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DEVELOPMENT AND CHARACTERIZATION OF FLOATING TABLETS OF ACEBUTOLOL HYDROCHLORIDE

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ABSTRACT

The goal of this investigation was to compare the efficiency of various polymers, natural and synthetic origin on *In vitro* and *In vivo* buoyancy and *In vitro* drug release from the floating tablets of Acebutolol hydrochloride, an antihypertensive drug by direct compression method. The prepared tablets were evaluated for various pre-compression and post-compression parameters like thickness, hardness, weight variation, friability, *In vitro* buoyancy, *In vitro* dissolution studies and release mechanism studies. From the results it was revealed that formulation containing karaya gum, A7 was selected as an optimized formulation with respect to high buoyancy time and sustained drug release supported by *In vivo* studies. The optimized formulation followed zero order rate kinetics with non-Fickian diffusion mechanism. The optimized formulation was evaluated with FTIR studies and observed no interaction between the drug and the polymers.

KEYWORDS

Gastroretentive floating tablets, Hydroxyl propyl methyl cellulose and Karaya gum.

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INTRODUCTION

Oral route of administration though it gains popularity as the most frequent route of administration the major disadvantage is short gastric emptying time makes less drug release in the absorption window of the drug leads to reduction in bioavailability of the drug. This can be overcome by formulating the drug in gastro-retentive drug delivery system which increases the gastric residence time and eventually bioavailability of the

drug[1]. Gastro retentive drug delivery system (GRDDS) improves bioavailability and therapeutic efficacy of the drug thereby increases patient compliance by reduction of dose. Gastro retentive drug delivery system have the ability to prolong the duration and sustained release of drugs from formulations which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine[2]. The main objective for the development of gastro retentive system was to maintain a constant level of drug in the blood plasma. These drug delivery systems posses a significant benefit that they will be retained in the stomach and help in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GIT[3].

Acebutolol hydrochloride is an angiotensin II receptor antagonist used in the management of hypertension. Acebutolol is well absorbed from the gastrointestinal tract. The bioavailability of acebutolol is only about 40% due to extensive first-pass metabolism in the liver. The terminal elimination half life is about 3 to 4 hours[4]. The aim of the present study is to develop floating tablets of Acebutolol hydrochloride with effervescent approach and compare the effectiveness of floating behavior of natural and synthetic polymers by direct compression method.

MATERIAL AND METHODS

Acebutolol hydrochloride was provided by Hetero Pharmaceutical, Hyderabad. HPMC (E15 and K15), Carbopol (934P and 940P), Ethyl cellulose, Guar gum, Xanthan gum, Karaya gum, Chitosan, Sodium alginate, sodium bicarbonate, citric acid, talc and magnesium stearate were obtained as gift samples from Granules India Pvt Ltd, Loba chemical Mumbai, Yarrow chemicals Ltd, Ranbaxy Research Laboratories, Merck Ltd Mumbai, Scientific Lab. All other reagents and chemicals were of analytical grade.

Development of gastroretentive floating tablets (GRFT) of Acebutolol hydrochloride[5]

Floating tablets of Acebutolol hydrochloride were prepared by direct compression method according to the formula shown below from Table No.1. Acebutolol hydrochloride was mixed with remaining excipients which were already passed through sieve No.60 seperately in a geometrical order except talc and magnesium stearate. Finally, talc and magnesium stearate were added and mixed well which was compressed into tablets using flat round punch in a 8-station tablet compression machine.

Determination of λ max for Acebutolol hydrochloride in Simulated Gastric Fluid pH 1.2 (SGF)

About 100 mg of Acebutolol hydrochloride was accurately weighed into 100 ml volumetric flask and dissolved in small amount of simulated gastric fluid pH 1.2 which was then made upto 100 ml using the same. From this solution 20 ml was pipetted out and diluted to 100 ml in 100 ml volumetric flask using simulated gastric fluid pH 1.2. The above solution was scanned in the range of 200-400nm using Shimadzu ultra violet (UV) spectrophotometer with simulated gastric fluid pH 1.2 as blank solution. From the spectrum obtained, the λmax for Acebutolol hydrochloride in simulated gastric fluid pH 1.2 was confirmed to be 232 nm.

