Available online on www.ijcpr.com
International Journal of Current Pharmaceutical Review and Research, 4(1), 10-26

ISSN: 0976-822X

Research Article

Design and Evaluation of Atenolol Floating Drug Delivery System

*D. V. Charan, C.P.Meher, B.Pochaiah

Department of Pharmaceutics, Maheshwara institute of Pharmacy, chitkul (V), Isnapur "X" Road, patancheru, Hyderabad.

ABSTRACT

Gastroretentive floating drug delivery systems (GFDDS) of Atenolol, an antihypertensive drug, with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) have been designed. Polyox WSR Coagulant was used as the polymer and sodium bicarbonate as gas generating agent to reduce floating lag time. The tablets were prepared by direct compression method.The optimized formulation containing Atenolol 50 mg, Polyox WSR Coagulant 60 mg and Sodium bicarbonate 50 mg has displayed almost first order release kinetics with a floating lag time of only 4.7 minutes. This formulation released more than 80% drug in 12 hours. This study proves that GFDDS of Atenolol can be designed using Polyox WSR Coagulant as polymer, which provides nearly first order release kinetics and thus possible enhancement of oral bioavailability of the drug.

Keywords: Atenolol; Gastroretentive floating drug delivery systems; Hydrodynamically balanced systems; Polyox WSR Coagulant.

INTRODUCTION

Floating drug delivery system or hydrodynamically balanced system (HBS) is a formulation of drug in gel forming hydrocolloid meant to remain buoyant on stomach contents. This not only prolongs GI residence time but also does so in an area of the GIT that would maximize drug reaching its absorption site. The most commonly used polymers are HPMC and sodium alginate. HPMC comes in various grades like Methocel K4M, Methocel K50M, Methocel K100M, Methocel E4, Methocel E50, Methocel E100 etc[1]. When a dosage form is immersed

Author for correspondence: Email: vishnu.dyaga79@gmail.com

in a specific medium, hydration occurs, which leads to gel formation. The process of erosion causes the de-aggregation and the creation of new gel layers, affecting both the volume and the weight of the dosage form. This in turn causes the controlled drug release. It has been observed that only hydrophilic polymers are not sufficient for floating characteristics and better results are possible with use of some soluble or gas-evolving excipients[2], the release rate was indirectly proportional to viscosity and concentration of the polymer used[3]. Sodium alginate gel system has been evaluated for sustained release oral delivery system with a potential for prolonged gastric residence. The gelatin and the cross linking of alginate molecules are due to stacking of the glucuronate blocks in the alginate chains, with the formation of the "egg-box junction upon adding chelating divalent cations such as Ca^{++}. The ratio of mannuronate blocks to glucoronate blocks in alginate molecules is related to release of drug from alginate gel beads[4]. A novel floating system based on the ion exchange resins has been investigated. The method relies on the ion exchange resins loaded with bicarbonate, which on contact with media containing hydrochloric acid, release carbon dioxide causing the resin to float. This has been achieved in using theophylline as a model drug[5].

Atenolol is a beta-adrenoreceptor antagonist or more commonly known as a beta-blocker used in the treatment of hypertension and angina pectoris. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50%, while the remaining is excreted unchanged in faeces. This is because of its poor absorption in lower gastrointestinal tract[6]. It undergoes little or no hepatic first pass metabolism and its elimination half-life is 6 to 7 hours[7]. Therefore, it is selected as a suitable drug for the design of a gastro-retentive floating drug delivery system (GFDDS) with a view to improve its oral bioavailability.

MATERIAL & METHOD

Materials: All the chemicals used were of pharmacopeial grade. Dissolution apparatus- ElectrolabTDL08L,

UV Spectrophotometer- Lab india UV3000+, Ten stationary compression machine- RIMEK, Roche friabilator- Electrolab, Electronic weighing balance- Afcoset, Hardness tester- Monsanto.

Method:

Table-1:Formulation Tables (for 1 tablet)

s.no	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	ATENOLOL	50	50	50	50	50	50	50	50	50
2.	HPMC K4M	45	-	-	-	-	-	-	-	-
3.	HPMC E4M	-	45	-	-	-	-	-	-	-
4.	HE 250HHX	-	-	45	-	-	-	-	-	-
5.	Polyox WSR Coagulant	-	-	-	45	-	45	45	45	60
6.	Polyox N80	-	-	-	-	-	25	-	-	-
6.	Sodium alginate	-	-	-	-	45	-	-	-	-
7.	Povidone K30	9	9	9	9	9	9	9	9	9
8.	Sodium bi carbonate	30	30	30	30	30	30	50	50	50
9.	Lactose	120	120	120	120	120	95	100	140	125
10.	DCP	40	40	40	40	40	40	40	-	-
11.	Mg.Stearate	6	6	6	6	6	6	6	6	6
Total		300	300	300	300	300	300	300	300	300
		Direct Compresion								

