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FORMULATION AND EVALUATION OF MATRIX SUSTAIN RELEASED TABLETS OF ATENOLOL

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ABSTRACT

Matrix tablets of Atenolol were prepared utilizing natural polymer chitosan. The tablets represented sustained drug release which is required for the drugs like Atenolol with low bioavailability and low half life. The tablets can sustain the drug release which can overcome such problems. Moreover the tablets contain chitosan which also is a permeability enhancer and hence could be utilized to increase the permeability of the drugs like Atenolol with very low permeability. The tablets possess high potential for being developed as sustained release dosage forms for drugs with low permeability, bioavailability and lower half life. Oral route is one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage form Over 90% of the formulations manufactured today are ingested orally. This shows that this class of formulation in the most popular worldwide and the major attention of the researcher is toward this direction. With advanced in technology and increase in awareness, toward modification in standard tablets is done to achieve better acceptability as well as bioavailability because of which newer and more efficient tablet dosage forms are being developed.

KEYWORDS: Atenolol, HPMC 15cps, Na- CMC.

INTRODUCTION

Oral route is one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage form. Over 90% of the formulations manufactured today are ingested orally. This shows that this class of formulation in the most popular worldwide and the major attention of the researcher is toward this direction. With advanced in technology and increase in awareness, toward modification

in standard tablets is done to achieve better acceptability as well as bioavailability because of which newer and more efficient tablet dosage forms are being developed. The main reasons behind formulation of different type of the tablets are to create a delivery system that is relatively simple and in expensive to manufacture, provide the dosage form that is convenient from patients perspective and utilize an approach that is unlikely to add complexity during regulatory approval process. To understand each dosage form, tablets here are classified by their route of administration and by the type of drug delivery system they represent within route (Indian Pharmacopoeia, 2010; Indian Pharmacopoeia, 1996). (Lachman *et. al*., 1991).

Matrix Tablets

These are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid nonswellable hydrophobic materials or plastic materials (Patel et. al., 2009; Khemariya *et. al*., 2010).

Classification of Matrix Tablets

A. On the basis of Retardant Material Used: Matrix tablets can be divided into 5 types

1. Hydrophobic Matrices (Plastic matrices)
2. Lipid Matrices
3. Hydrophilic Matrices
4. Biodegradable Matrices
5. Mineral Matrices

B. Porosity of matrix based classification

1. Macroporous system
2. Microporous system
3. Non-porous system

Advantage of matrix tablets (Patel *et. al*., 2009; Goyel *et. al*., 2009)

a) Easy to manufacture.
b) Versatile effective and low cost.
c) Minimize the local and systemic side effect
d) Sustain release formulations have potential to improve the patients compliance.

e) Increase the solubility by protecting the drug from hydrolysis or other derivative change in the gastrointestinal tract,

Disadvantage of matrix tablets

a) High coast of the preparation.
b) The release rate affected by various factor such as food and rate transit through the gut.
c) The remaining matrix must be removed after the drug has been released.

Drug Release from Matrix systems

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix (Sharma *et. al*., 2009; Saikh *et. al*., 2011).

Derivation of the mathematical model to describe this system involves the following assumptions:

a) A pseudo-steady state is maintained during drug release;
b) The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;
c) The bathing solution provides sink conditions at all times.

Matrix technology

Classically matrix products exhibit first order (or perhaps square root of time) drug release charecteristics. In order to achieve zero order release characteristics, its necessary to employ specially designed material or strategies that seek to manipulate tablet structure or geometry for which combination of conventional HPMC matrix technology with upper and lower layer is necessary. This help to moderate drug release by increase in the surface area with concomitant reduction in drug concentration within the device (Patel *et. al*., 2011; Mehta *et. al*., 2011).

MATERIALS AND INSTRUMENTS

Table 1: List of materials.

Material	Procured From
Atenolol	MCW laboratories, Bhopal
HPMC 15cps	Peekay scientific center,Bhopal
Na- CMC	Peekay scientific center,Bhopal
Gar Gum	Peekay scientific center,Bhopal
Mg- Stearate	Peekay scientific center, Bhopal
Lactose	Peekay scientific center, Bhopal

Table 2: List of instruments.

