Research Article **ISSN: 2349 – 7106**

Asian Journal of Research in Chemistry and Pharmaceutical Sciences

Journal home page: www.ajrcps.com

FUNCTIONALITY COMPARISION OF NATURAL AND SYNTHETIC POLYMERS IN DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM OF ATENOLOL

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ABSTRACT

GRDDS is an approach to prolong gastric residence time and are suitable for drug having low bioavailability and therapeutic efficacy. Atenolol is a β-blocker used for the maintenance of hypertension. The biological half-life of Atenolol is 6-7 hours with poor bioavailability up to 50%. In the present study, direct compression method was employed to prepare atenolol floating tablets using different polymers and gas generating agent. Floating tablets were characterized for pre and post-compression parameters like, drug excipients interaction studies, swelling index, hardness, friability, weight variation, drug uniformity and *In vitro* drug release study. FTIR studies reveals that there was no interaction between the excipients and drug used in the formulations. Pre and Post-compression parameters of floating tablets of atenolol were in the standard limits. From the studies it was concluded that, among various formulation, F6 showed better and prolong release over a period of 24 hours. Hence this formulation shows, that FDDS will be a promising one to improve the bioavailability and therapeutic efficacy of atenolol.

KEYWORDS

Atenolol, Gastroretentive drug delivery system (GRDDS), Hydro dynamically balanced system, HPMC and Guar gum.

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INTRODUCTION

Atenolol is a selective beta blockers used in the treatment of hypertension. It works by slowing down the heart rate and reducing workload of heart, there by producing antihypertensive action. Atenolol is weakly basic drug and having oral bioavailability of about 50%[1].

Gastro retentive drug delivery systems (GRDDS) is an approach to prolong gastric residence time and are suitable for the drugs which are (i) locally active on

the stomach (antacids), (ii) having narrow absorption window in GIT, (iii) less soluble or degraded in intestinal pH, GRDDS are useful for these drugs which having low bioavailability and low therapeutic efficacy[2]. Floating systems or hydrodynamically controlled systems are low-density systems that float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time[3]. Natural or semi synthetic polymers are commonly used for the preparation of floating drug delivery system.

Hydrodynamically controlled drug delivery systems are safe, since they are non-ionic and have minimal interaction with the acidic, basic or other electrolytic system. These systems are highly suitable for most of the drugs. Generally cellulose derivatives are most widely used in the formulation of hydrodynamically controlled drug delivery systems. Hence, the release rate of drugs are controlled by formation of gel layer which results from hydration of polymer[4].

MATERIAL AND METHODS

Atenolol (gift sample) was obtained from Aurobindo Pharma, Hyderabad. HPMC K4M and HPMC K100M were obtained from Colorcon Asia Pvt. Ltd., Goa. Guar gum, microcrystalline cellulose, talc, magnesium stearate, citric acid, sodium bicarbonate and aerosil were obtained from S.D. Fine Chem. Ltd., Mumbai, India. All other chemicals used were of analytical grade.

Direct compression method was used to prepare floating tablets of Atenolol using different grade of HPMC (K4M, K100M) and guar gum as a rate controlling polymer along with sodium bicarbonate as gas generating agents. The composition of various formulations of Atenolol floating tablets shown below in Table No.1. All the ingredients were weighed accurately, the drug was mixed with the rate retarding polymers and along with other excipients in an ascending order of their weight. The above mixture powder was blended for 20 mins to have uniform distribution of drug in formulations, continued by lubrication process by addition of magnesium stearate[5]. The blended powder was then compressed into 250 mg tablets on a single punch 8 station rotary tablet compression machine (Riddhi Pharma) with 8 mm, round shape flat punches.

FTIR Spectroscopy

FTIR spectroscopy is a technique mostly used in formulation, to determine the functional groups level interaction and it was performed on Fourier transform infrared spectroscopy (Shimadzu 8400S). Spectra for pure drug, physical mixture of drug with different polymers were obtained by scanning over the range of 4000-400 cm^{-1} using KBr pellet technique[6,7].

Pre-compression properties

The prepared blend mixture of each formulation were involved to determine the pre-compression parameters such as bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio. The results were reported as the mean (±) standard deviation of three measurements as mentioned in Table No.2.