Table-2: Preformulation Studies

Code	Angle of repose()	Bulk density (g/cm^3)	Tapped density (gm/cm^3)	Hausener's ratio (H)	Carr index (I)
F-1	27.364±0.355°	0.542±0.012	0.612±0.041	1.140	11.2
F-2	25.252±0.257°	0.552± 0.044	0.654 ±0.051	1.161	14.5
F-3	27.210±0.352°	0.522± 0.059	0.625±0.088	1.133	12.0
F-4	27.05±0.250°	0.583± 0.033	0.675±0.050	1.172	13.6
F-5	24.625±0.374°	0.575± 0.048	0.680±0.061	1.182	15.5
F-6	28.560±0.385°	0.624± 0.045	0.695±0.043	1.105	9.8
F-7	24.844±0.982°	0.610±0.057	0.667±0.063	1.099	9.0
F-8	29.653±0.784°	0.605±0.086	0.682± 0.049	1.127	11.3

F-9	27.044±0.243°	0.637±0.032	0.658±0.067	1.164	11.2

Table-3: Trial formulation 1 (Method: direct compression)

Sl. No.	Ingredients	qty (mg)
1.	Atenolol	50
2.	HPMC K4M	45
3.	Povidone K30	9
4.	Sodium bi carbonate	30
5.	Lactose	120
6.	Dicalcium phosphate	40
7.	Mg. stearate	6
	Total tablet weight	300
Observation	Floating was not occurred	

Table-4: Trial formulation 2 (Method: direct compression)

Sl. No.	Ingredients	qty (mg)
1.	Atenolol	50
2.	HPMC E4M	45
3.	Povidone K30	9
4.	Sodium bi carbonate	30
5.	Lactose	120
6.	Dicalcium phosphate	40
7.	Mg. stearate	6
	Total tablet weight	300
Observation	Floating was not occurred	

Table-5: Trial formulation 3 (Method: direct compression)

Sl. No.	Ingredients	qty (mg)
1.	Atenolol	50
2.	HEC 250 HHX	45
3.	Povidone K30	9
4.	Sodium bi carbonate	30
5.	Lactose	120

6.	Dicalcium phosphate	40
7.	Mg. stearate	6
	Total tablet weight	300
Observation	Floating was not occurred	

Table-6: Trial formulation 4 (Method: direct compression)

Sl. No.	Ingredients	qty (mg)
1.	Atenolol	50
2.	Polyox WSR coagulant	45
3.	Povidone K30	9
4.	Sodium bi carbonate	30
5.	Lactose	120
6.	Dicalcium phosphate	40
7.	Mg. stearate	6
	Total tablet weight	300
Observation	Floating was occured	
Floating time	11 min 12 seconds	

Table-7: *In-vitro* drug release data of trial formulation 4

Time (Hrs)	% drug released
1	21.5
2	32.5
4	51
5	73.5
6	77.5
8	89
10	89.5
12	89
24	92

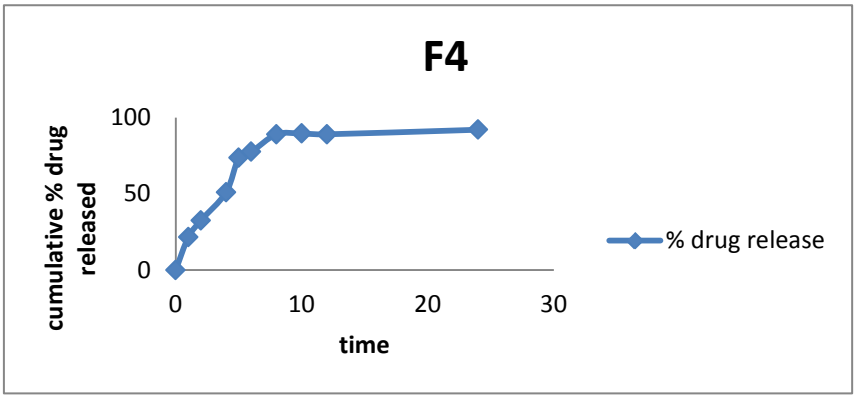


Fig-1: In-vitro drug dissolution profile of formulation F4

Table-8: Trial formulation 5 (Method: direct compression)

