CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND *INVITRO* EVALUATION OF ATENOLOL SUSTAINED RELEASE TABLETS

Kantlam Chamakuri*[1], Gnapika Vallamdasu [2]

[1]Associate Professor, Netaji Institute of Pharmaceutical Sciences, Toopranpet, Choutuppal, Nalgonda-508252, Telangana state, India.

[2]Student, Netaji Institute of Pharmaceutical Sciences, Toopranpet, Choutuppal, Nalgonda-508252, Telangana state, India.

Abstract:

The aim of the present study was to develop sustained release formulation of Atenolol to maintain constant therapeutic levels of the drug for over 12 hrs. Various natural polymers such as Guar gum Sodium CMC and Chitosan were employed as polymers. Atenolol dose was fixed as 50 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 60, 90 and 180 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e.,96.10 % in 12 hours. It followed zero order release kinetics mechanism.

Keywords: *Atenolol, Guar gum, Chitosan, Sodium CMC and sustained release tablets.*

***Corresponding author:**

Kantlam Chamakuri,

Associate Professor, Dept. of Pharmaceutical Analysis & Q.A.,
Netaji Institute of Pharmaceutical Sciences,
Toopranpet, Choutuppal, Nalgonda-508252.
Telangana state, India
E Mail: kantlam3@gmail.com

QR code

Please cite this article in press as ***Kantlam Chamakuri, Formulation And Invitro Evaluation Of Atenolol Sustained Release Tablets****, Indo Am. J. Pharm. Sci, 2015; 2(11).*

INTRODUCTION:

The present work is most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms.

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized" . Several types of modified-release drug products are recognized:

Extended-release drug products. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products.

Delayed-release drug products. A dosage form that releases a discrete portion or portions of drug, at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

Targeted-release drug products. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

Modified-release drug products are designed for different routes of administration based on the physicochemical, pharmacologic and pharmacokinetic properties of the drug and on the properties of the materials used in the dosage form. Several different terms are now defined to describe the available types of modified-release drug products based on the drug release characteristics of the products.

MATERIALS AND METHODS:

The Materials, which were Atenolol, Guargum, Chitosan, Sodium CMC, MCC pH 102, Magnesium stearate, and Talc, were purchased from Merck Specialities Pvt Ltd, Mumbai, India.

The different instruments were used in this work, which were Weighing Balance(Sartourious), Hardness tester(Sisco, Mumbai, India).Tablet Compression Machine (Multistation)(Labindia, Mumbai, India), Vernier calipers(Mitutoyo, Japan,) UV-Visible Spectrophotometer,(Labindia, Mumbai, India).

Analytical method Development

Determination of Absorption Maxima

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation Calibration Curve

100mg of Atenolol pure drug was dissolved in 100ml of 0.1 N HCl (stock solution)10ml of solution was taken and make up with100ml of 0.1 N HCl (100µg/ml).from this 10ml was taken and make up with 100 ml of 0.1 N HCl (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20,25,30,35 and 40µg/ml of Atenolol per ml of solution. The absorbance of the above dilutions was measured at 298 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of Repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula: Tan $\theta = h / r$, Tan θ = Angle of repose,
h = Height of the cone ,
r = Radius of the cone base

Table no 1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk Density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.
The bulk density was calculated using the formula: Bulk Density = M / V_o, Where, M = weight of sample, V_o = apparent volume of powder

Tapped Density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula: Tap = M / V, Where, Tap= Tapped Density, M = Weight of sample, V= Tapped volume of powder

Measures of powder Compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas: Carr's Index = [(tap - b) / tap] × 100, Where, b = Bulk Density, Tap = Tapped Density

Table no 2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation Development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 6.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Atenolol. Total weight of the tablet was considered as 300mg.

Procedure

Atenolol and all other ingredients were individually passed through sieve no ≠ 60.
All the ingredients were mixed thoroughly by triturating up to 15 min.
The powder mixture was lubricated with talc.
The tablets were prepared by using direct compression method.