Bulk density (D_b), Tapped density (D_t) and Hausner's ratio

10 gm of powder was introduced into dried and clean 100ml measuring cylinder, at a constant height the cylinder was tapped for 100 times from a constant height and the tapped volume (gm/cc) was read in the case of tapped density determination. But the bulk density was determined from the bulk volume using the formula given below. From this, the Hausner's ratio was calculated by using the below mentioned formula[8].

$D_b = M/V_o$

Where, D_b = Bulk density (gm/cc)
M = mass of the powder (g)
V_o = bulk volume of powder (cc)

$D_t = M/V_o$

Where, D_t = Tapped density (gm/cc)
M = mass of the powder (g)
V_o = bulk volume of powder (cc)

Hausner's ratio = D_t / D_b

Compressibility index

The compressibility of powder was determined by the Carr's compressibility index[8].

Carr's index (%) = [(TBD-LBD) x 100] / TBD

Where, TBD = Tapped bulk density
LBD = Loose bulk density

Angle of repose (Ɵ)

It is defined as the angle formed between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used in this study. A funnel was fixed with its tip at given height (h), above a flat plane surface on which a graph paper was placed. The powder were allowed to flow through the funnel freely onto the graph paper. The angle of repose was then calculated using formula[9].

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

Where, Ɵ = angle of repose

h = height of pile (cm)

r = radius of the base of the pile (cm)

Evaluation of post-compression parameters

The prepared floating tablets were evaluated for their hardness, friability thickness, weight variation, floating lag time, swelling index, drug content and *in vitro* drug release studies. The values were mentioned in Table No.3.

Weight variation

From each formulation 20 tablets were weighed individually using electronic balance (Shimadzu electronic balance) and their average weight were calculated[10].

Thickness

The thickness of 10 tablets from each formulation were measured using Vernier calipers. The extent to which the thickness of each tablet deviated from ±5% of the standard value was determined[11].

Hardness and Friability

The hardness of 3 tablets from each formulation were determined by Monsanto hardness tester. The friability of 20 tablets were determined using Roche friabilator[12].

Swelling studies

The degree of swelling of release rate retarding polymer is an important factor for floating system. In this study, the tablet was weighed and immersed in a petri dish containing simulated gastric fluid (0.1 N HCl) at 37ºC ± 0.5ºC for 24 hrs. For every one hour time interval the dimensional changes like tablet diameter and thickness were observed. As like the same, the % weight gain and water uptake of tablets were determined by using the formula[13,14].

Swelling index = $(W_t - W_0)/W_0 \times 100$

Where, W_t = weight of tablet at time 't'

W_0 = weight of tablet at time '0'

Buoyancy lag time and floating time

The time between the introduction of the tablet into the medium and rise to upper one third of the dissolution vessel is termed as floating lag time. The time taken by the dosage form in gastric fluid to float is known as floating time. These tests were generally performed in 0.1 N HCl as simulated gastric fluid maintained at 37ºC ± 0.5ºC. The time taken for the tablets to rise the surface for floating was determined and recorded[15,16].

Drug content

The drug content assay for all the formulations were performed as per described in specified monograph[17].

***In vitro* drug release and drug kinetic studies**

The USP type II dissolution apparatus was used to study the release of each formulation of floating tablets. The dissolution medium consisted of 900 ml of stimulated gastric fluid (pH 1.2). The release was performed at 37ºC±0.5ºC, with rotation speed of 75 rpm. Aliquots of 5 ml were withdrawn at predetermined time interval (1,2,3,.....24hrs) and the sink condition was maintained by equivalent amount of fresh buffer. The aliquots were filtered through whattman filter paper and analyzed after appropriate dilution by using UV-visible spectrophotometer (1800 Shimadzu, Kyoto, Japan) at 225 nm against suitable blank and cumulative percentage drug release was calculated and mentioned in Table No.4[18,19]. The release kinetics of all formulations were determined such as zero order, first order, higuchi and korsemeyer-peppas[20] and the kinetics data of F6 were reported in Table No.5.