Sl. No.	Ingredients	qty (mg)
1.	Atenolol	50
2.	Sodium alginate	45
3.	Povidone K30	9
4.	Sodium bi carbonate	30
5.	Lactose	120
6.	Dicalcium phosphate	40
7.	Mg. stearate	6
	Total tablet weight	300
Observation	Floating was occurred	
Floating time	04 min 53 seconds	

Table-9: *In-vitro* drug release data of trial formulation 5

Time (Hrs)	% drug release
1	10.5
2	20.5
4	50
5	68
6	73
8	86
10	89
12	92.5

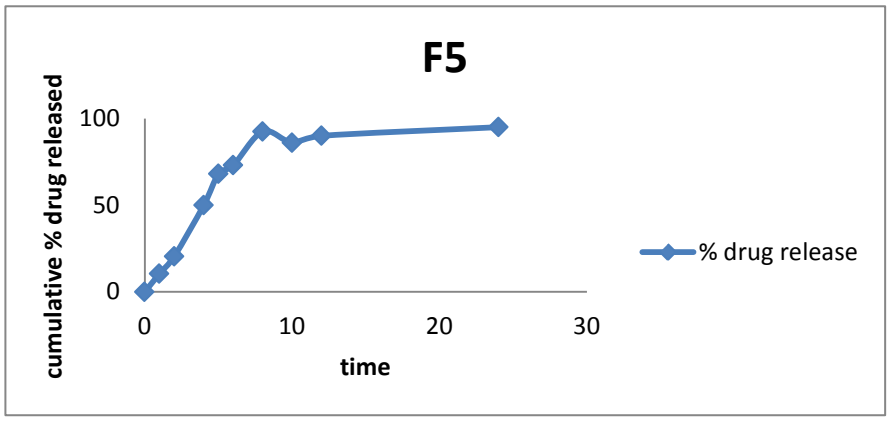


Fig-2: In-vitro drug dissolution profile of formulation F5

Table-10: Trial formulation 6 (Method: direct compression)

Sl. No.	Ingredients	qty (mg)
1.	Atenolol	50
2.	Polyox WSR coagulant	45
3.	Polyox N80	25
4.	Povidone K30	9
5.	Sodium bi carbonate	30
6.	Lactose	95
7.	Dicalcium phosphate	40
8.	Mg. stearate	6
	Total tablet weight	300
Observation	Floating was occurred	
Floating time	16 min 13 seconds	

Table-11: *In-vitro* drug release data of trial formulation 6

Time (Hrs)	% drug release
1	41
2	50
4	72
5	88.5

6	92.5
8	98
10	98.5
12	99
24	100

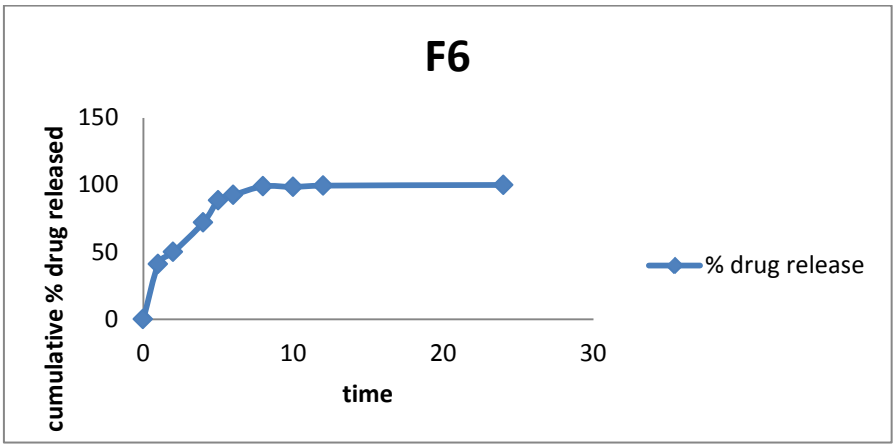


Fig-3: In-vitro drug dissolution profile of formulation F6

Table-12: Trial formulation 7 (Method: direct compression)

Sl. No.	Ingredients	qty (mg)
1.	Atenolol	50
2.	Polyox WSR coagulant	45
3.	Povidone K30	9
4.	Sodium bi carbonate	50
5.	Lactose	100
6.	Dicalcium phosphate	40
7.	Mg. stearate	6
	Total tablet weight	300
Observation	Floating was occured	
Floating time	14 min 30 seconds	

Table-13: Trial formulation 8 (Method: direct compression)

