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Formulation and evaluation of sustain released matrix tablet of atenolol

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ABSTRACT

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. The aim of present investigation was to develop matrix tablets of atenolol using different polymers. Atenolol matrix tablets were prepared by direct compression and wet granulation method using different polymers. All the formulations were evaluated for weight variation, thickness, hardness, friability and dissolution. Tablets of atenolol were prepared utilizing natural polymer chitosan. 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.

Keywords: Atenolol, Sustained release Matrix tablets, Direct compression, Wet granulation method.

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1. INTRODUCTION

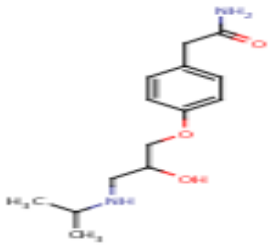
Oral route is one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage form [1]. Over 90% of the formulations manufactured today are ingested orally. This shows that this class of formulation in the most popular worldwide and the major attention of the researcher in 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 patient's 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 [2-8].

Tablet ingested orally are meant to be swallowed intact along with sufficient quantity of the potable water. Exceptions are chewable tablet and oral dispersible tablets. Standard compressed tablets this class includes tablets like, multiple compressed tablets, compression coated tablets, layered tablets, modified released tablets etc [9-12].

In the present work, Atenolol will be utilized with a natural polymer chitosan and HPMC to formulate tablets against hyperglycemia. Atenolol has low bioavailability as is evident from the available literature although it is freely soluble in water, because it is a BCS class III drug which is known for their high solubility but low permeability and hence low bioavailability. Natural polymer chitosan is known for its permeability enhancement through mucosal membrane and will enhance drug absorption. This in turn will reduce the dose size and dosing frequency and subsequently will result in result in efficient drug therapy and patient compliance [13-20].

2. EXPERIMENTAL WORK

2.1. Drug profile

Name	**Atenolol**
Description	A cardioselective beta-adrenergic blocker possessing properties and potency similar to propranolol, but without a negative inotropic effect.
Structure	
Brand name mixtures	
Categories	Antihypertensive Agents Adrenergic Agents Adrenergic beta-Antagonists Sympatholytics Antiarrhythmic Agents Anti-Arrhythmia Agents
CAS number	29122-68-7
Chemical Formula	$C_{14}H_{22}N_2O_3$
IUPAC Name	2-(4-{2-hydroxy-3-[(propan-2-yl)amino]propoxy}phenyl)acetamide
Taxonomy	
Kingdom	Organic
Classes	Phenols and Derivatives Ethers Phenethylamines Anisoles
Substructures	Hydroxy Compounds Aliphatic and Aryl Amines Phenols and Derivatives Amino Ketones Ethers Benzene and Derivatives Carbamates and Derivatives Amino Alcohols Phenethylamines Aromatic compounds Anisoles Carboxamides and Derivatives Carboxylic Acids and Derivatives Alcohols and Polyols Phenyl Esters
Pharmacology	
Indication	For the management of hypertension and long-term management of patients with angina pectoris
Pharmacodynamics	Atenolol, a competitive beta(1)-selective adrenergic antagonist, has the lowest lipid solubility of this drug class. Although it is similar to metoprolol, atenolol differs from pindolol and propranolol in that it does not have intrinsic sympathomimetic properties or membrane-stabilizing activity. Atenolol is used alone or with chlorthalidone in the management of hypertension and edema.
Mechanism of action	Like metoprolol, atenolol competes with sympathomimetic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart and vascular smooth muscle, inhibiting sympathetic stimulation. This results in a reduction in resting heart rate, cardiac output, systolic and diastolic blood pressure, and reflex orthostatic hypotension. Higher doses of atenolol also competitively block beta(2)-adrenergic responses in the bronchial and vascular smooth muscles.
Absorption	Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces.
Protein binding	Plasma protein binding is 6-16%
Metabolism	Hepatic (minimal)
Route of elimination	Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Unlike propranolol or metoprolol, but like nadolol, atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal

	excretion.
Half life	6-7 hours
Toxicity	LD_{50}=2000-3000 mg/kg(orally in mice). Symptoms of an atenolol overdose include a slow heart beat, shortness of breath, fainting, dizziness, weakness, confusion, nausea, and vomiting.
Properties	
State	Solid
Melting point	146-148Oc
Experimental Properties	**Property** / **Value** / **Source** water solubility / 13.5 mg/mL / PhysProp logP / 0.5 / PhysProp Caco2 permeability / -6.44 [ADME Research, USCD] / BiGG
Drug Interactions	
Food Interactions	Consult your doctor before taking large amounts of Vitamin K (Green leafy vegetables). Take 30-60 minutes before meals, take at the same time each day.