DISCUSSION

FTIR study reveals that there was no such specific chemical interaction between the drug molecules and excipients used in the formulation (Figure No.1). Studies for various physicochemical characterization includes pre-compression and post-compression parameters were evaluated. The pre-compression parameters report shows that all the formulations were within the specific range. Post-compression parameters such as weight variation and thickness were found to

be 248.43±4.36 to 251.63±2.99 and 3.16±0.05 to 3.51±0.18 respectively. The hardness and friability of prepared floating tablets were found to be 4.2±0.45 to 5.9±0.25 and 0.37±0.42 to 0.72±0.41 respectively. Drug content of prepared floating tablets were reported in the ranges of 99.42±0.28 to 99.91±0.23. Buoyancy lag time and floating time were found to be 45 to 58 sec.

This indicates that the prepared floating tablets can remain in the gastric region for prolong duration and hence significantly prolong the gastric residence time of atenolol. The % CDR of prepared tablets were reported in Table No.4. From the drug release (Figure No.2) and drug kinetics studies, formulation F6 showed prolonged gastric retention which may improve the bioavailability by means of prolonged gastric retention of drugs in the gastric medium.

RESULTS

Table No.1: Composition of floating tablets Atenolol by direct compression method

S.No	Ingredients(in mg)	F1	F2	F3	F4	F5	F6	F7
1	Atenolol	50	50	50	50	50	50	50
2	Microcrystalline cellulose	98	98	98	98	98	98	98
3	HPMC K4M	75	-	-	37.5	-	37.5	31.5
4	HPMC K100M	-	75	-	37.5	37.5	-	31.5
5	Guar gum	-	-	75	-	37.5	37.5	12.5
6	Sodium bicarbonate	22.5	22.5	22.5	22.5	22.5	22.5	22.5
7	Aerosil	2	2	2	2	2	2	2
8	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
9	Total weight of each tablet	250	250	250	250	250	250	250

Table No.2: Data for pre-compression parameters of various formulations

S.No	Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hausner's Ratio	Angle of repose (Ɵ)
1	F1	0.45±0.045	0.52±0.09	15.60±0.2	1.15±0.02	28.06±0.31
2	F2	0.45±0.045	0.50±0.07	12.23±0.6	1.11±0.04	27.58±0.15
3	F3	0.44±0.044	0.50±0.09	12.58±0.8	1.13±0.08	28.44±0.11
4	F4	0.45±0.045	0.52±0.04	15.19±0.1	1.15±0.06	28.36±0.13
5	F5	0.44±0.044	0.52±0.01	15.48±0.6	1.18±0.08	28.52±0.19
6	F6	0.45±0.045	0.51±0.04	13.48±0.8	1.13±0.09	29.32±0.19
7	F7	0.51±0.045	0.59±0.04	14.48±0.8	1.15±0.09	29.69±0.19

Table No.3: Data for post-compression parameters of various formulations

S.No	Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Floating lag time (sec)	Swelling index (%)	Drug content (%)
1	F1	248.43±4.36	3.28±0.20	4.7±0.54	0.72±0.41	47	33.32	99.78±0.24
2	F2	250.81±4.02	3.33±0.22	4.4±0.75	0.37±0.42	50	35.66	99.70±0.38
3	F3	250.14±3.89	3.28±0.17	4.2±0.45	0.40±0.38	52	30.91	99.51±0.32
4	F4	249.53±3.99	3.16±0.05	5.9±0.25	0.46±0.36	53	32.33	99.94±0.21
5	F5	251.08±3.49	3.34±0.05	5.3±0.13	0.61±0.34	49	35.11	99.42±0.28
6	F6	251.63±2.99	3.25±0.06	5.4±0.13	0.67±0.35	45	38.18	99.91±0.23
7	F7	250.23±2.89	3.51±0.18	5.5±0.14	0.63±0.34	58	36.55	99.58±0.24

