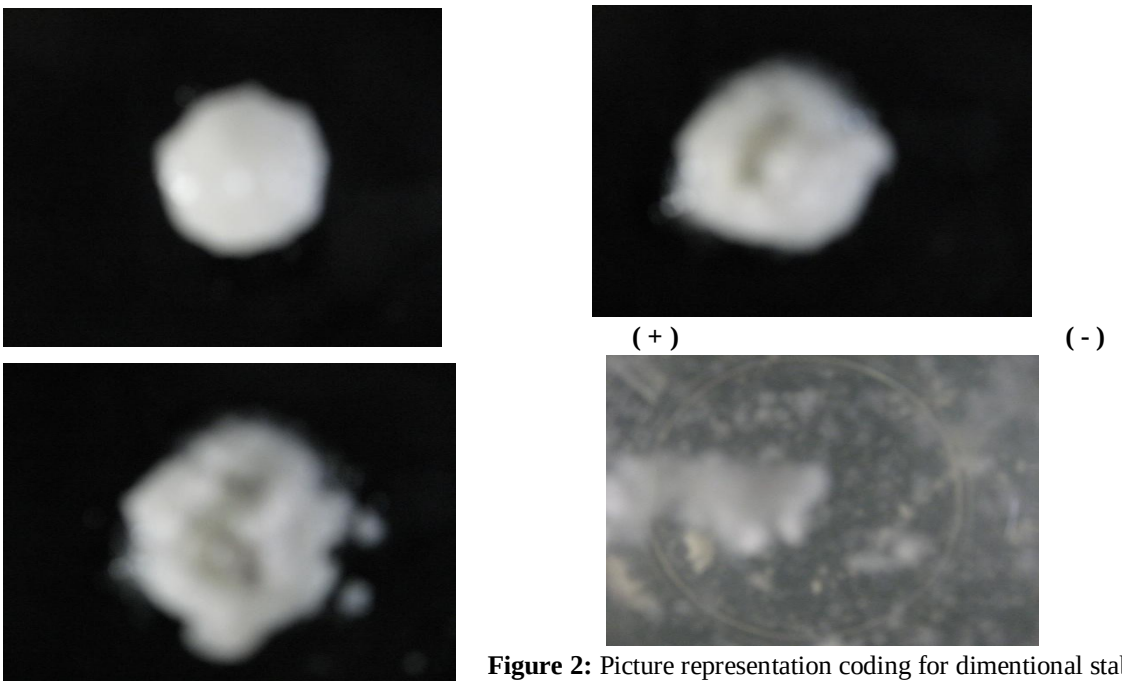

Figure 2: Picture representation coding for dimentional stability

Table 5: Tablet density and drug content of Propafenone HCl high density tablet

Formulation	Tablet density [x] (gm/cm^3)	Drug content [x] (%)	Dimensional stability
H1	1.32±0.02	99.31±0.21	++
H2	1.37±0.01	99.39±0.15	+++
H3	1.41±0.03	99.49±0.09	+++
H4	1.38±0.02	99.20±0.18	+++
H5	1.47±0.02	99.27±0.12	+++
H6	1.46±0.03	99.59±0.19	+++
H7	1.42±0.01	99.24±0.05	+++
H8	1.46±0.01	99.56±0.11	+++
H9	1.48±0.01	99.39±0.14	+++
H10	1.42±0.02	99.19±0.06	+++
H11	1.51±0.04	99.52±0.09	+++
H12	1.55±0.02	99.37±0.13	+++
H13	1.60±0.03	99.43±0.11	+++
H14	1.61±0.01	99.62±0.06	+++
H15	1.63±0.02	99.71±0.28	+++
H16	1.63±0.02	99.25±0.07	+++

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 H1-H6 releases drug in 6-8 h due to single use of polymer. In the later batches H7-H16 use of combination of polymers in that case it exhibits good drug release up to the 12 h. Formulation H15 shows maximum drug release 94.10% with controlled manner showed in Table 6 and 7.