Table no 3: Formulation composition for Tablets

Formulation No.	Atenolol	Sodium CMC	Guar Gum	Chitosan	Mag. Stearate	Talc	MCC pH 102
F1	50	60	-	-	6	6	QS
F2	50	90	-	-	6	6	QS
F3	50	180	-	-	6	6	QS
F4	50	-	60	-	6	6	QS
F5	50	-	90	-	6	6	QS
F6	50	-	180	-	6	6	QS
F7	50	-	-	60	6	6	QS
F8	50	-	-	90	6	6	QS
F9	50	-	-	180	6	6	QS

All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation Test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table no 4: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100, Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of Drug Content

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Meloxicam were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV–Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* Drug Release studies**

Dissolution parameters

Apparatus	_USP-II, Paddle
Method	
Dissolution Medium	_ 0.1 N HCl , pH 6.8 Phophate buffer
RPM	_50
Sampling intervals (hrs):	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	_37°c ± 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 2 hours and then the medium 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 298 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data are fitted to the following equation: $F = K_o t$, Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First Order Release Rate Kinetics The release rate data are fitted to the following equation: Log (100-F) = kt,

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi Release model To study the Higuchi release kinetics, the release rate data were fitted to the following equation: F = k t1/2

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.M_t/

$M_\infty = K t^n$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n> 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell Release model: $(100-Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

RESULT AND DISCUSSION:

The present study was aimed to developing extended release tablets of Atenolol using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Graphs of Atenolol was taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 298 nm and 294 nm respectively.

Table no 5: Observations for graph of Atenolol in 0.1N HCl (298nm)

Conc[µg/ml]	Abs
5	0.104
10	0.205
15	0.302
20	0.411
25	0.503
30	0.608
35	0.710
40	0.808

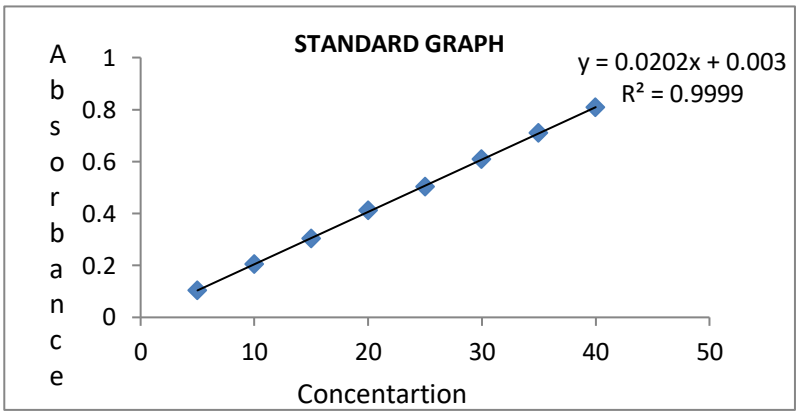

Figure no 1 : Standard graph of Atenolol in 0.1N HCl

Table no 6: Observations for graph of Atenololin p H 6.8 phosphate buffer (294nm)

Conc [µg/ml]	Abs
5	0.098
10	0.195
15	0.298
20	0.392
25	0.490
30	0.595
35	0.690
40	0.776

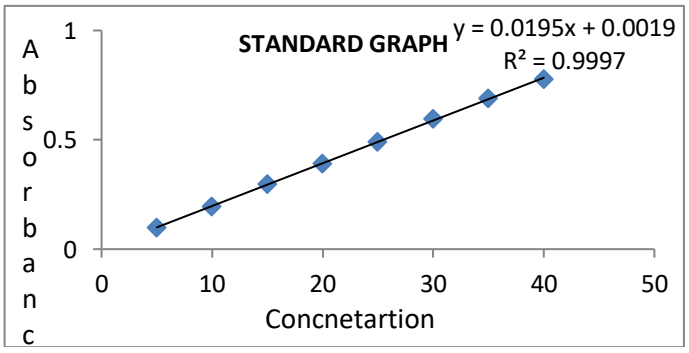

Figure no 2: Standard graph of Atenolol p^{H}6.8 phosphate buffer (294nm)