3. Preformulation Study

Pre-formulation may be described as a phase the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms [21-25]. Ideally the pre-formulation phase begins early in the discovery process such that the appropriate physical and chemical data is available to aid the selection of the new chemical entities that enter the development process **Table 1** [26-33].

3.1 Organoleptic property:

Table 1: Description of the drug (Atenolol).

S NO.	Description	Atenolol drug
1	State	Solid
2	Colour	White
3	Odour	Odourless
4		Amorphous powder

3.2 Solubility studies:

Determination of solubility of drug by visual observation. An excess quantity of Atenolol was taken separately and add in 10 ml of different solutions. These solutions were shaken well for few minutes. Then the solubility was observed and observations are shown in the **Table 2**-

Table 2: Solubility studies of drug in different solvents.

S NO.	Solvents	Solubility of Atenolol
1	Water	Freely soluble
2	Methanol	Soluble
3	Acetone	Insoluble
4	Alcohol	Sparingly soluble
5	Methylene chloride	Practically insoluble

3.3 Melting point:

Melting point of the drug was determined by the capillary method using melting point apparatus. It can be performed by filling of the drug in capillary tube by pressing the open end gently into pure drug sample and packed by tapping the bottom of the capillary on a hard surface so that the drug pack down into the bottom of the tube. The apparatus was started and the temperature was noted at which the drug method. And dip the thermometer in this liquid paraffin and the note the point which drug started melting in the capillary. Melting point of drug has been shown in the **Table 3**.

Table 3: Melting point of drug

Drug	Specification	Observation
Atenolol	146-148^{o}C	147-149^{o}C

3.4 Standard calibration curve for Atenolol:

Preparation of standard solution:

10 mg of drug was weighed accurately and transferred to 10 ml of volumetric flask. Then 0.1N HCL was added to dissolve the drug completely. The volume was made up to 10 ml with 0.1N HCL .The prepared sample was 1000µg/ml. 1ml of above solution was then transferred to another 10-ml volumetric flask and diluted it upto the mark with 0.1 N HCL. This sample was 100µg/ml. Then 1 ml of above solution was then transferred to another 10ml volumetric flask and diluted it upto the mark with ethanol. This sample was 10µg/ml. Now scanned this sample by UV (**Figure 1**).

3.5 Standard Calibration Curve

Preparation of standard calibration curve of Atenolol in HCL

Preparation of stock solution

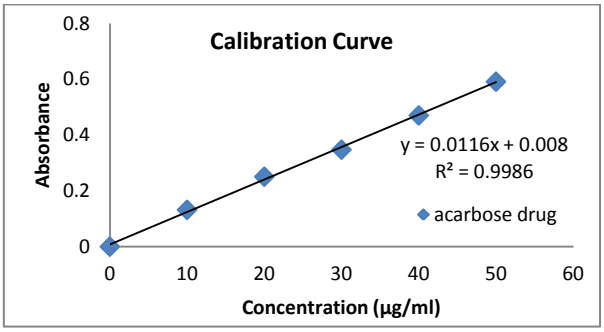
10 mg of drug was weighed accurately and transferred to 10 ml of volumetric flask. Then 0.1N HCL was added to dissolve the drug completely. The volume was made up to 10 ml with 0.1N HCL .The prepared sample was 1000µg/ml. 1ml of above solution was then transferred to another 10-ml volumetric flask and diluted it up to the mark with 0.1 N HCL. This sample was 100µg/ml (**Figure 1**).

Preparation of dilution from stock solution

For the dilution 0.2ml of above stock solution was taken and diluted it upto 10ml with 0.1N HCL to get concentration of 2 µg/ml an in the similar way dilution of 4, 6. 8and 10 µg/ml was obtained. The absorbance was measured by UV visible spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve **Table 4**.

Table 4: Absorbance of different aliquots of Atenolol at 225nm

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



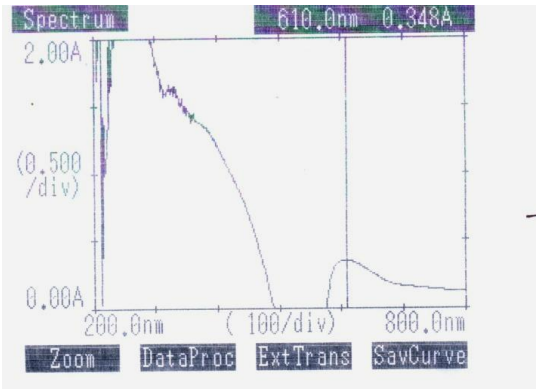


Figure 1: Graph showing linearly regressed calibration curve of Atenolol

Formulation of Matrix Tablet:

Sustained release Matrix Tablet of Atenolol with other excipient was prepared by wet granulation method. The weight of Atenolol was kept constant in all the prepared tablet at 350mg/tablet. Accurately weight quantity of polymer (for particular formulation), Atenolol, Lactose were taken in mortar and mixed. Starch paste 6% was added to the dry blend gradually with constant kneading to ensure a homogenous mass (**Table 5**).