Instrument	Manufactured By
Digital electronics balance	Shimadzu Aux-220
calorimetry	EI
FTIR	Elico-198
Melting point apparatus	MP-I
UV Visible spectrophotometer	UV – 1700 Shimadzu

Preparation of sample tablet

Prepared 0.01N $KMnO_4$ solution and 0.1N NaOH solution and mixed 5ml of $KMnO_4$ of the solution in 5ml of NaOH solution. Withdrawn 0.1, 0.2,0.3,0.4,0.5 ml from stock solution and added 5ml of mixture of $KMnO_4$ in NaOH solution and up to volume upto 10ml with the help of distilled water. Drug solution was scanned on UV Visible spectrophotometer to obtain λmax of the drug which was found to be 610 nm. Absorbance of different aliquots was measured at the λmax specific for that drug on UV Visible spectrophotometer **(Model: UV – 1700 Shimadzu, Japan)** at 610nm (Sinha *et. al*., 2012). Linear regressed calibration curve was constructed which has been represented in graph given table no 3.6.

Ingredients(mg)	SR1	SR2	SR3	SR4	SR5
Atenolol	50	50	50	50	50
HPMC 15cps	35	55	75	-	-
Na- CMC	70	50	30	25	30
Gar Gum	-	-	-	45	40
Mg- Stearate	3.5	3.5	3.5	305	3.5
Lactose	188	188	188	223	223
Talc	3.5	3.5	3.5	3.5	3.5
Total	350	350	350	350	350

Fig no. 1: Preliminary screening of formulation of sustained release layer of atenolol using natural, hydrophillic and hydrophobic polymers.

3.7 Standard calibration curve for Atenolol

Preparation of standard solution

For preparation of standard solution 10mg of drug was dissolved in 10 ml of distilled water (upto 10 ml). This is stock solution.

Preparation of sample

Prepared 0.01N $KMnO_4$ solution and 0.1N NaOH solution and mixed 5ml of $KMnO_4$ of the solution in 5ml of NaOH solution. Withdrawn 0.1, 0.2,0.3,0.4,0.5 ml from stock solution and added 5ml of mixture of $KMnO_4$ in NaOH solution and up to volume upto 10ml with the help of distilled water. Drug solution was scanned on UV Visible spectrophotometer to obtain λmax of the drug which was found to be 610 nm. Absorbance of different aliquots was measured at the λmax specific for that drug on UV Visible spectrophotometer **(Model: UV – 1700 Shimadzu, Japan)** at 610nm (Sinha *et. al*., 2012). Linear regressed calibration curve was constructed which has been represented in graph given table no 3.6.

Table no: Absorbance of different aliquots of Atenolol at 610 nm.

S.NO	Concentration (µg/ml)	Absorbance
1	10	0.132
2	20	0.251
3	30	0.348
4	40	0.471
5	50	0.529

Preparation of calibratiobiobn curve

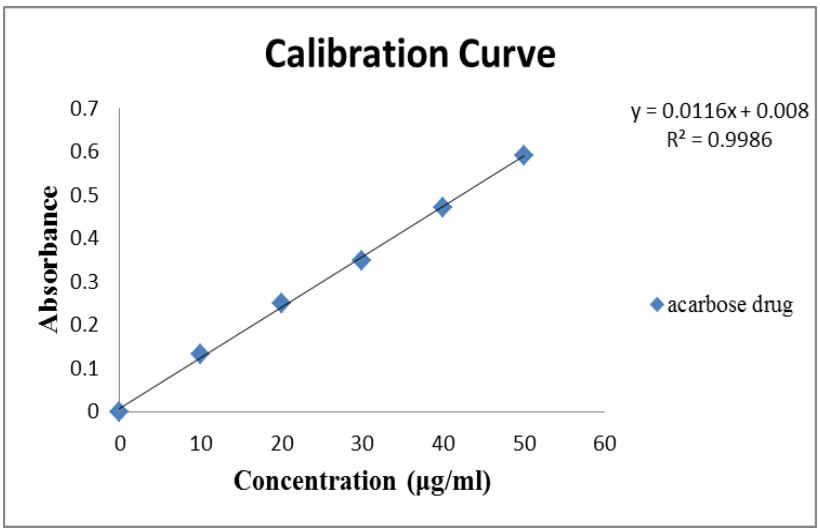


Figure no. 1: Graph showing linearly.