Calibration curve for Acebutolol hydrochloride in Simulated Gastric Fluid pH 1.2 (SGF)

About 100 mg of Acebutolol hydrochloride was weighed accurately and taken in a 100 ml volumetric flask. Then it was dissolved in small amount of simulated gastric fluid pH 1.2 and the volume was made upto 100 ml with the same. Solutions ranging from 1 to 10µg/ml were prepared using simulated gastric fluid pH 1.2 separately and their absorbances were measured at λmax of 232 nm using UV spectrophotometer with simulated gastric fluid pH 1.2 as blank solution.

Drug excipient compatibility studies by Fourier Transform Infra Red (FTIR) spectroscopy[5]

The spectrums for Acebutolol hydrochloride alone and optimized formulation were recorded by FTIR

spectroscopy (Perkin elmer) using potassium bromide disc method in the scanning range of 450 to 4000 cm^{-1}.

Evaluation of pre-compression parameters[6]

The powder blend of each formulation was subjected to evaluation of pre-compression parameters like bulk density, tapped density, carr's index and hausner's ratio. Bulk density of the powder blend was determined by introducing weighed amount of blend into 100 ml measuring cylinder without compacting which was carefully leveled and unsettled bulk volume, Vo was recorded. The bulk density was calculated using the formula, ρ_b = M / Vo where ρ_b , M and Vo were bulk density, weight of sample and bulk volume of powder, respectively. The above blend was tapped for 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement is less than 2 % and then tapped volume, V_f was measured, to the nearest graduated unit. The tapped density was calculated, in gm/ml, using the formula ρ_{tap} = M / V_f where ρ_{tap}, M and V_f were tapped density, weight of sample and tapped volume of powder respectively. Carr's index and hausner's ratio were calculated from the formulas, Carr's Index = 100(ρ_{tap} - ρ_b) / ρ_{tap}, and Hausner's Ratio = ρ_{tap} / ρ_b, where ρ_b and ρ_{tap} are bulk density and tapped density, respectively. Various pre-compression parameters of powder blend are tabulated in Table No.2.

Evaluation of post-compression parameters

The prepared tablets from each formulation were evaluated for various post-compression parameters like general appearance, thickness, weight variation, hardness, friability, *In vitro* buoyancy time, uniformity of drug content and *in vitro* release study. All the tablets were evaluated for its elegance[7]. Thickness of randomly selected tablets from each formulation was measured with vernier caliper[7]. Hardness of six tablets was measured using the Monsanto hardness tester[6]. The friability of a sample weight equal to 6.5 grams was dusted and placed in a Roche friabilator and operated for 100 revolutions which was then re-dusted and weighed. Percentage loss was calculated using the formula, (initial weight-final weight/initial weight) x 100. The percentage loss should be within 0.5 to 1%w/w[8]. Weight variation test was conducted with randomly selected twenty tablets from each formulation using Shimadzu electronic balance. The individual weight of each tablet was compared with the average weight and percentage deviation was calculated[9]. *In vitro* buoyancy studies was carried out by placing randomly selected tablet from each formulation in beaker containing 100 ml SGF pH 1.2 as a testing medium maintained at 37^0C. The time period for the tablet to come to the surface and float was calculate as floating lag time (FLT). The duration of time the tablet constantly remained on the surface of medium was determined as the total floating time (TFT) (including floating lag time)[10]. The results for thickness, hardness, friability, weight variation, floating lag time and total floating time are shown in Table No.3.

Uniformity of drug content was performed for each formulation. Twenty tablets from each formulation were individually weighed and pulverized to a fine powder and amount of powder equivalent to average weight was dissolved in 100 ml of SGF pH 1.2. The solution was filtered through 0.45µ membrane filter, diluted suitably and the absorbance of resulted solution was measured spectrophotometrically at 232 nm for Acebutolol hydrochloride using SGF pH 1.2 as blank. The drug content was determined from standard calibration curve[10]. The results for drug content are shown in Table No.3.