Sl. No.	Ingredients	qty (mg)
1.	Atenolol	50
2.	Polyox WSR coagulant	45

3.	Povidone K30	9
4.	Sodium bi carbonate	50
5.	Lactose	140
6.	Dicalcium phosphate	---
7.	Mg. stearate	6
	Total tablet weight	300
Observation	Floating was occured	
Floating time	02 min 53 seconds	

Table-14: *In-vitro* drug release data of trial formulation 8

Time (Hrs)	% drug release
1	47.5
2	59.5
4	81.5
5	86.5
6	89.5
8	92.5
10	99
12	99.5
24	100

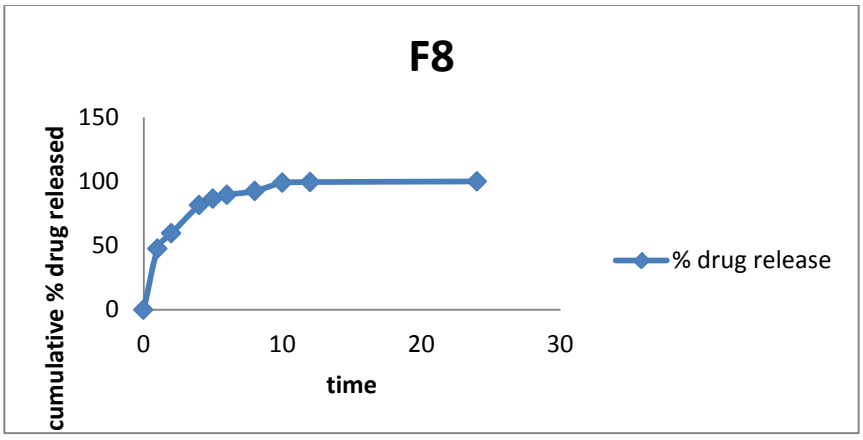


Figure 4: In-vitro Drug Release Profile of Formulation F8

Cumulative Percent Drug Released Vs Time Plots of formulations F4, F5, F6 and F8

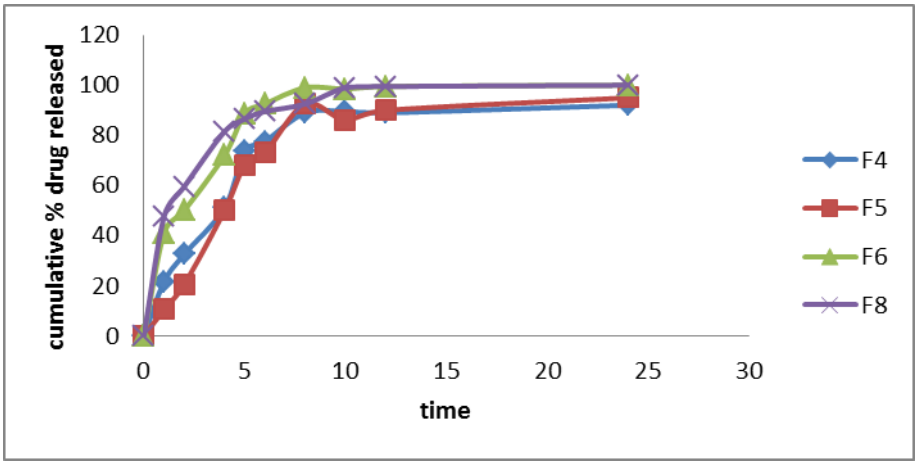


Fig-5 : Comparison of In-vitro Drug Release Profiles of Atenolol Formulations F4, F5, F6 and F8.

OPTIMIZED FORMULA:

Table-15: Trial formulation 9 (Method: direct compression)

Sl. No.	Ingredients	qty (mg)
1.	Atenolol	50
2.	Polyox WSR coagulant	60
3.	Povidone K30	9
4.	Sodium bi carbonate	50
5.	Lactose	125
6.	Dicalcium phosphate	---
7.	Mg. stearate	6
	Total tablet weight	300
Observation	Floating was occurred	
Floating time	04 min 07 seconds	