Table 6: Cumulative % drug release of formulated high density tablet

Time (h)	Cumulative % drug release [x]							
	H1	**H2**	**H3**	**H4**	**H5**	**H6**	**H7**	**H8**
0.25	7.31± 0.58	6.84±0.61	6.61±0.09	6.53±0.85	5.38±1.01	5.51±0.91	5.05±0.69	3.43±0.44
0.5	12.38±0.91	11.74±1.73	8.58±0.98	9.27±1.03	9.40±1.68	7.73±1.13	8.43±1.26	7.14±0.96
1	21.85±1.68	17.58±2.37	16.66±1.55	15.72±2.16	14.43±1.97	10.41±1.65	9.71±1.75	11.53±1.51
2	37.73±2.43	32.67±3.55	28.04±2.31	29.90±2.73	23.74±2.13	19.73±2.38	17.49±2.01	19.47±2.84
3	49.92±3.58	42.92±3.06	38.16±3.76	41.58±2.94	31.48±2.47	27.51±3.29	30.78±2.90	25.73±2.93
4	64.17±3.96	53.84±4.17	46.43±3.43	49.38±3.25	41.79±2.61	38.33±2.77	43.82±3.83	35.07±3.07
6	89.62±3.68	76.37±3.89	61.79±3.13	64.66±4.78	56.28±2.84	52.71±3.08	60.75±3.85	52.89±3.81
8	-	84.76±3.52	88.65±3.79	89.39±4.47	69.31±3.98	61.02±3.51	73.44±3.89	69.30±3.47
10	-	-	-	-	90.33±2.83	84.88±4.72	81.86±2.15	83.44±3.26
12	-	-	-	-	-	-	91.85±1.42	92.41±1.04

x= mean; ± SD; n= 3

Table 7: Cumulative % drug release of formulated high density tablet

Time (h)	Cumulative % drug release [x]							
	H9	**H10**	**H11**	**H12**	**H13**	**H14**	**H15**	**H16**
0.25	3.34±0.25	3.98±0.37	4.01±0.41	6.83±0.09	8.78±1.19	7.16±1.21	7.03±0.95	4.53±0.08
0.5	5.15±0.88	7.49±0.84	8.52±0.62	9.41±1.18	13.73±1.82	10.52±1.38	9.19±1.38	7.24±0.83
1	9.43±1.17	12.78±1.36	13.81±1.80	16.98±2.74	23.79±2.35	19.44±1.43	15.42±1.41	13.75±1.40
2	16.73±1.97	19.44±2.49	19.44±1.66	26.43±2.17	37.11±2.74	28.87±2.58	25.71±2.58	22.14±1.58
3	23.43±2.43	27.67±3.85	26.48±2.38	38.18±3.03	48.54±2.96	33.74±3.61	33.86±2.77	29.65±1.53
4	31.69±2.83	34.44±3.83	32.65±2.61	49.55±3.73	55.68±3.73	46.61±4.79	42.27±3.96	39.81±3.45
6	43.90±2.47	53.78±3.51	51.74±3.05	62.14±3.65	73.62±3.25	67.35±4.48	58.38±3.86	53.48±3.82
8	53.17±3.33	76.64±4.62	67.95±3.69	70.46±3.31	83.46±3.38	78.35±4.81	76.84±3.73	70.34±3.91
10	69.64±3.85	93.98±3.85	82.63±3.27	81.28±3.09	92.78±2.41	86.25±3.64	85.49±2.07	81.37±3.27
12	85.43±2.63	-	89.68±0.14	85.21±1.67	-	90.36±2.06	94.10±1.16	90.18±2.77

x= mean; ± SD; n= 3

Accelerated stability study

Propafenone HCl optimized formulation was found to be stable during accelerated stability studies for drug content 99.71, 99.61, 99.48 and 99.36% 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 94.10, 93.68, 91.73 and 91.08% at 0, 1, 2 and 3 months respectively at 40^0c / 75%RH. Tablet density of optimized formulation was found to be 1.63, 1.63, 1.62 and 1.62 gm/cm^3 at 0, 1, 2 and 3 months respectively at 40^0c / 75%RH. Results obtained are 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		
	Drug content (%)	**% drug release**	**Tablet density (gm/cm^3)**
Initial	99.71	94.10	1.63
One month			
Ambient	99.65	93.73	1.63
40^0c / 75%RH	99.61	93.68	1.63
Two month			
Ambient	99.56	92.18	1.63
40^0c / 75%RH	99.48	91.73	1.62
Three month			
Ambient	99.49	91.58	1.63
40^0c / 75%RH	99.36	91.08	1.62

CONCLUSION

The present study concludes that the Propafenone HCl high density tablet pH could be successful option for the gastroretentive drug delivery system for cardiac arrhythmias. Loading and maintenance dose was maintained with the proper selection of controlled release polymers such as, HPMC E5 and HPMC K100M. Zinc oxide highly increases density of the tablet. Thus, the designed formulation can be considered as one of the promising formulation techniques for preparing Propafenone HCl high density tablet for the gastroretentive drug delivery system in management of cardiac arrhythmias and other diseases.

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