FORMULATION, EVALUATION AND OPTIMIZATION OF FAST DISINTEGRATING ATENOLOL MALEATE 100 MG. TABLET BY USING SUPER DISINTEGRANTS

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Abstract.

The most common preferred route is oral rout of administration. Today oro-dispersible tablet from novel drug delivery system gain importance from patient. Which is administer to the patient to control the attack of angina or hypertension, but for immediate control, Oro-dispersible tablet is oral solid dosage form in which the tablet gets dispersed in oral cavity in absence of water. Various manufacture are formulated this formulation by various method. The most importance thing in this formulation are masking of taste of drugs. Generally oro-dispersible tablet are prepared by direct compression method. Dry granulation, wet granulation, Spry drying is the various methods for preparation of oro-dispersible tablet. Oro-dispersible tablet generally contains filler, glidant, anti-adherent super disintegrate, sweetener and resins. Evaluation parameter includes hardness, friability, wetting time, moisture uptake, disintegration test, and dissolution test. Wetting time, Disintegration time, and Dissolution test is directly proportional to the hydrophobic ingredient added for lubrication, anti-adherent, Glidant action. These hydrophobic ingredient are Magnesium Stearate. To oppose the action of magnesium stearate, hydrophilic additives are incorporated viz Sodium lauryl sulphate, Cross carmillose sodium, sodium starch glycol ate are added.

Keywords: Oro-dispersible tablet, wetting time, Dissolution test

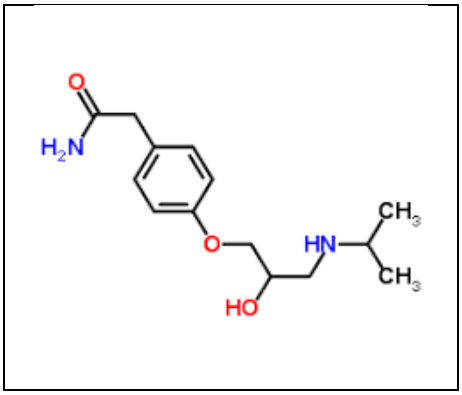
1. INTRODUCTION

Quality are built in the pharmaceutical formulation by design the formulation. The total quality in the product are known as Total Quality Management. To gain this goal of optimized quality product, the knowledge obtained from pharmaceutical development studies and manufacturing provides the scientific background. Although it is based on different pharmaceutical studies, but it has its aim that it minimizes the end product testing and Increases the chances of regulatory acceptance by different pharmaceutical governing bodies. The aim and objective of the present study is to develop and evaluate oro dispersible tablet of Atenolol Maleate and enhance the onset of action of Atenolol Maleate and also to study the influence of excipients on the physical characteristics of the tablets by applying two level three factor factorial designs taking Atenolol Maleate as model drug which is used in the treatment of the Hypertension, Angina Pectoris, cardiac arrhythmia. The study of this formulation to select the best possible excipient combination of semi synthetic & natural and artificial additives to development of formulation. Super disintegrants viz Cross carmillose sodium are added to formulate the dispersible tablets and other Additives, diluents and disintegrants used. Finally the effect of the additives or various excipients ratio and super disintegrants on various properties of the tablet were also determined.

2. MATERIAL AND METHOD

2.1 API Structure Characterization:

Formula : $C_{14}H_{22}N_2O_3$
Molar mass : 266.3361
Physical Properties : It is white crystalline powder.



Structure and IUPAC Name of Atenolol:

2-(4-{2-hydroxy-3- [(propan-2-yl) amino] propoxy} phenyl) acetamide

Atenolol is a cardio selective beta-blocker used in a variety of cardiovascular conditions.

Sir James Black, a Scottish pharmacologist, pioneered the use of beta-blockers for the management of angina pectoris in 1958 for which he received the Nobel Prize. Beta-blockers quickly became popular in clinical use and where subsequently investigated for use in myocardial infarction, arrhythmias, and hypertension during the 1960s. Later they continued to be investigated for use in heart failure throughout the 1970-1980s. Atenolol itself was developed early on in this history by Alvogen Malta under the trade name Tenormin and received FDA approval in September, 1981.