Table-16: *In-vitro* drug release data of trial formulation

Time (Hrs)	% drug release
1	34
2	44
4	57
5	69

6	73.5
8	75
10	81.5
12	83
24	100

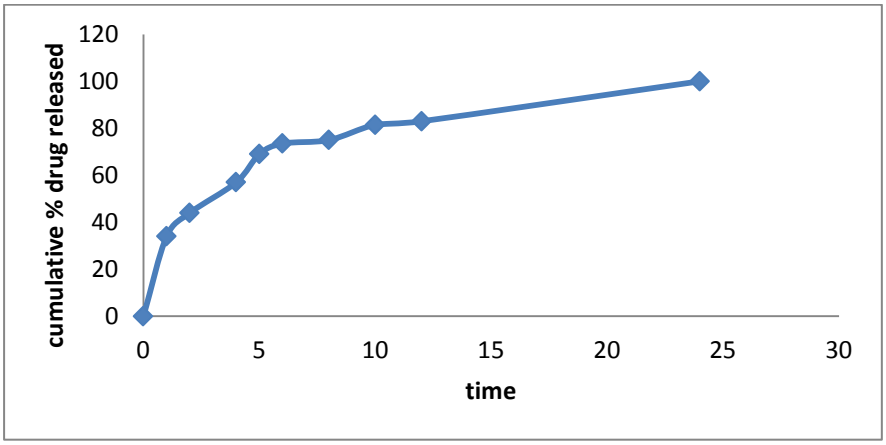


Fig-6: Cumulative Percent Drug Released Vs Time Plots of formulation F9

DISSOLUTION PROFILE FOR FINAL OPTIMIZED TRAIL

Apparatus: USP-I basket apparatus,Media: 0.1 N HCl, 500ml, RPM: 100 , TIME: 24 hours

Table-17: *In-vitro* drug release data of formulation F9

Time	Cumulative % drug release	Cumulative % drug to be released	log cumulative % drug to be released	cubic root of % drug to be released	log cumulative % drug release	log time	SQRT time
0	0	100	2	4.6415	0	#NUM!	0
1	34	66	1.819543936	4.0412	1.531478917	0	1
2	44	56	1.748188027	3.8258	1.643452676	0.30103	1.414214
4	57	43	1.633468456	3.5033	1.755874856	0.60206	2
5	69	31	1.491361694	3.1413	1.838849091	0.69897	2.236068
6	73.5	26.5	1.423245874	2.9813	1.866287339	0.77815	2.44949
8	75	25	1.397940009	2.9240	1.875061263	0.90309	2.828427
10	81.5	18.5	1.267171728	2.6447	1.911157609	1	3.162278

12	83	17	1.230448921	2.5712	1.919078092	1.07918	3.464102
24	100	0	#NUM!	0	2	1.38021	4.89898

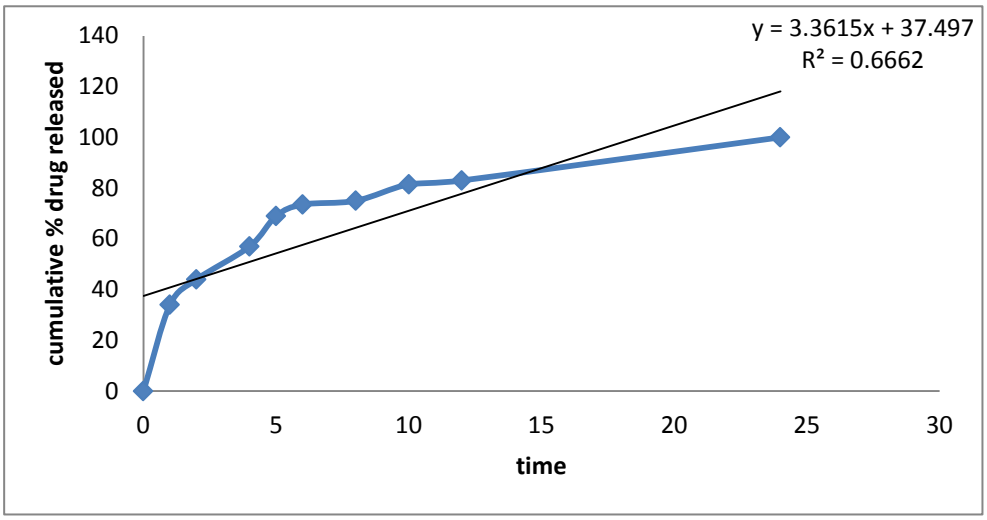
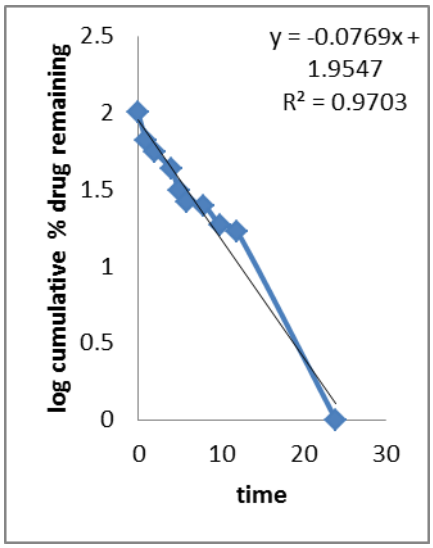