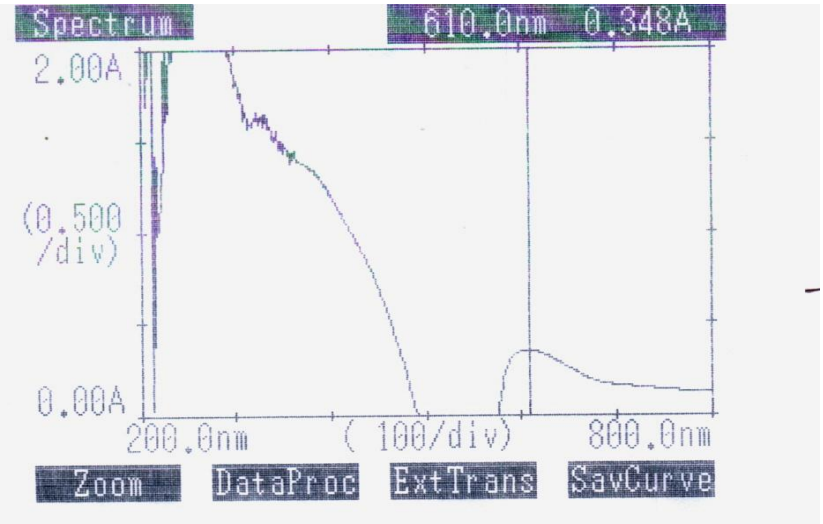


Fig no. 2: Regressed calibration curve of Atenolol.

3.8 Drug-Excipient compatibility studies

The pure drug and along with formulation excipients were subjected to compatibility studies and studies were carried out by mixing definite proportion of drug and excipients and kept in glass vials which were stored at 40°C±2°c and 75±5%RH for one month. Drug- Excipient compatibility studies have been shown in table no 5.7.

Table no. 9: Atenolol- Excipients compatibility studies.

S NO.	Drug-excpients	Initial	Condition RT40ºC/75%RH		Final
			2 week	4 week	
1	Atenolol+HPMC (1:1)	White colour	NC	NC	White colour
2	Atenolol+ Chitosan (1:1)	Off white colour	NC	NC	Off white colour
3	Atenolol+ Dicalciumphosphate (1:1)	White colour	NC	NC	White colour
4	Atenolol+Lactose (1:1)	Off white colour	NC	NC	Off white colour
5	Atenolol+MCC (1:1)	White colour	NC	NC	White colour
6	Atenolol+mgstearate (1:1)	Off white colour	NC	NC	Off white colour
7	Atenolol+Talc (1:1)	Off white colour	NC	NC	Off white colour

NC: No change

FTIR (Fourier transform infrared) Studies

I R analysis of drug was carried out at ITL Lab. (FT-IR-4100 type A).

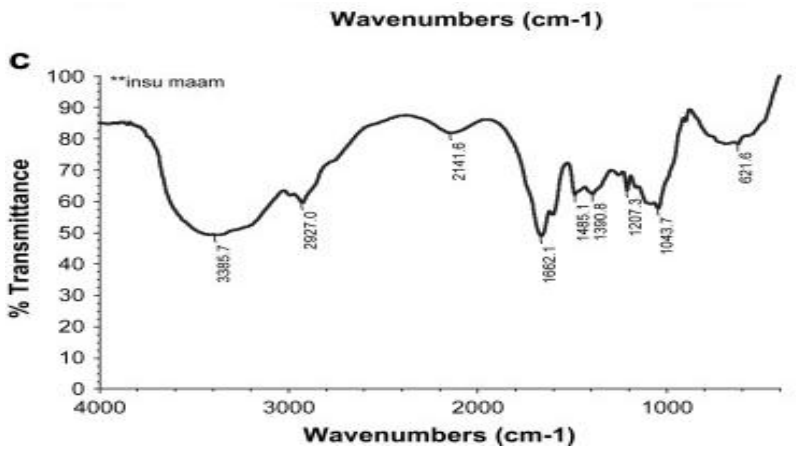
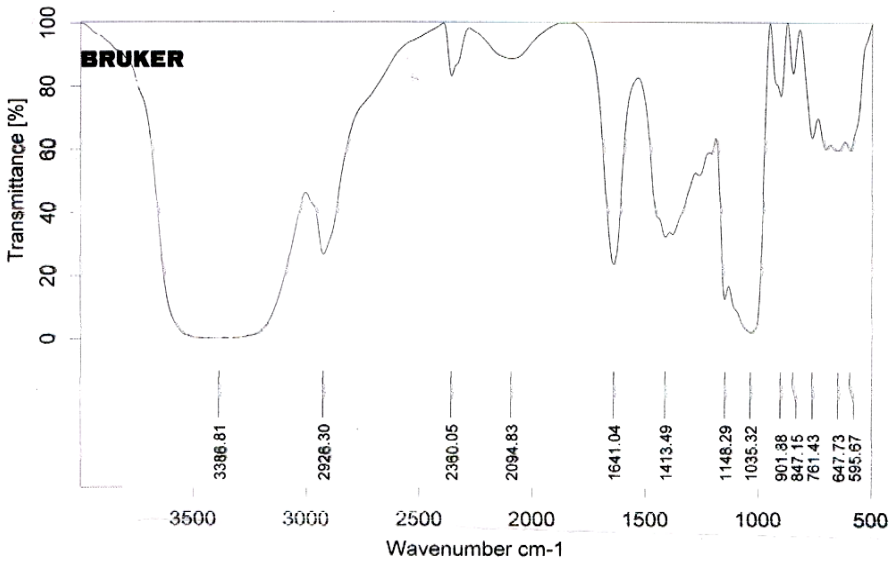


Figure no. 3: Standard IR graph of Atenolol.