Preformulation parameters of powder blend

Table no 7: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.49±0.04	0.54±0.04	16.21±0.06	0.86±0.06
F2	25.67	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03
F4	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F5	25.34	0.52±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F6	24.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09
F7	25.18	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.05	0.55±0.08	0.5 2±0.03	17.54±0.09	1.17±0.02

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.58±0.06 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For Tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Table no 8: *In- vitro* quality control parameters for Tablets

Formulation codes	Weight Variations(mg)	Hardness(kg/cm$^{2)}$	Friability (%loss)	Thickness (mm)	Drug Content (%)
F1	**312.5**	**4.5**	**0.50**	**6.8**	**99.76**
F2	**305.4**	**4.5**	**0.51**	**6.9**	**99.45**
F3	**298.6**	**4.4**	**0.51**	**4.9**	**99.34**
F4	**310.6**	**4.5**	**0.55**	**6.9**	**99.87**
F5	**309.4**	**4.4**	**0.56**	**6.7**	**99.14**
F6	**310.7**	**4.5**	**0.45**	**6.5**	**98.56**
F7	**302.3**	**4.1**	**0.51**	**6.4**	**98.42**
F8	**301.2**	**4.3**	**0.49**	**6.7**	**99.65**
F9	**298.3**	**4.5**	**0.55**	**6.6**	**99.12**

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***in-vitro* Drug Release Studies**

Table no 9: Dissolution Data of Atenolol Tablets Prepared With Sodium CMC In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F1	F2	F3
0.5	25.5	20.1	16.4
1	46.7	39.4	26.7
2	76.5	55.3	34.6
3	98.4	75.3	42.4
4	-	87.3	55.4
5	-	99.4	67.4
6	-	-	85.4
7	-	-	91.5
8	-	-	97.3

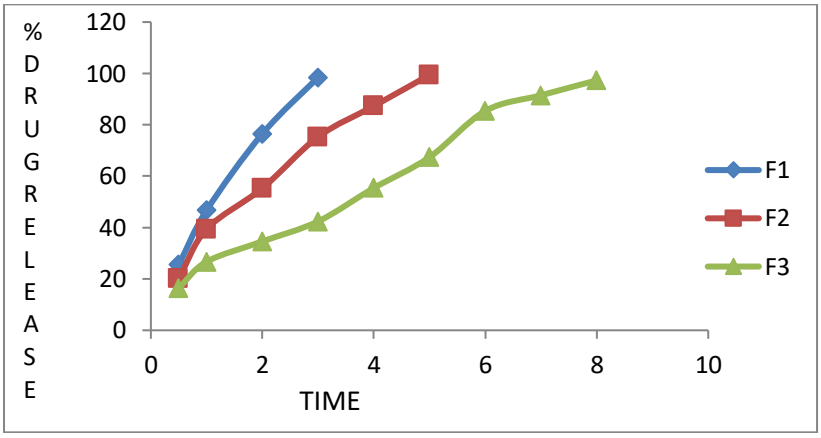

Fig no 3: Dissolution profile of Atenolol (F1, F2, F3 formulations).

Table no 10: Dissolution Data of Atenolol Tablets Prepared With Guar gum In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F4	F5	F6
0.5	17.25	16.42	14.62
1	38.26	25.73	19.86
2	54.16	36.63	22.35
3	72.01	45.04	31.45
4	88.26	58.25	39.80
5	97.10	65.33	45.25
6	-	76.41	58.24
7	-	84.84	66.73
8	-	97.80	71.34
9	-	-	75.52
10	-	-	82.17
11	-	-	87.10
12	-	-	96.10