Fig-7: Cumulative Percent Drug Released Vs Time Plots (Zero Order)



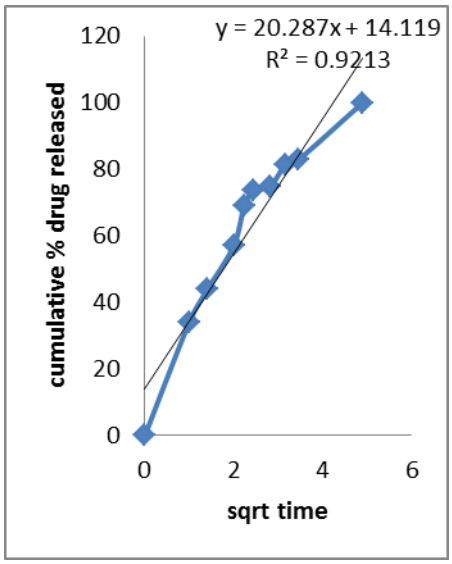


fig-8(a) (b)fig-9

(a)Log Cumulative Percent Drug Remaining Vs Time Plots (First Order)

(b)Cumulative Percent Drug Released Vs Square Root of Time (Higuchi's Plots)

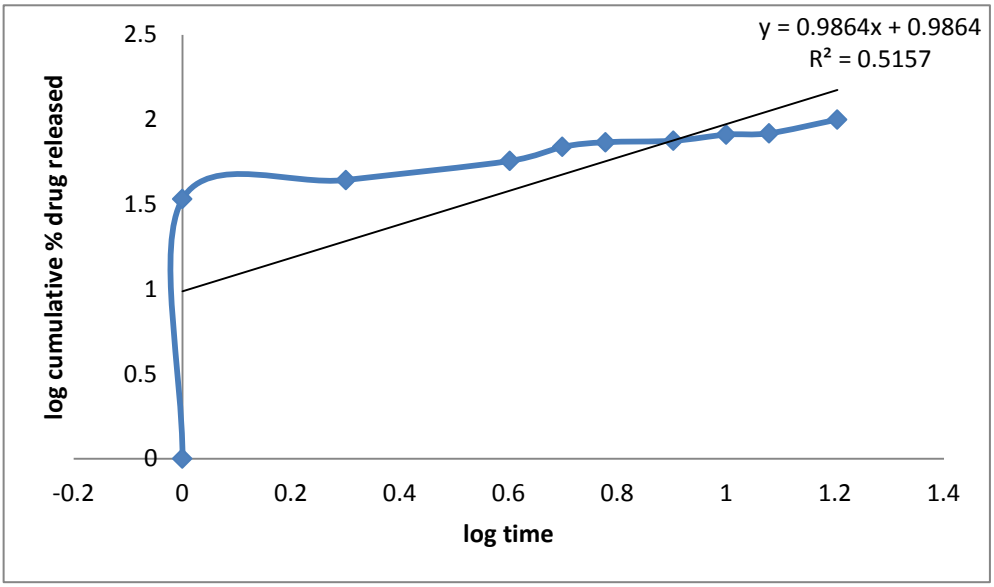


Fig-10: Log Cumulative Percent Drug Released Vs Log Time (Peppas Plots)

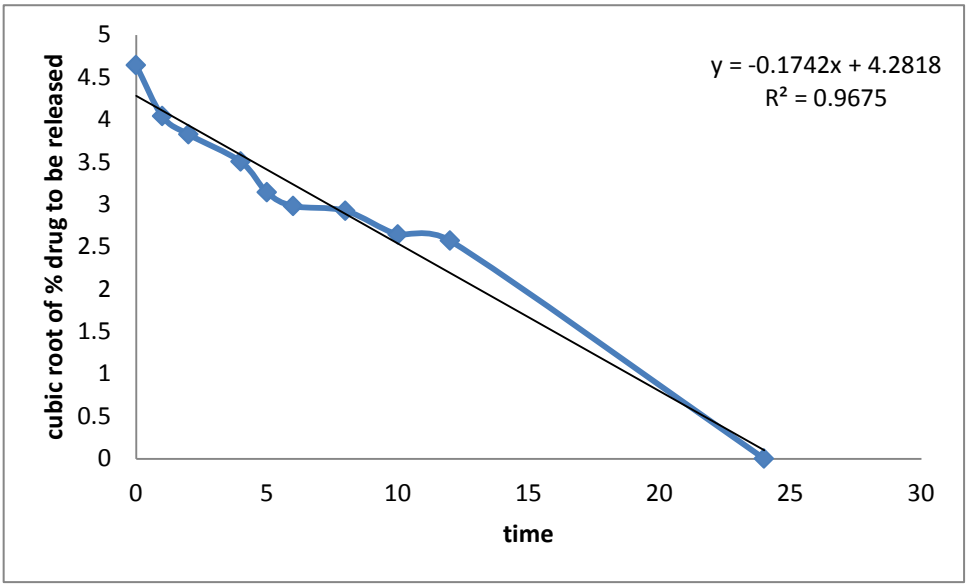


Fig-11: Cubic root of % drug to be released Vs time (Hixon plots)