In vitro dissolution studies of the floating tablets of Acebutolol hydrochloride were performed in USP Type-II dissolution apparatus (Lab India Disso 2000) employing a paddle stirrer revolved at 50 rpm using 900 ml of SGF pH 1.2 at 37°C ± 0.5°C as dissolution medium for 6 tablets from each formulation. About 10 ml of sample was withdrawn for 10 hours at each time interval and replaced immediately with equal volume of fresh medium in apparatus. The samples collected were filtered and their absorbances were measured at 232 nm for Acebutolol hydrochloride using SGF pH 1.2 as blank in UV spectrophotometer[10]. The results for *In*

vitro dissolution studies for all formulations are shown in Table No.2 and Figure No.1.

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. To examine the mechanism of drug release from the tablet formulations, *In vitro* drug release data was determined according to zero order, first order, Higuchi square root, Korsmeyer-Peppas model. The criteria for selecting the most appropriate model was chosen on the basis of goodness of fit test.

Zero order equation: % drug released = kt where k is constant and t is time

First order equation: Log % drug released = kt/2.303 where k is constant and t is time

Korsmeyer - Peppas equation: $M_t / M_\infty = kt^n$ where M_t / M_∞ represents the fraction of drug release at time t, k is the release rate constant and n is the diffusion coefficient. or Log drug released = log k + n log t where n is release exponent Higuchi equation: % drug released = $kt^{0.5}$

The respective order of drug release from matrix tablet formulations was given by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi or erosion equation. The 'n' value is obtained as a slope for different batches of matrix tablets by plotting log percent drug dissolved against log time. If the value of n = 0.45 indicates Fickian (case I) release; >0.45 but <0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II transport. Case II is with refererence to the erosion of the polymeric chain and non-Fickian diffusion refers to a combination of both diffusion and erosion mechanism from the controlled drug release tablets[10,11]. The various plots of kinetic studies for *in vitro* dissolution data for optimized formulations of floating tablet of Acebutolol hydrochloride (A7) are shown from Figure No.2 to 5.

Stability studies for optimized formulation of Acebutolol hydrochloride[12]

Optimized floating tablet of Acebutolol hydrochloride was packed in HDPE bottles and loaded at accelerated conditions like $40^{O}C \pm 2\ ^{O}C$ / 75% ± 5% RH for 3 months. Various post-compression parameters were evaluated for a period of initial stage and at the end of every one month. The results are shown in Table No.3.

***In vivo* X-ray studies for optimized formulation of Acebutolol hydrochloride**[13]

An *In vivo* X-rays study was approved by the Institutional Animal Ethical Committee (IAEC/XLVIII/05/CLBMCP/2016). The floating property of the optimized floating tablet was studied by X-ray technique. Male rabbits with weight of 1.5 kg and with age of 12 months were selected. The animal was housed individually under environmental condition (12 h light and dark cycle). The rabbit was fasted 36 h and allowed free accesses to water only. The rabbit was administrated with optimized formulation of Acebutolol hydrochloride. The tablet was administered orally by placing them in hollow polyethylene tube. The tube was inserted into the mouth of rabbit and blown using rubber bulb. X-rays were taken a time- interval of 0, 1, 2, 3, 4, 5 and 10 h. The X-ray photographs are shown in Figure No.6.

RESULTS AND DISCUSSION

In pre-formulation studies, drug -excipient compatibility were determined by comparing Fourier Transform Infra Red spectrum for pure drug with optimized formulation of floating tablet of Acebutolol hydrochloride and found that there was no appearance or disappearance of major peaks in drug concluded that there was no chemical interaction between drug and excipients.

The floating tablet of Acebutolol hydrochloride was formulated with various synthetic (HPMC (E15 and K15), Carbopol (934P and 940P) and natural polymers (Guar gum, Xanthan gum, Karaya gum, Chitosan) in same concentration (10% w/w of total tablet weight) with effervescent agent (sodium bicarbonate and citric acid), diluent (Microcrystalline cellulose), lubricant (Talc) and glidant (Magnesium stearate) and evaluated for various pre-compression and post-compression parameters. From the results of pre-compression

parameters tabulated in Table No.2, it was concluded that powder blends of all formulations exhibited excellent flow properties. From the results of post-compression parameters tabulated in Table No.3, it was revealed that all the formulations good appearance without chipping and cracking with sufficient hardness in the range of 4.76 to 5.06 kg/cm^2 and within ± 5% deviation in weight as per I.P limits. The formulation containing karaya gum (A7) floated for long time in simulated gastric fluid pH 1.2 than other formulations and sustained release of drug till 10 hours follows zero order non-fickian diffusion controlled confirmed by kinetic plots of dissolution data are shown from Figure No.2 to 5. The sustained floating of the dosage form may be due to the increased swelling and viscosity of the gel that retards the drug release from the matrix. This high degree of swelling of the polymer is due to increased uptake of water from the medium surrounding it. The optimtized formulation was subjected to stability studies showed that there was no drastic change in post-compression parameters before and after stability period.