The Dough mass was passed through a # 14mesh sieve. Then granules were dried at 50^0 and dried granules were lubricated with talc and magnesium stearate and compressed into tablet using 10mm punches. Each tablet contain 50mg of Atenolol.

The drug matrix ratio was varied to obtain the matrix tablet of polymer concentration.

During this evaluation, possible interactions with various inert ingredients intended for use in final dosage form is also considered in the present study. The following data must be considered (Goyal *et. al*., 2009).

Table 5: Preliminary screening of formulation of sustained release layer of Atenolol using natural, hydrophilic and hydrophobic polymers

Ingredients(mg)	F1	F2	F3	F4	F5
Atenolol	50	50	50	50	50
HPMC 15cps	35	55	75	-	-
Chitosan	70	50	30	25	30
Gar Gum	-	-	-	45	40
Mg- Stearate	3.5	3.5	3.5	3.5	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

4. Evaluation of Pre-compression Parameters

4.1. Angle of repose

The angle of repose was determined by fixed funnel method. A funnel was kept vertically in a stand at a specified height above a paper place on a horizontal surface. The funnel was closed and a granule was filled in funnel. Then funnel was opened to release the granules on the paper to form a smooth conical heap. The height and radius of heap was measured and the angle of repose was calculated by using the following formula (**Table 6**).

$$Ø = \tan^{-1} h/r$$

Where Ø = Angle of repose, h =height of heap and r = radius

Table 6: Relationship between Angel of repose (Ø) and flow properties.

Angle of repose (Ø)	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

4.2. Bulk Density

A known amount of granules was transferred in to a 25-ml measuring cylindrical carefully level the granules without compacting and measure the bulk volume. The bulk density was determined by using the formula

Bulk density = Weight of granules/ bulk volume

4.3. Tapped Density:

Tapped density was determined by digital bulk density apparatus. A known amount of granules was transferred into the measuring cylinder and tapped up to 100 times and measure the tapped volume. The tapped density was determined by using the formula.

Tapped Density = Weight of granules / tapped volume

4.4. Compressibility Index (Table 7)

Compressibility Index=

[Tapped density- Bulk density/Tapped density] ×100

Table 7: Practical Consideration of Compressibility Index

% Compressibility index	Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very Poor
>40	Very

4.5. Hausner's Ratio (Table 8)

Hausner's Ratio was determine by following formula

Hausner's Ratio= Tapped density / Bulk density

Table 8: Practical Consideration of Hausner's Ratio

Hausner's ratio	Flow
<1.25	Good
>1.25	Poor
1.25-1.5	Very poor

4.6. Hardness

In the measurement of hardness, the crushing strength of the tablets is measured. It gives the table breaking force and the strength of the physical tablets are represented by the hardness. Hardness was measured using a Pfizer hardness tester. Hardness to be measured of ten tablets. The V was measured in Newton. The average hardness, relative standard deviation, standard deviations were reported. The hardness of the tablets were measured start and between the compression.

4.7. Weight variation test

To study weight variation, 20 tablet of each formulation were collected randomly during compression and weight using an electronic balance to obtain average weight of each tablet. Also the individual tablet was weighted.

Limit: Weight of individual tablet should be in the limit of average weight ±5%

4.8. Friability:

The test was carried out using ROCHE FRIABILATOR. Ten tablets were taken and carefully dedusted prior to testing the tablets were weighted accurately, and placed the tablets in drum. The drum was allowed to be rotated 100 times, and after that the tablet were removed. Removed loose dust from the tablets as before, and weighted accurately.

The % loss was determined by using following formula:

$$\%\text{Weightloss} = \frac{\text{Initial Weight-Final Weight}}{\text{Initial Weight}}$$

A maximum loss of mass not greater than 1.0%is considered acceptable

4.9. Uniformity of drug content (Table 9)

Five tablets were weighed individually and powdered. The powdered equivalent to average weight of tablet was weighed and drug was extracted in 0.1N HCL. Undissolved material was filtered out. Fitrate was analysed in uv spectrometer at 225nm after suitable dilution. Absorbance value was substituted in the equation of standard curve of Atenolol determined earlier.