Table-18: Table R^2 values of all formulations

Formulation code	Zero order kinetics (R^2)	First order kinetics (R^2)	Higuchi's model (R^2)	Korsmeyer and peppas model (R^2)
F1	---	---	---	---
F2	---	---	---	---

F3	---	---	---	---
F4	0.556	0.708	0.825	0.831
F5	0.596	0.777	0.831	0.715
F6	0.466	0.639	0.779	0.849
F7	---	---	---	---
F8	0.444	0.961	0.767	0.879
F9 (optimized)	0.666	0.970	0.921	0.515

Swelling index:--Optimized formulation (F9) :

Tablet weight : 0.30065

Basket weight : 10.77

Tablet with basket weight : 11.0707

Table-19: Swelling index data of optimized formulation F9

Time (min)	Swelling index (%)		
15	191.88	180	226.27
30	193.94	240	220.51
45	221.78	300	215.62
60	237.38	360	212.86
120	238.94	600	150.5

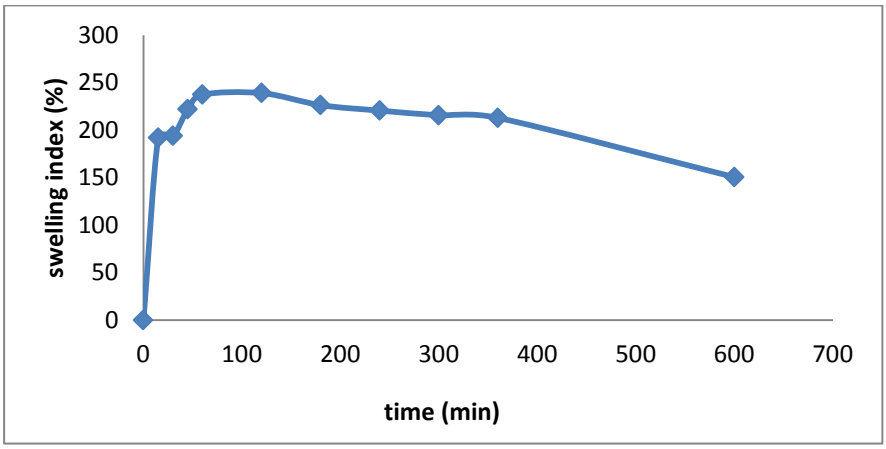


Fig-12: Percentage swelling index of optimized formulation

Table-20: Evaluation of trial formulations

formulation	hardness	Friability	Mean Drug Content %±SD	Floating lag time (min)	Floating time (hrs)
F1	4.54	0.55	96.83±1.32	---	---
F2	4.49	0.61	97.09±1.34	---	---
F3	4.42	0.68	94.57±0.71	---	---
F4	4.62	0.53	97.15±2.05	11 min 12sec	24
F5	4.59	0.65	95.70±4.08	4 min 53 sec	24
F6	4.51	0.69	93.49±1.49	16 min 13sec	24
F7	4.69	0.57	95.42±0.68	14 min 30sec	24
F8	4.67	0.62	95.77±1.79	2 min 53 sec	24
F9	4.66	0.64	95.55±2.42	4 min 07 sec	24

Stability studies: Short-term stability studies were performed at a temperature of 45°±1°C over a period of three weeks (21 days) on the promising HBS tablet formulation F9. Sufficient number of tablets (15) were packed in amber colored screw capped bottles and kept in hot air-oven maintained at 45°±1°C. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and In-vitro floating studies were performed to determine the drug release profiles, In-vitro floating lag time and floating time.