Wavenumber	Abs. intensity	Rel. intensity	Width	Found if threshold <	Shoulder
3386.8084	0.002	0.998	819.3735	99.516914	0
2926.3026	0.269	0.230	79.1725	19.379833	0
2360.0535	0.833	0.167	60.3735	16.650850	0
2094.8317	0.888	0.102	283.1233	9.518667	0
1641.0440	0.239	0.653	85.8945	58.850266	0
1413.4943	0.324	0.436	504.7881	31.091932	0
1148.2850	0.129	0.061	170.8220	4.061526	0
1035.3205	0.022	0.981	196.9900	97.669777	0
901.8749	0.770	0.233	49.4244	22.936014	0
847.1526	0.843	0.151	27.9472	13.850245	0
761.4299	0.637	0.116	1061.0450	6.299144	0
647.7276	0.599	0.069	119.7672	2.664022	0
595.6672	0.599	0.396	240.7933	39.267700	0

Figure no. 4: IR graph of Atenolol.

DSC (Differential scanning calorimetry) studies

DSC was used to examine the thermal behavior of pure drug and drug additives mixtures. Compatibility studies were carried on samples of 1:1 physical mixtures of the drug (Atenolol) with polymer (chitosan). The 2 mg of sample were heated in a hermetically sealed aluminium pans in the temperature range of 25-300°C at heating rate of 10°C/min under nitrogen flow of 30 ml/min. (Kultida et al., 2011). The DSC report has been shown below.

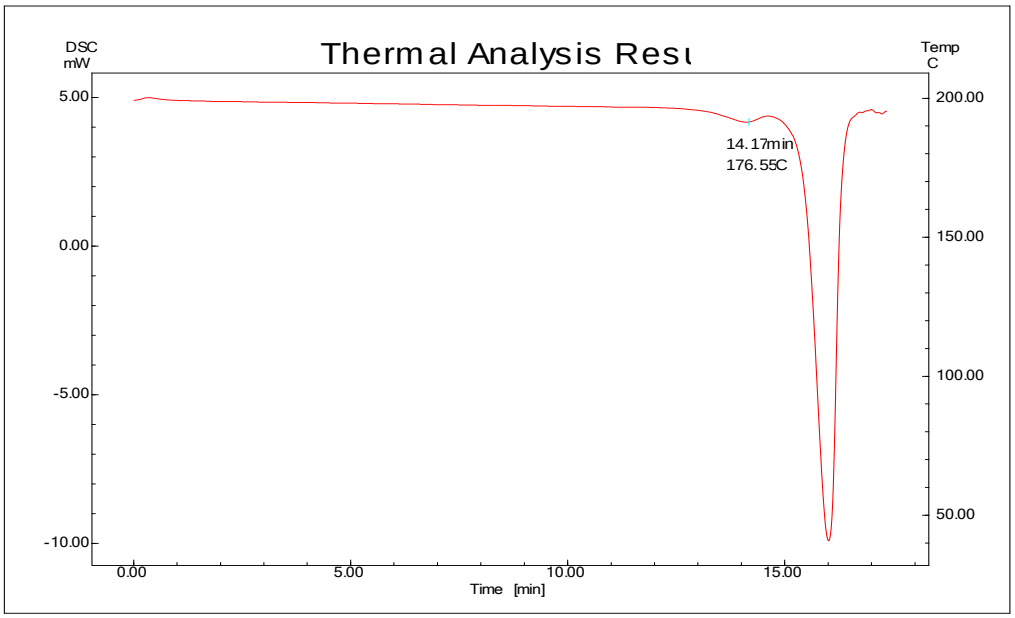


Figure no 5: DSC thermogram of Atenolol.