The *In vivo* X- ray studies was performed for optimized formulation of Acebutolol hydrochloride (A7) revealed that the formulation was found intact till 10 hours in the gastric region of the rat confirms that there was no change in the floating behavior of optimized floating tablet of Acebutolol hydrochloride (A7) in both *In vitro* and *In vivo* studies.

Physical evaluation of blend was done by determining bulk density, tapped density, compressibility index and hausner ratio. From the results, the flow property of all formulation was found to be excellent.

Table No.1: Development of floating tablets of Acebutolol hydrochloride

S.No	Name of the ingredients in a tablet/ Formulation Code	A1	A2	A3	A4	A5	A6	A7	A8
1	Acebutolol hydrochloride*	443.2	443.2	443.2	443.2	443.2	443.2	443.2	443.2
2	Carbopol 934P	60	-	-	-	-	-	-	-
3	HPMC E 15	-	60	-	-	-	-	-	-
4	HPMC K15	-	-	60	-	-	-	-	-
5	Carbopol 940P	-	-	-	60	-	-	-	-
6	Guar gum	-	-	-	-	60	-	-	-
7	Xanthan gum	-	-	-	-	-	60	-	-
8	Karaya gum	-	-	-	-	-	-	60	-
9	Chitosan	-	-	-	-	-	-	-	60
10	Sodium bicarbonate	30	30	30	30	30	30	30	30
11	Citric acid	6	6	6	6	6	6	6	6
12	Microcrystalline cellulose	42.8	42.8	42.8	42.8	42.8	42.8	42.8	42.8
13	Talc	12	12	12	12	12	12	12	12
14	Magnesium stearate	6	6	6	6	6	6	6	6
15	Total	600	600	600	600	600	600	600	600

* 110.8 mg of Acebutolol hydrochloride is equivalent to 100 mg of Acebutolol

* Note: All the ingredient are mentioned in mg/tablet

Pre-compression parameters of blend

Table No.2: Pre-compression parameters of blend of Acebutolol hydrochloride

S.No	Formulation Code	Bulk Density (g/ml)	Tapped density (g/ml)	Carr's Compressibility index (%)	Hausner ratio
1	A1	0.676	0.716	5.59	1.06
2	A2	0.736	0.810	9.14	1.10
3	A3	0.720	0.791	8.97	1.10
4	A4	0.468	0.509	7.99	1.09
5	A5	0.443	0.479	7.65	1.08
6	A6	0.671	0.710	5.49	1.06
7	A7	0.714	0.789	9.50	1.11
8	A8	0.453	0.492	7.9	1.09

Post-compression parameters of floating tablets of Acebutolol hydrochloride

Table No.3: Post-compression parameters of floating tablet of Acebutolol hydrochloride

S.No	Formulation Code	Thickness (mm) (n = 6) Avg ± S.D	Hardness (kg/cm^2) (n=6) Avg ± S.D	Friability (%) (n = 20)	Weight variation (g) (n=20) Avg ± S.D	Floating lag time (FLT) (sec)	Total floating time (TFT) (min)	Drug content (mg)
1	A 1	2.97 ± 0.005	4.76 ± 0.12	0.56	0.597 ± 0.004	1	275	96.52
2	A 2	2.72 ± 0.004	4.90 ± 0.11	0.23	0.604 ± 0.003	1	365	101.54
3	A 3	3.03 ± 0.008	5.06 ± 0.21	0.16	0.602 ± 0.005	1	320	95.16
4	A 4	2.8 ± 0.004	4.86 ± 0.14	0.19	0.595 ± 0.008	1	280	98.52
5	A 5	3 ± 0	4.84 ± 0.18	0.32	0.594 ± 0.008	1	335	98.74
6	A 6	2.72 ± 0.004	4.76 ± 0.12	0.55	0.606 ± 0.004	1	400	102.97
7	A 7	2.78 ± 0.004	4.90 ± 0.11	0.51	0.598 ± 0.005	1	590	97.84
8	A 8	2.97 ± 0.005	4.84 ± 0.18	0.39	0.605 ± 0.008	1	465	91.68