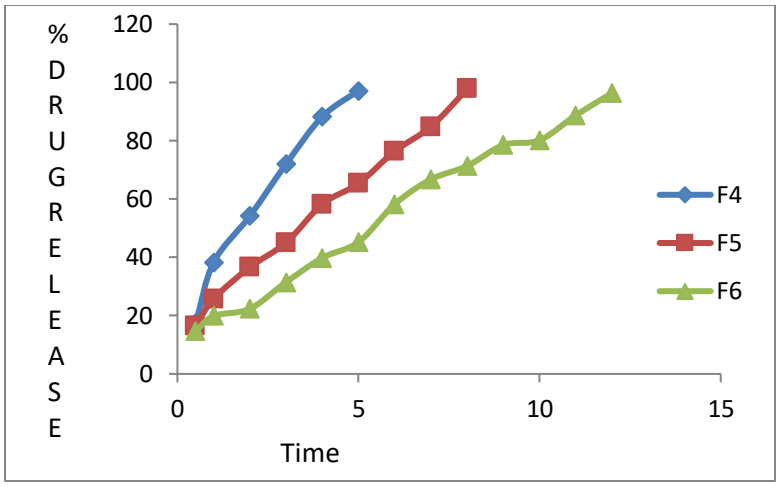

Fig no 4: Dissolution profile of Atenolol(F4, F5, F6 formulations)

Table no 11 : Dissolution Data of Atenolol Tablets Prepared With Chitosan In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F7	F8	F9
0.5	10.4	9.4	8.5
1	16.5	15.6	14.5
2	28.6	21.4	18.4
3	39.5	36.7	23.4
4	48.5	42.4	28.2
5	59.4	49.6	34.8
6	69.2	55.3	40.2
7	74.5	60.3	44.8
8	82.3	72.8	50.4
9	87.78	83.52	63.34
10	98.78	88.65	69.27
11	-	96.56	74.86
12	-	-	79.97

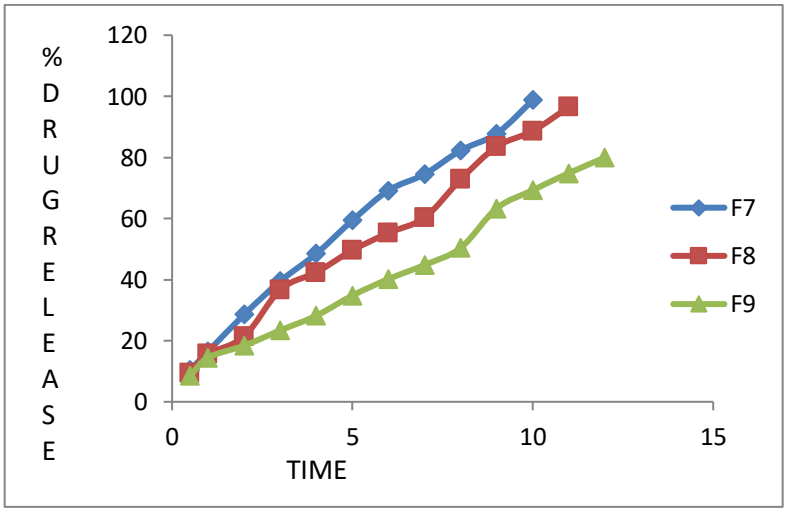

Fig no 5: Dissolution profile of Atenolol (F7, F8, F9 formulations)

From the dissolution data it was evident that the formulations prepared with Sodium CMC as polymer were unable to retard the drug release up to desired time period i.e., 12 hours. Whereas the formulations prepared with Guar gum retarded the drug release in the concentration of 180 mg showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.10% in 12 hours with good retardation.

The formulations prepared with Chitosan showed more retardation even after 12 hours they were not shown total drug release. Hence they were not considered.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table no 12: Release Kinetics Data For Optimised Formulation