2.2 Drug and Excipients studies:

S. No.	Drug+ Excipients	Duration (months)	Result
1	Atenolol Maleate+ Starch DC	6 Months	Stable
2	Atenolol Maleate+ Mannitol	6 Months	Stable
3	Atenolol Maleate + Lactose	6 Months	Stable
4	Atenolol Maleate + Aspartame	6 Months	Stable
5	Atenolol Maleate + Talcum	6 Months	Stable
6	Atenolol Maleate + Magnesium Stearate	6 Months	Stable
7	Atenolol Maleate + Cross carmillose sodium	6 Months	Stable
8	Atenolol Maleate + Sodium Starch Glycolate	6 Months	Stable
9	Atenolol Maleate + Methyl Paraben	6 Months	Stable
10	Atenolol Maleate + Propyl Paraben	6 Months	Stable
11	Atenolol Maleate + Sodium Lauryl Sulphate	6 Months	Stable

2.3 MATERIAL: MATERIAL AND THEIR USE WITH OBTAINED SOURCES:

Sr. No.	Material	Uses of Ingredients	Sources
1	Atenolol Maleate	Active Pharmaceutical Ingredients	J.B. chemical. Ankaleshwer Bharuch. Gujrat
2	Starch DC	Diluents	Pacific India. A farmacutical Exporter, Villalge: Dhana, Baghbania. Nalagarh. Solan. Himachal Pradesh
3	Lactose	Diluents	
4	Mannitol	Sweetener	
5	Aspartame	Sweetener	
6	Talcum	Glidant	
7	Magnesium Stearate	Antiadhrants	
8	CCS	Super disintegrants	
9	SSG	Lubricants	
10	Methyl Paraben	Preservative	
11	Propyl Paraben	Preservative	
12	Sodium Lauryl Sulphate	Disintegrants	

2.4 Preparation of Atenolol Maleate 100 mg tablet by direct compression method.

Formulation table.

Sr. No.	Ingredients	C1 (mg)	C2 (mg)	C3 (mg)	C4 (mg)	C5 (mg)
1	Atenolol Maleate	100	100	100	100	100
2	Starch DC	120	123	126	129	132
3	Lactose	95	95	95	95	95
4	Mannitol	90	90	90	90	90
5	Aspartame	18	18	18	18	18
6	Talcum	15	15	15	15	15
7	Mag. Stearate	15	15	15	15	15
8	CCS	20	17	14	11	8
9	SSG	12	12	12	12	12
10	Methyl Paraben	4	4	4	4	4
11	Propyl Paraben	1	1	1	1	1
12	SLS	10	10	10	10	10

	Total weight	500 mg	500 mg	500 mg	500 mg	500 mg

All the ingredients viz active ingredients, additives were passed through 60 # sieve separately, Magnesium stearate & Talc through 40 #. Then the ingredients were weighed and mixed in double dilution order or Geometric mixing and tablets were compressed with 9 mm sizes biconvex round punch to get tablet using Rimeck double rotary Compression Machine.

3. Post compression Parameters:

3.1 Thickness of compressed tablet.

The thickness of the compress tablets of Atenolol Maleate 100 mg was determined using a Digital Vernier calliper. Ten tablets from each type of formulation were used and average values were calculated. It is expressed in mm.

3.2 Hardness

The resistance of tablets during passing through hopper, Blister Cartooning, breakage, under conditions of storage, transportation and Handling before usage are directly proportional to its hardness. For each formulation, the hardness of 6 tablets was determined using the Pfizer Hardener Tester and Monsanto hardness tester. The tablet was held along its oblong axis in Between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob in Monsanto tester and in case of Pfizer directly force applied until the tablet breakdown in the pieces. The reading the both cases at this point was noted.

3.3 Friability Test:

Friability Test is generally used the measure of tablet strength. Roche Friability tester was used for testing the friability using. In This test subjects a number of compressed tablets to the combined effect of shock abrasion by utilizing a circular plastic chamber which revolves at a speed of 25 revolution per minutes for 4 minutes i.e. 100 rpm, dropping the compressed tablets of Atenolol Maleate to a distance of 6 inches in each revolution. A sample of weighed 6 compressed tablets of was placed in Roche friability chamber which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then de-dusted, and broken tablet are removed and reweighed. A loss of less than 1 % in weight in generally considered acceptable according to Pharmacopeia. Percentage friability (% F) was calculated as follows:

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

3.4 Weight variation test:

As per the limitation of Pharmacopeia to find out weight variation test, 20 tablets of each type of formulation were weighed individually using single pan balance or an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

Specifications for tablets as per Indian Pharmacopeia. 1996.