Table No.4: *In vitro* dissolution studies data for floating tablets of Acebutolol hydrochloride

S.No	Time (min)	% Drug released							
		A1	A2	A3	A4	A5	A6	A7	A8
1	0	0	0	0	0	0	0	0	0
2	5	14.48	15.54	13.48	16.54	13.28	14.45	3.25	5.38
3	10	25.84	25.15	25.54	25.29	28.68	26.25	6.54	14.21
4	30	32.84	33.98	36.87	39.35	36.64	32.49	12.45	22.51
5	60	46.45	39.46	52.15	58.48	41.38	41.57	21.49	31.67
6	90	52.15	46.38	61.68	66.68	46.59	49.24	29.57	44.18
7	120	61.64	55.19	69.18	75.27	58.49	56.49	36.16	55.91
8	180	68.87	61.65	78.29	83.15	66.67	69.15	42.98	62.24
9	240	79.57	76.58	82.67	87.98	79.48	77.28	55.46	69.43
10	300	88.74	84.82	87.49	90.54	87.24	83.84	62.32	76.57
11	360		88.84	90.35		91.37	89.45	70.42	82.19
12	420		92.45				93.48	77.29	88.73
13	480							81.37	93.82
14	540							88.61	
15	570							94.42	
16	600							98.81	

Table No.5: Stability studies data for optimized floating tablet of Acebutolol hydrochloride

S.No	Parameters	Initial	After three months
1	Hardness (kg/cm^2)	4.90	5.1
2	Friability (%)	0.51	0.58
3	Floating lag time (sec)	1	1
4	Total floating time (min)	590	592
5	Drug content (mg)	97.84	97.28

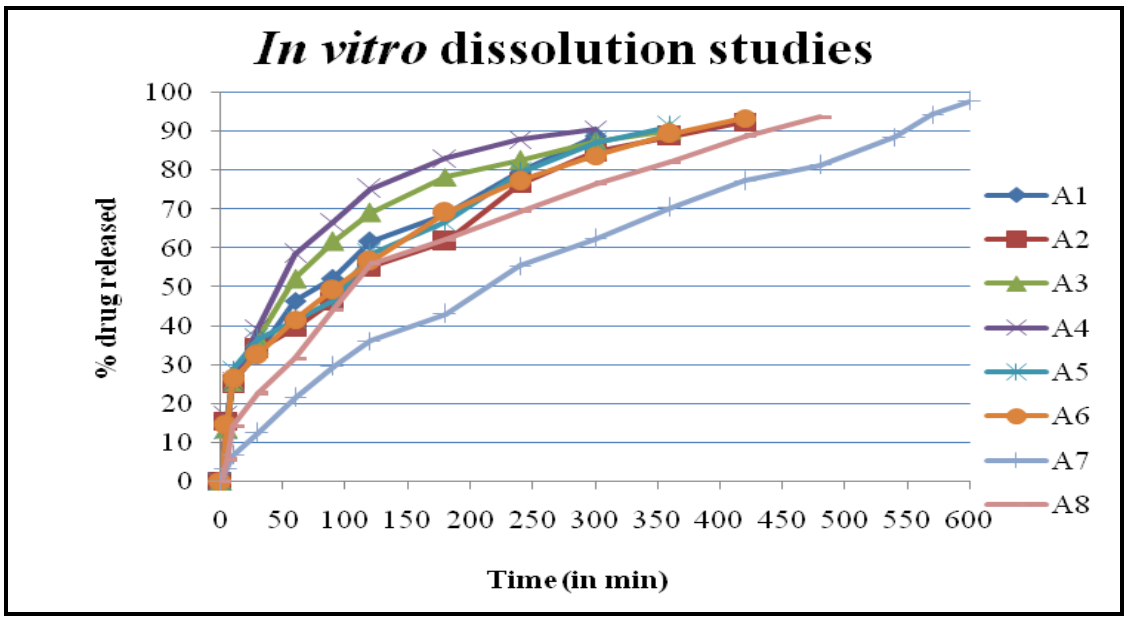

Figure No.1*: In vitro* dissolution profile for floating tablet of Acebutolol hydrochloride