CUMULATIVE(%)RELEASE Q	TIME (T)	LOG (%) RELEASE	LOG (%) REMAINING	RELEASE RATE (CUMULATIVE % RELEASE/t)	1/CUM% RELEASE	PEPPAS LOG Q/100	%DRUG REMAINING
0	0		2.000				100
14.62	0.5	1.165	1.931	29.240	0.0684	-0.835	85.38
19.86	1	1.298	1.904	19.860	0.0504	-0.702	80.14
22.35	2	1.349	1.890	11.175	0.0447	-0.651	77.65
31.45	3	1.498	1.836	10.483	0.0318	-0.502	68.55
39.8	4	1.600	1.780	9.950	0.0251	-0.400	60.2
45.25	5	1.656	1.738	9.050	0.0221	-0.344	54.75
58.24	6	1.765	1.621	9.707	0.0172	-0.235	41.76
66.73	7	1.824	1.522	9.533	0.0150	-0.176	33.27
71.34	8	1.853	1.457	8.918	0.0140	-0.147	28.66
75.52	9	1.878	1.389	8.391	0.0132	-0.122	24.48
82.17	10	1.915	1.251	8.217	0.0122	-0.085	17.83
87.1	11	1.940	1.111	7.918	0.0115	-0.060	12.9
96.1	12	1.983	0.591	8.008	0.0104	-0.017	3.9