Drug content was calculated by following formula.

Table 9: Evaluation of Precompression parameters

Parameters	F1	F2	F3	F4	F5
Angle of Repose(n=3)	28.2	28.5	31.1	33.6	35.24
Bulk Density(n=3)	0.52	0.54	0.56	0.60	0.64
density(n=3)	0.60	0.59	0.65	0.70	0.76
Carss's Index(%)(n=3)	11.66	12.0	14.47	15.11	16.66
Hausner's Ratio(n=3)	1.13	1.14	1.16	1.18	1.2
Thickness(mm)(n=20)	2.44	2.46	2.51	2.52	2.56
Friability (%)(n=10)	0.2	0.28	0.31	0.46	0.5
Weight Variation (%)(n=20)	2.20	2.22	2.26	2.28	2.3

4.10. In- vitro Dissolution Study

In-vitro drug release study of tablet was performed in USP dissolution apparatus type -2 (Paddle). The dissolution test was performed using 900 ml of 0.1 N HCL at 37°C.

0.5 °C with 50 rpm. A sample (3 ml) was withdrawn from the dissolution apparatus and volume equivalent to the amount of the sample withdrawn was replaced with fresh dissolution medium. The sample was filtered and suitable concentration with 0.1 N HCL. Absorbance of these solutions was measured at 225nm using UV spectrophotometer. Cumulative percentage drug dose was calculated using an equation obtained from standard curve.

4.11. In- Vitro Drug Release Kinetic Study

Kinetic model had described drug dissolution from solid dosage form were the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablet, drug release data was analyzed according to zero order, first order, Higuchi square root, Korsmeyer, Peppas model. The regression coefficient R^2 value nearer to 1 indication the model fitting of the release mechanism (**Table 10**).

Table 10: Release kinetic study

Time	% Cumulative Drug Release				
(hr)	F1	F2	F3	F4	F5
0.5	08.23	07.14	07.24	08.23	07.23
1	12.32	18.23	11.45	10.45	10.45
1.5	26.23	22.42	24.23	23.76	31.23
2	38.45	40.32	45.23	44.23	48.23
3	52.34	54.11	61.21	65.71	50.56
4	61.23	67.33	68.11	82.34	55.00
6	70.55	71.13	72.13	83.00	56.00
8	81.00	85.10	7523	83.21	57.25
12	83.21	89.57	79.26	83.50	57.85

5. RESULT AND DISCUSSION

In the matrix tablet, HPMC and chitosan were used as retardant materials for sustained release action. Preformulation of the drug was carried out with respect to different parameters. Drug was separately tested for their physicochemical characteristics. Melting point of Atenolol was found to be 146-148°C respectively. Similarly solubility studies were conducted for the drug in different solvents. It was found that the drug was freely soluble in water, soluble in methanol, insoluble in acetone, sparingly soluble in alcohol and practically insoluble in methylene chloride.

UV spectroscopy of the drug was also performed and the drug was scanned on different wavelengths. λ_{max} of Atenolol was found to be 225 nm. All the values calculated were found to be concordant which that of the standard values reported in Standard Pharmacopoeial books. It was observed that there was no significant shift in the melting point of the drug when taken alone or in combination with that of polymer used. On the basis of the compatibility studies, it was found that drug is compatible with all other excipients selected for the study and hence can be used in combination for the preparation of the tablets.

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.1.5. In the matrix tablet, HPMC were selected as retardants material for the sustained released action (more than 20% drug released in 1 hrs). Starch past was selected as a binder with 6%. Lactose was selected as diluents with 17.6% and Magnesium stearate was selected as lubrication and Talc was selected as a glident. All different formulation containing different amount of HPMC, Lactose 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.

It was observed that hardness of the all sustained released tablets were measured Pfizer hardness tester. The thickness of all SR matrix tablets was measured by vernier caliper and was ranged between 2.44-2.56. On the basis of the parameters viz. weight variation, hardness and friability the best formula was selected. F-2 formulation was found to be the best formula and hence was taken as the optimized formula. Tablets prepared out of formula F-2 represented a weight variation of 2.22±0.11, hardness of 5.3±0.32, friability of 0.28±0.01. The tablets prepares from lactose as an excipient acquired a sticky nature and hence were not taken for consideration for further study.

The tablets prepared out of the optimized formula were 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 matrix 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.

6. SUMMARY & 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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