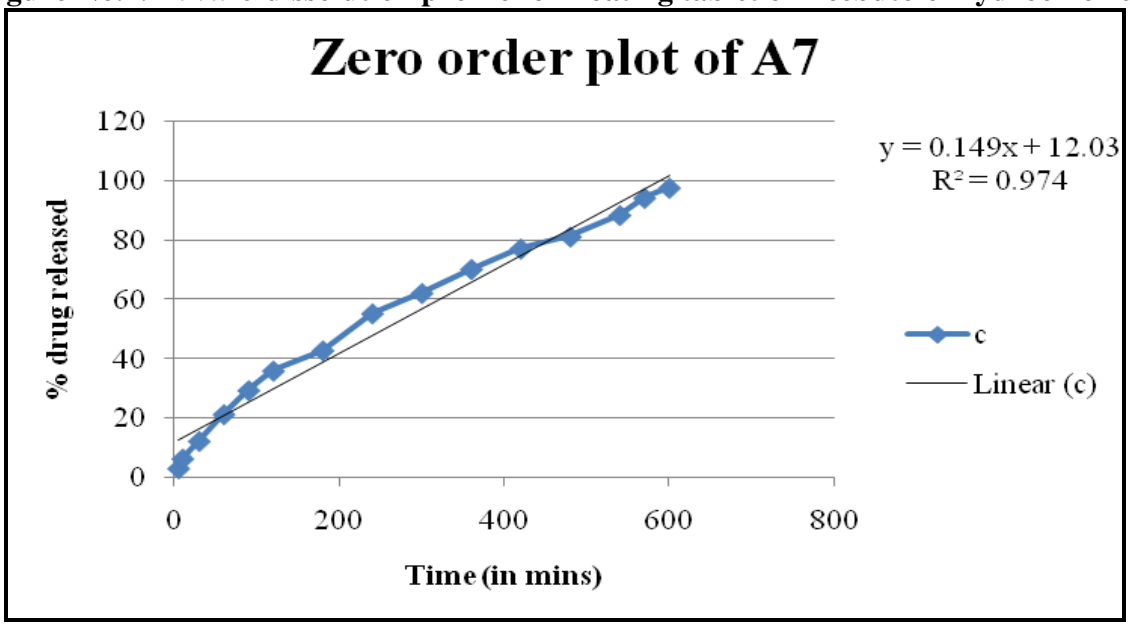

Figure No.2: Zero order plot for optimized formulation of floating tablet of Acebutolol hydrochloride (A7)

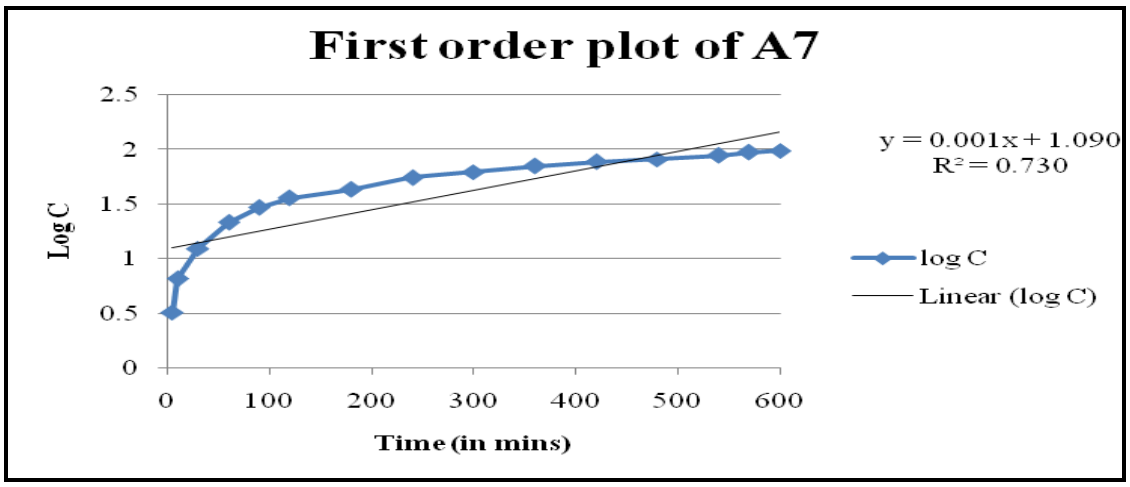

Figure No.3: First order plot for optimized formulation of floating tablet of Acebutolol hydrochloride (A7)