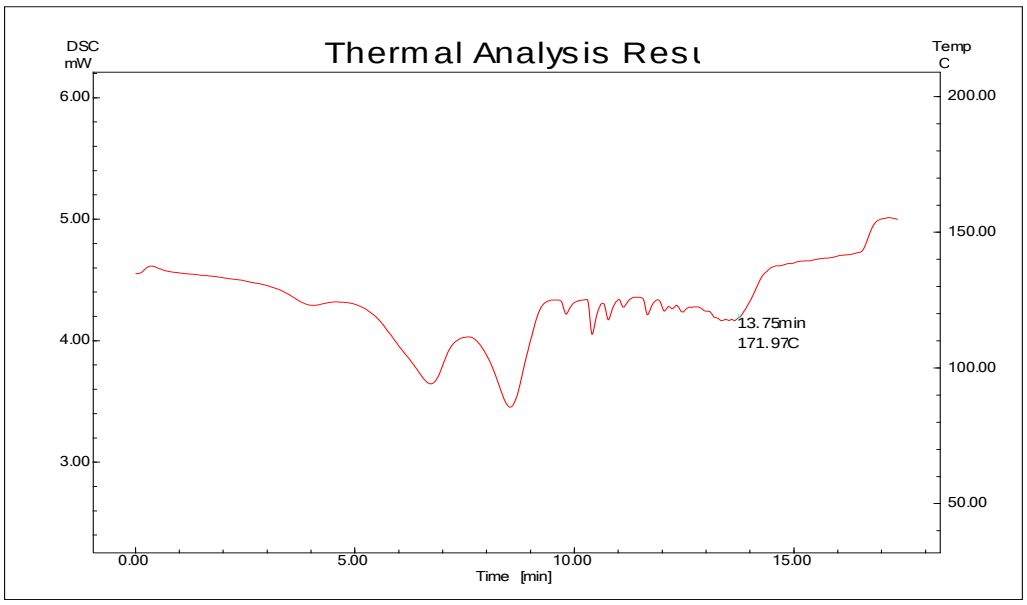


Figure no 6: DSC thermogram of drug (Atenolol) and drug with polymer (chitosan).

RESULT AND DISCUSSION

Atenolol sustained release matrix tables were prepared by wet granulation method, different formula were designed to formulate the tablets which have been mentioned in table no.9. In the matrix tablet, HPMC were selected as retardants material for the sustained released action (more than 20% drug released in 1 hrs). MCC was selected as a binder with 8%. Lactose and Dicalciumphosphate was selected as a diluents with 17.6% and Magnesium stearate was selected as a lubrication and Talc was selected as a glident. All different formulation containing different amount of HPMC, Lactose and Dicalciumphosphate were prepared to

formulate the tablets. Angle of repose was found to be between 28.2°- 35.24°, where some of the blend fell between the specified limit of 20°-30° representing good flow. Bulk density was found to be between 0.52 – 0.64 g/ml. Tapped density was found to be between 0.60 – 0.76 g/ml. Carr's index (%) was found to be in the range of 11.66 – 16.66, all the powder blend are well within the specification limit. Hausner's ratio was found to be between 1.13 - 1.2. With this the powder blends were found to be free flowing material and showed suitability to be compressed as tablets of expected weight.

The tablets prepared out of the optimized formula was taken into consideration for further in vitro dissolution drug release study. In- vitro dissolution studies of the sustained release matrix tablets of Atenolol were performed using USP type II dissolution apparatus (paddle) at 50 rpm. The study was performed for 12 hours, and percentage drug release was calculated at 1 hours time intervals. The drug release profile were characterized by an initial burst effect (more than 18% drug release in 1 hrs) followed by a sustained release thereafter. The formulation F-2 contained chitosan which might have sustained the release since it is also known for its polymeric sustaining effect. The formulation F-2 gave 89.57±0.24% of the drug release in 12 hrs of study. This is in fact true for the polymeric tablets since the surface drug gives a burst effect thereby releasing a amount of drug at once and since polymer like chitosan and HPMC are present which provide matrixing to the tablet, the further release is sustained. The drug release also resembles a higuchi pattern which indicates sustained drug release from the matrix tablets. This is again due to the presence of the polymer like chitosan and HPMC.

Summary and Conclusion

Matrix tablets of Atenolol were prepared utilizing natural polymer chitosan. The tablets represented sustained drug release which is required for the drugs like Atenolol with low bioavailability and low half life. The tablets can sustain the drug release which can overcome such problems. Moreover the tablets contain chitosan which also is a permeability enhancer and hence could be utilized to increase the permeability of the drugs like Atenolol with very low permeability. The tablets possess high potential for being developed as sustained release dosage forms for drugs with low permeability, bioavailability and lower half life.

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