Table-21: data of stability studies

	1st week	2nd week	3rd week
Physical appearance	No change	No change	No change
Hardness	4.66	4.65	4.67
Lag time	4 min 07 sec	4 min 05 sec	4 min 10 sec
Drug content	95.55±2.42	95.55±2.44	95.55±2.41

DISCUSSION

In the present study, hydrodynamically balanced systems of Atenolol were prepared by Polyox WSR coagulant polymer at different drug to polymer ratios along with a gas generating agent, sodium bicarbonate. HBS tablets were prepared and evaluated for hardness, friability, uniformity of weight, uniformity of drug content, swelling index, floating lag time, *In-vitro* floating time, *In-vitro* dissolution, short-term stability and drug-polymer interaction. The hardness of the prepared of Atenolol was found in the range of 4.42 to 4.69 Kg/cm². The

friability of all tablets was less than 1% i.e., in the range of 0.53 to 0.69%. The percentage deviation from the mean weights of all the batches of prepared HBS were found within the prescribed limits as per IP. The low values of standard deviation indicates uniform drug content in all the batches prepared as observed from the data (table-5.30).Swelling index of the tablets increases with an increase in the content of polymer and the gas generating agent ($NaHCO_3$). *In-vitro* floating studies were performed by placing tablets in USP dissolution the apparatus-I containing 500 ml of 0.1N HCl maintained at a temperature of 37±0.5ºC. The floating lag time and floating time was noted visually. The results are given in tables-5.27. With formulations containing the same amount of polymer, floating lag time decreased with increase in concentration of sodium bicarbonate. For formulation F8, it is lowest (2 min 53 sec) as the drug-polymer (Polyox WSR coagulant) ratio is 1:1.2 and sodium bicarbonate is in highest proportion among all formulations and the tablet bursts into pieces within 30 minutes. All the designed formulations have displayed a floating time of more than 24 hours. *In-vitro* drug release study was performed using USP XXIII dissolution test apparatus-I at 100 rpm using 500 ml of 0.1N HCl maintained at 37±0.5ºC as the dissolution medium. The results were shown in table 5.23. From the above data, it is evident that as the proportion of polymer in the formulation increases, cumulative percent drug release in 10 hours decreases, and as the proportion of the gas generating agent increases, the drug release increases. Among the nine trial batches, formulations F4 and F5 have released 89.5% and 86% drug in 10 hours respectively, whereas formulations F6 and F8 have released 98.5% and 99% during the same period. And F9 formulation released 81.5 % at 10^{th} hour.

CONCLUSION

Hydrodynamically balanced systems of Atenolol with shorter lag time can be prepared by direct compression method using POLYOX WSR Coagulant and $NaHCO_3$ as gas generating agent. All the prepared tablet formulations were found to be good without capping and chipping. As the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent ($NaHCO_3$) increases the drug release increases and at the same time floating lag time decreases. Most of the designed formulations of Atenolol HBS displayed first order release kinetics.Short-term stability studies of optimized formulation F9 indicate, that there are no significant changes in drug content and dissolution parameter values after 3 weeks storage at 45±1ºC. FT-IR spectroscopic studies indicated that there are no drug - excipient interaction in the optimized

formulation. The optimized formulation F9 can be considered as a promising gastro-retentive drug delivery system of Atenolol providing nearly first order drug release over a period of 24 hours. The In-vitro Atenolol release data from the most satisfactory formulation F9 was fitted to various kinetic equations and the mechanism of drug release was studied from the R^2 values obtained. Thus the most satisfactory formulation F9 satisfied the physico-chemical parameters, In-vitro drug release profile requirements for floating formulation of Atenolol and shorter lag time (<5min).

REFERENCE

1. Sangekar S, Vadino WA, Chaudry I, Parr A, Beihn R, Digenis G. Evaluation of effect of food and specific gravity of tablets on gastric retention time. Int J Pharm. 1987; 35: 187-191.
2. Hilton AK, Desay PB. *In-vitro* and *in vivo* evaluation of an oral sustained release dosae form of amoxycilline trihydrate. Int J Pharm. 1992; 86: 79-88.
3. Stockwell AF, Davis SS, Walker SE. *In-vitro* evaluation of alginate gel system as sustained release drug delivery systems. J Control Release. 1986; 3: 167-175
4. Kikuchi A, Kawabuch M, Watanbe A, Sugihara MY, Sakurai, Okano T. J Control Release. 1999; 58: 21.
5. Atyab F, Sharma HL, Mohammad HAH, Fell JT. *In vivo* evaluation of a novel gastric retentive formulation based on ion exchange resins. J Control Release. 1996; 42: 105-108.
6. Shrivastava AK, Saurabh Wadhwa, Poonam D, Ridhuekar, Mishra B. Oral sustained delivery of atenolol from floating matrix tablets – Formulation and *In-vitro* evaluation. Drug Development and Industrial Pharmacy. 2005; 31: 367-371.
7. Martindale. The Complete Drug Reference. 33rd Edition. Pharmaceutical Press, London. 2002: 841.