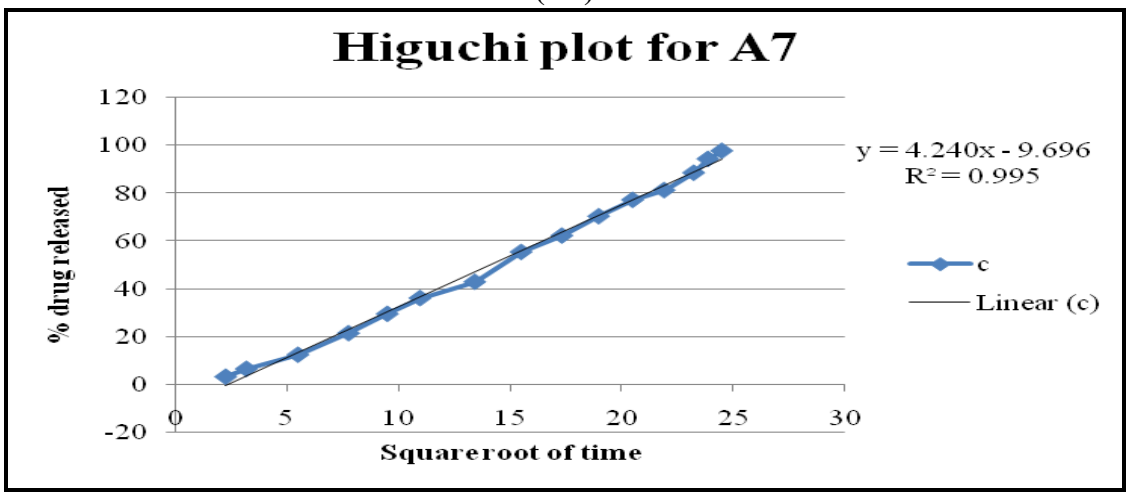

Figure No.4: Higuchi plot for optimized formulation of floating tablet of Acebutolol hydrochloride (A7)

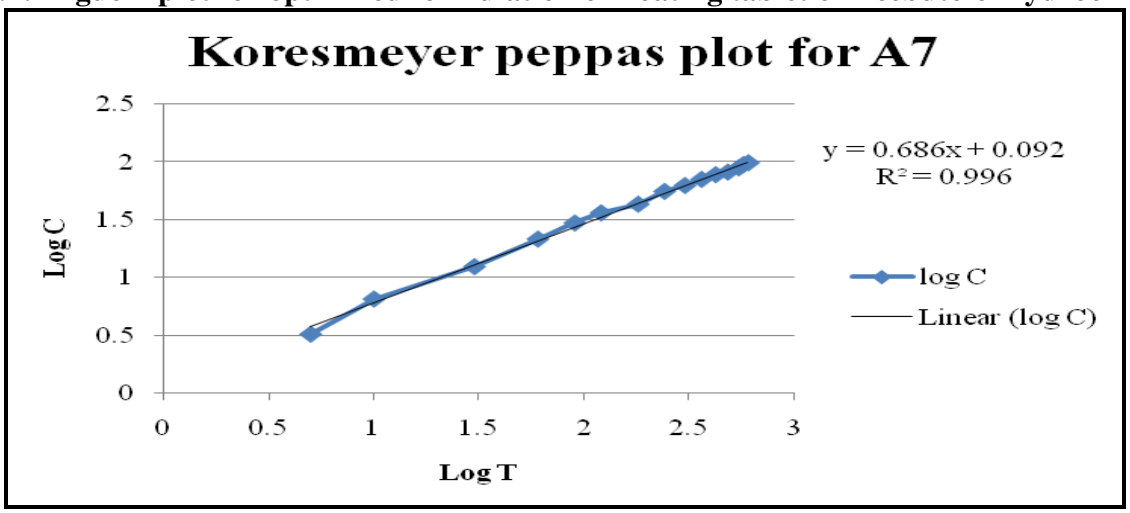

Figure No.5: Koresmeyer peppas plot for optimized formulation of floating tablet of Acebutolol hydrochloride (A7)