Table No.4: Cumulative percentage of drug release from tablets

Time (hrs)	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	2.06±0.098	1.67±0.099	1.40±0.150	2.32±0.159	1.96±0.099	6.69±0.000	3.08±0.057
2	4.42±0.098	3.80±0.057	3.31±0.150	4.92±0.421	4.13±0.098	9.35±0.197	5.54±0.057
3	8.39±0.114	7.38±0.100	7.11±0.057	8.59±0.114	8.00±0.057	14.20±0.11	9.51±0.057
4	11.09±0.24	10.79±0.14	10.10±0.05	11.55±0.37	10.86±0.15	19.39±0.00	12.23±0.11
5	16.87±0.06	15.32±0.06	14.60±0.15	17.29±0.39	16.37±0.11	24.59±0.09	17.98±0.11
6	22.38±0.09	20.84±0.06	20.40±0.11	22.80±0.31	21.75±0.00	30.65±0.05	23.62±0.09
7	34.04±0.12	32.92±0.04	32.21±0.11	34.38±0.28	33.79±0.05	35.81±0.22	35.17±0.05
8	40.48±0.06	39.20±0.13	38.52±0.05	41.00±0.39	39.87±0.09	41.16±0.15	41.84±0.00
9	49.55±0.06	48.01±0.05	46.92±0.11	49.46±0.05	48.27±0.15	46.93±0.51	50.80±0.00
10	60.53±0.10	54.92±0.69	57.92±0.11	61.13±0.59	59.82±0.05	52.43±0.05	62.05±0.15
11	71.05±0.15	69.70±0.17	68.52±0.09	71.93±0.73	70.16±0.11	61.19±0.05	73.18±0.11
12	79.12±0.14	78.42±0.18	77.22±0.05	79.62±0.56	78.89±0.11	75.27±0.03	80.80±0.05
16	84.63±0.28	83.02±0.12	81.98±0.05	84.74±0.15	83.62±0.05	90.19±0.05	86.02±0.0
20	89.94±0.17	88.59±0.13	87.69±0.11	90.52±0.54	89.07±0.11	97.27±0.03	92.22±0.05
24	91.98±0.23	90.23±0.32	89.63±0.15	92.52±0.31	91.44±0.15	99.16±0.14	93.61±0.20

Table No.5: Kinetic values obtained from different plot of formulation (F6)

S.No	Order of kinetics		F6
1	Zero order (r^2)		0.8927
2	First order (r^2)		0.9693
3	Higuchi (r^2)		0.9230
4	Kosermeyer/peppas	Slope (n)	2.7586
		r^2	0.9106