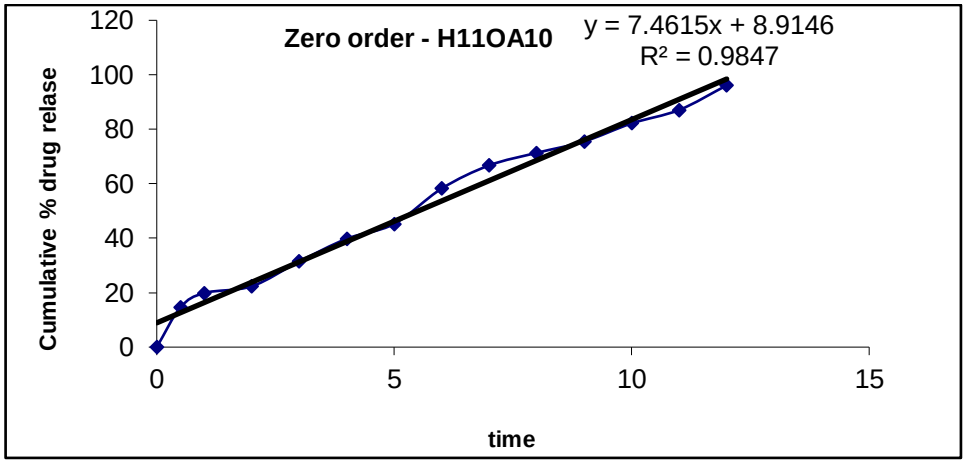

Fig no 6 : Zero Order Release Kinetics graph

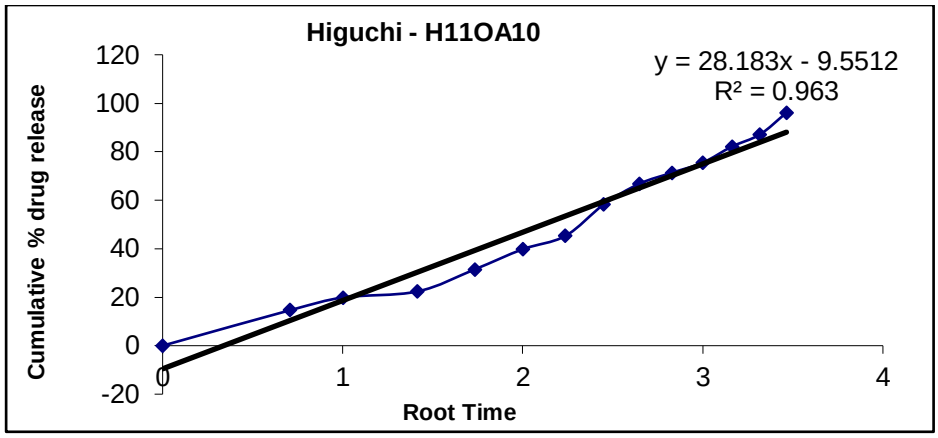

Fig no 7 : Higuchi Release kinetics graph

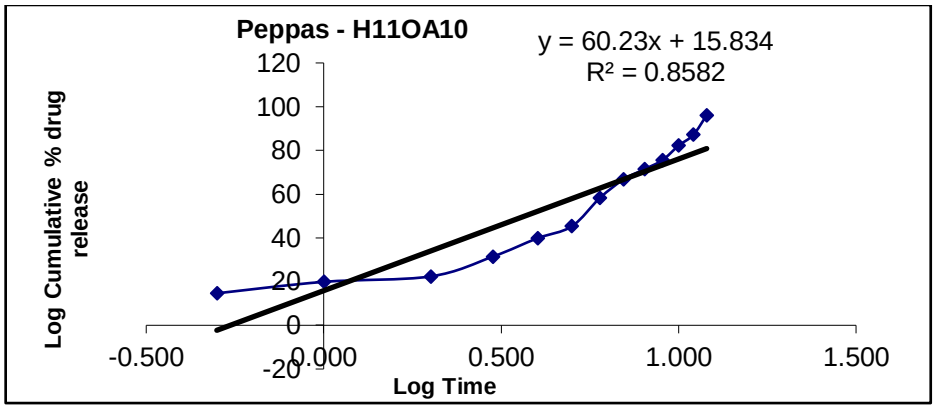

Fig no 8: Kars mayer peppas graph

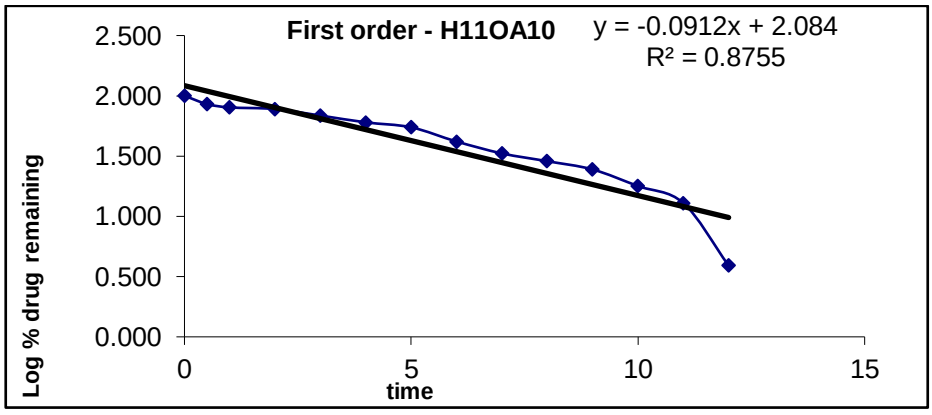

Fig no 9: First Order Release Kinetics graph

From the above graphs it was evident that the formulation F6 was followed Zero order release kinetics.

CONCLUSION

The aim of the present study was to develop sustained release formulation of Atenolol to maintain constant therapeutic levels of the drug for over 12 hrs. Various natural polymers such as Guar gum Sodium CMC and Chitosan were employed as polymers.Atenolol dose was fixed as 50 mg. Total weight of the tablet was considered as 300 mg. Polymers were used in the concentration of 60, 90 and 180 mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits.

Whereas from the dissolution studies it was evident that the formulation (F6) showed better and desired drug release pattern i.e.,96.10 % in 12 hours. It followed zero order release kinetics mechanism.

ACKNOWLEDGMENT:
Authors are thankful to the authorities of Netaji Institute of Pharmaceutical Sciences, Toopranpet, Choutuppal, Nalgonda-508252, Telangana state, India,
for providing research facilities.

REFERENCES:

1. Alfred martin, textbook of physical pharmacy, pgs 285 – 289, fifth edition.
2. Ana rita c. Duarte, christelle roy, arlette vega-gonzález, catarina m.m. Duarte and pascale subra-paternault., preparation of acetazolamide composite microparticles by supercritical anti-solvent techniques, *international journal of pharmaceutics*, volume 332, issues 1-2, 6 march 2007, pages 132-139.
3. Ranga RK, Siva P, Sajeeth CI. Formulation and evaluation of gastroretentive floating bioadhesive tablets of glipizide. *Int J Res Pharm.* 2011;2:252–60.
4. Rajput GC, Majumdar FD, Patel JK, Patel KN, Thakor RS, Patel BP, et al. Stomach specific mucoadhesive tablets as controlled drug delivery system – A review work. *Int J Pharm Biol Res.* 2010;1:30–41.
5. Acetazolamide, usp monograph and acetazolamide tablets, usp monograph, united states pharmacopoeia, 2008.
6. Barzegar-jalali m, siahi shadbad m.r, azarmi sh, barzegar-jalali a, mohammadi gh, adibkia kh., study on the release of acetazolamide from matrices containing tragacanth and acacia gums, *journal of faculty of pharmacy*, tabriz university of medical sciences, 2007.
7. Chien y.w., controlled- and modulated-release drug-delivery systems. Encyclopedia of pharmaceutical technology. New york, dekker, pgs 281-313, 1992.
8. Celine valeria liew, lai wah chan, ai ling ching and paul wan sia heng., evaluation of sodium alginate as drug release modifier in matrix tablets, *international journal of pharmaceutics*, volume 309, issues 1-2, 17 february 2006, pages 25-37.
9. Chapter 905, uniformity of dosage units and chapter 1151, pharmaceutical dosage forms, united states pharmacopoeia, 2008.
10. Fda guidance on "dissolution testing of immediate release solid oral dosage forms".
11. Fda guidance on "dissolution testing of immediate release solid oral dosage forms".
12. Gilbert s. Banker, christopher t. Rhodes, modern pharmaceutics, sustained - and controlled - release drug-delivery systems, pgs 505-506 fourth edition, 2002.
13. Gilbert s. Banker, christopher t. Rhodes, modern pharmaceutics, sustained - and controlled - release drug-delivery systems, pgs 507-508 fourth edition, 2002.
14. Gilbert s. Banker, christopher t. Rhodes, modern pharmaceutics, sustained - and controlled - release drug-delivery systems, pgs 510-511 fourth edition, 2002.
15. Gilbert s. Banker, christopher t. Rhodes, modern pharmaceutics, sustained - and controlled - release drug-delivery systems, pg 505 fourth edition, 2002.
16. Gilbert s. Banker, christopher t. Rhodes, modern pharmaceutics, sustained - and controlled - release drug-delivery systems, pg 513 fourth edition, 2002.
17. J. R. Robinson, s. P. Eriksen, theoretical formulation of sustained-release dosage forms. *J pharm sci.* 1966.
18. Juan m. Aceves, r. Cruz and e. Hernandez, preparation and characterization of furosemide-eudragit controlled release systems, *international journal of pharmaceutics*, volume 195, issues 1-2, 15 february 2000, pages 45-53.
19. Korsmeyer rw, gurny r, doelker e, buri p. Peppas na. Mechanisms of solute release from porous hydrophilic polymers. *Int j pharm.* 1983.
20. Leon shargel, susanna pong, andrew b.c., applied biopharmaceutics and pharmacokinetics, modified-release drug products, pg 515 fifth edition, 2004.
21. Leon lachman, the theory and practice of industrial pharmacy, sustained release dosage forms, pgs 430-431, third edition, 1987.
22. Leon shargel, susanna pong, andrew b.c., applied biopharmaceutics and pharmacokinetics, modified-release drug products, pg 535 fifth edition, 2004.
23. Leon shargel, susanna pong, andrew b.c., applied biopharmaceutics and pharmacokinetics, modified-release drug products, pg 534 fifth edition, 2004.
24. Leon shargel, susanna pong, andrew b.c., applied biopharmaceutics and pharmacokinetics,

modified-release drug products, pg 526 fifth edition, 2004.

25. Leon lachman, the theory and practice of industrial pharmacy, sustained release dosage forms, pgs 171-194, third edition, 1987.
26. Physicians desk reference, 62nd edition, pgs 1715-1717.
27. Raymond c rowe, paul j, sheskey and siân c owen., pharmaceutical excipients, fifth edition.
28. V. Jannin, e.pochard and o. Chambin, influence of poloxamers on the dissolution performance and stability of controlled-release formulations containing precirol ato 5, *pubmed*, 2005.