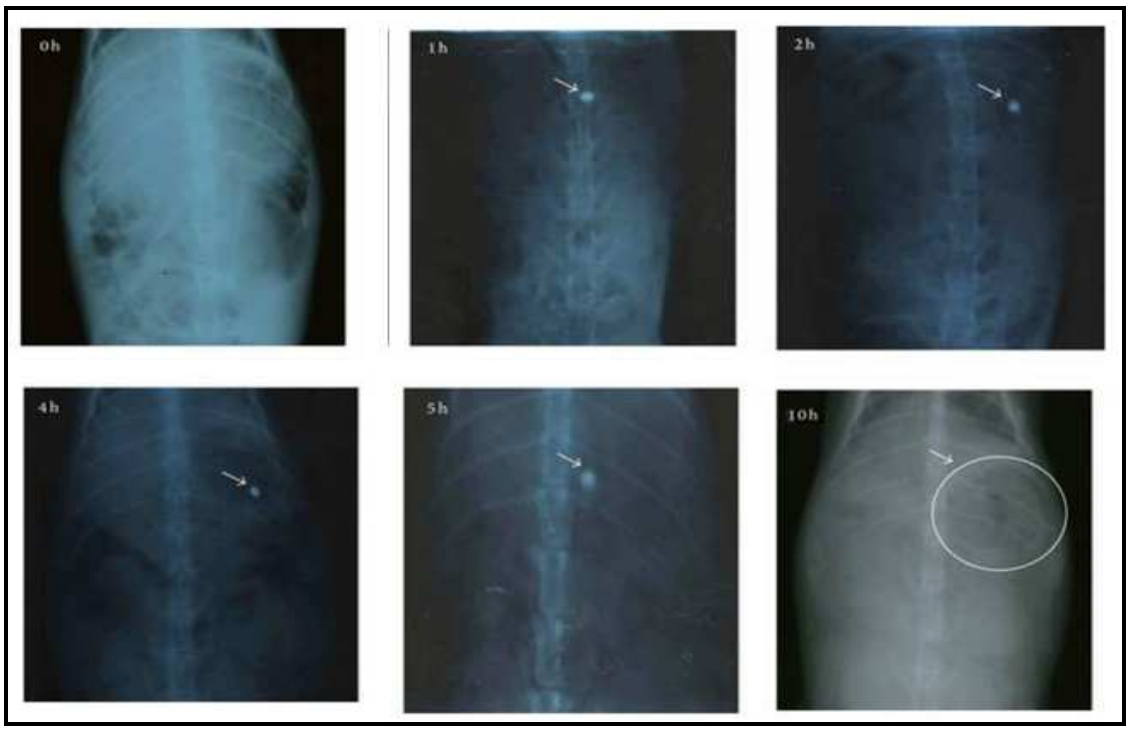

Figure No.6: *In vivo* X-ray photographs for optimized formulation of floating tablet of Acebutolol hydrochloride (A7)

CONCLUSION

The present investigation was performed to compare the effectiveness of various polymers of natural and synthetic origin in both *In vitro* and *In vivo* buoyancy effect of floating tablet of Acebutolol hydrochloride. From the results it was concluded that formulation containing karaya gum (A7) showed least floating lag time, highest total floating time with sustained drug release. Correlation co-efficient of formulation (A7) showed higher correlation with zero order plots confirms predominant drug release mechanism is controlled with non-fickian diffusion than other formulation. The sustained buoyancy effect of karaya gum in optimized formulation *in vitro* was further confirmed by remains intact *in vivo* also. The stability studies of optimized formulation showed low drastic changes in hardness, friability, *In-vitro* buoyancy and drug content during stability period. These results concluded that karaya gum was the best natural polymer for sustained drug release due to its high swelling and gelling capacity.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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