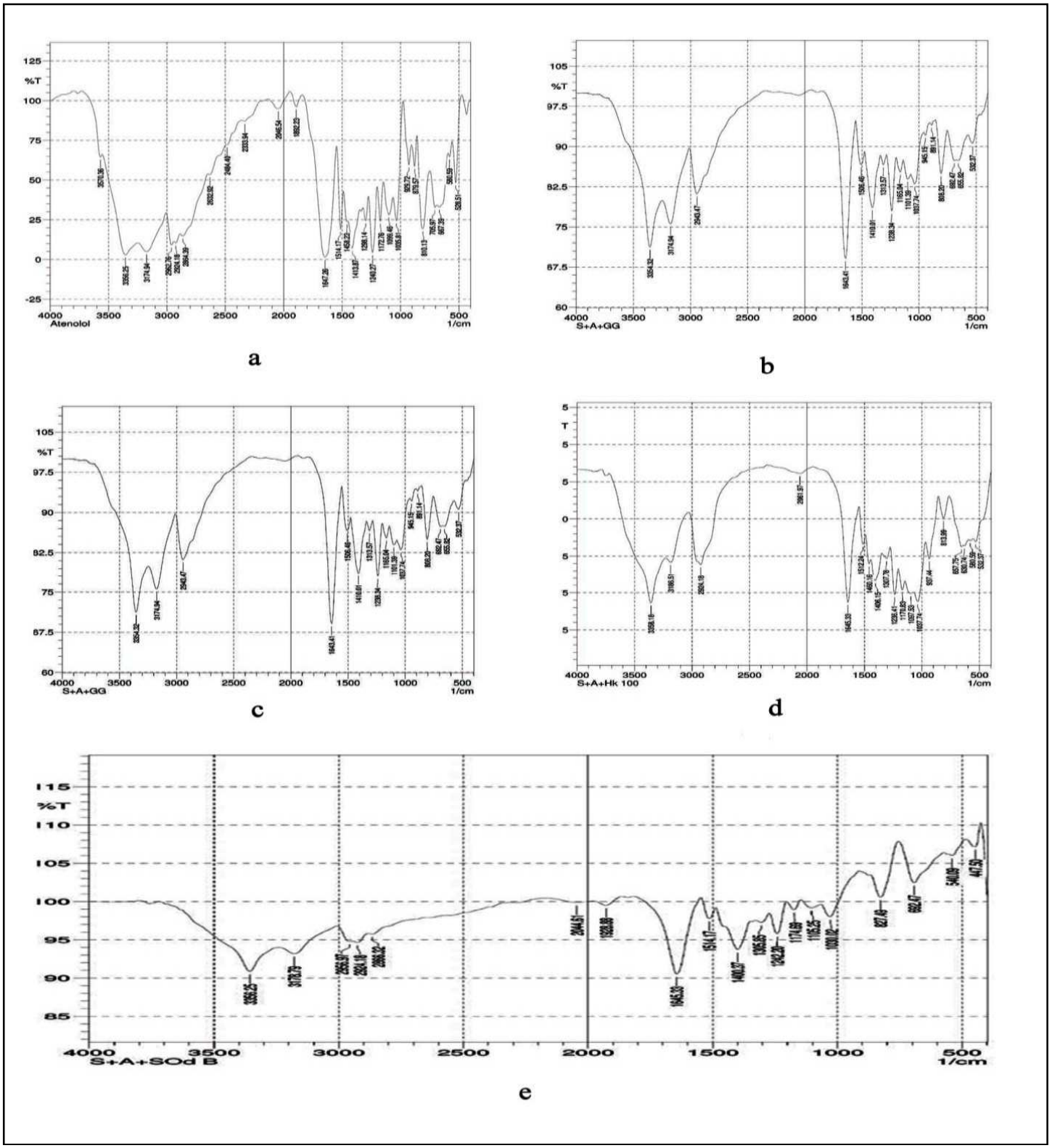

Figure No.1: FTIR spectra of: a) pure atenolol; b) atenolol and guar gum physical mixture; c) atenolol and HPMC K4M physical mixture; d) atenolol and HPMC K100M physical mixture; e) atenolol and $NaHCO_3$ physical Mixture

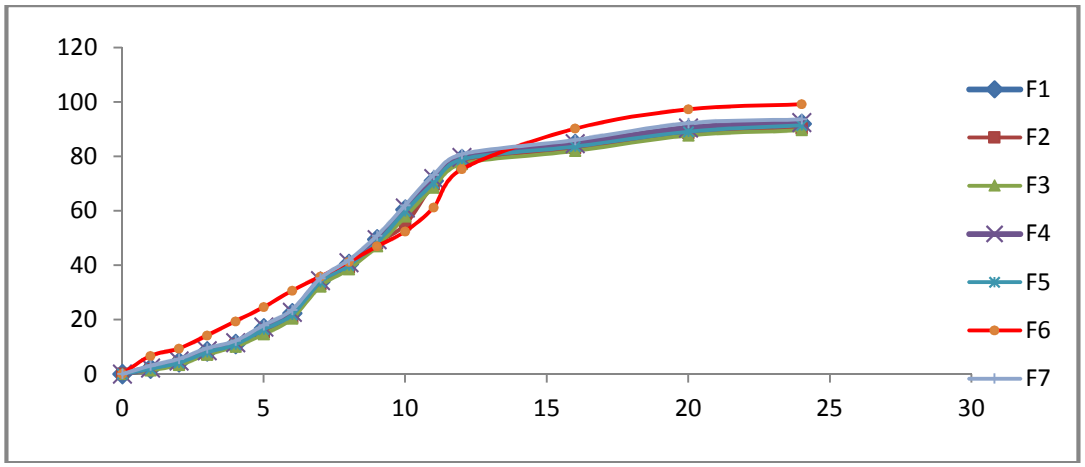

Figure No.2: Comparative *in- vitro* drug release profiles of Atenolol formulations F1-F7

CONCLUSION

Among the experimental floating tablets, formulation F6 containing 20% of HPMC K4M, 10% Guar gum, 9% of $NaHCO_3$ showed better drug release for 24 hrs with minimum floating lag time of 45 seconds. The prepared floating tablets were found to release the drug in a prolong manner for a period of 24 hrs. Further study in the direction of *in vivo* drug release in a suitable animal model may give a enormous idea in the formulation of atenolol floating tablets.

ACKNOWLEDGEMENT

The authors are thankful to East West College of Pharmacy for providing facilities to conduct this studies.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Saroj Kr. Sah *et al*. Functionality comparision of natural and synthetic polymers in development and *in vitro* characterization of gastroretentive floating drug delivery system of atenolol, *Asian Journal of Research in Chemistry and Pharmaceutical Sciences,* 4(2), 2016, 52-59.