S. No.	Percentage Deviation	Average Weight of Tablet (mg)
1	10	80 mg or less
2	7.5	More than 80 mg but less that 250 mg
3	5	250 or more

3.5. Uniformity of drug content:

Five tablets of each compression formulation are weighed and crushed in mortar Pastel and powder, or crushed equivalent to 10 mg of Atenolol Maleate was weighed and dissolved in 100 ml of 0.1N Hydrochloric acid (pH 1.2). This was the stock solution from which 0.2 ml sample was withdrawn and diluted to 10 ml with 0.1N Hydrochloric acid. The absorbance was measured at wavelength 237.5 nm using double beam Ultra Violet Visible spectro photometer. Content uniformity of the drug was calculated using formula.

% Purity of the Drug = 10 C (Au / As) -------

Where, C = Concentration,

Au and As=Absorbance's obtained from unknown preparation and standard Preparation.

3.6. Wetting time:

This method is applied to calculate tablet wetting time. A piece of tissue paper or absorbent folded twice was placed in a small Glass Petri dish having the diameter 6.5 cm, containing 10 ml of water. Compressed tablet was placed on the paper, and the time record or note for complete wetting. Three trials for each batch were performed and standard deviation are calculated

3.7. In vitro disintegration time:

The process of breakdown or convert the tablet into pieces or into smaller particles is called as disintegration. The in vitro Disintegration time of a tablet was determined using disintegration test apparatus as per Indian Pharmacopeia specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using distilled water maintained at 37° ± 2°C which is similar to body temperature. The assembly should be raised and lowered between 30 cycles per minute in the 0.1 N HCL or Distilled water maintained at 37° ± 2°C. The time in seconds taken for complete disintegration of the tablet.

In this disintegration test if the tablet are adhere to the 10 # sieve then continue the test till all tablet are completely disintegrated.

3.8. In vitro dissolution test:

Rate of dissolution are studied by using USP type-II apparatus having 50 rpm, using 900ml of 0.1 N Hydrochloric acid as dissolution solvent. Temperature of the dissolution medium was maintained at 37 ± 0.5°C. The sample of dissolution medium was withdrawn at every 5 min interval and first filtered. The absorbance of filtered solution was measured by using Ultra Violet spectrophotometric method at 237.5 nm and concentration of the drug was determined from standard calibration curve.

In vitro drug release studies details:

1. Dissolution test apparatus
2. 0.1 N HCL as Dissolution medium
3. 900 ml Dissolution medium volume
4. 37 ± 0.5°C as std. Temperature
5. 50 rpm Speed of basket paddle
6. 5 min sampling intervals
7. 10 ml volume Sample withdraw
8. 237.5 nm Absorbance measured

4. Result and Discussion:

4.1 Pre compression Parameter and studies

S. No.	Formulation code	Angle of Repose	Bulk density (weight/ml)	Taped Density (weight/ml)	Flow Time (100 gm)
1	C1	30.32±0.70	0.43±0.02	0.50±0.04	32 sec.
2	C2	29.10±0.58	0.42±0.03	0.48±0.02	26 sec
3	C3	27.86±0.67	0.44±0.03	0.47±0.04	25 sec.
4	C4	28.44±0.45	0.43±0.02	0.46±0.02	28 sec.
5	C5	24.40±0.65	0.43±0.03	0.48±0.02	27 sec.

4.2 Post compression Parameter Studies.

Formulation code	Hardness (KG/cm^2)	Friability (%)	Thickness (mm)	Diameter (mm)	Weight (mg)	Weight variation
C1	4.20	0.68	4.92	9.02	510	475-525 mg
C2	4.10	0.58	4.85	9.03	498	475-525 mg
C3	4.30	0.70	4.88	9.01	496	475-525 mg
C4	3.90	0.60	4.86	9.02	492	475-525 mg
C5	4.00	0.48	4.94	9.02	498	475-525 mg

4.3 Post compression Studies:

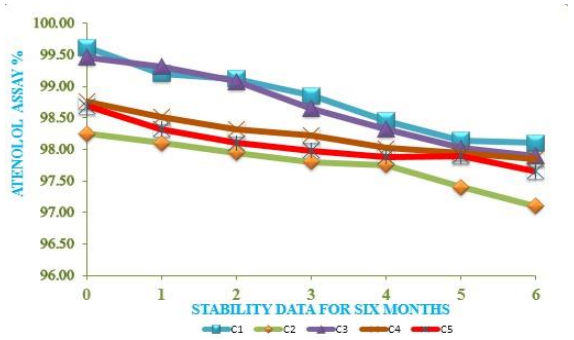
Formulation code	Assay of Drugs (%)	Water intake time (sec)	Disintegration time (sec)	Dissolution (%)
C1	99.62	16-19	9-11	94.83
C2	98.25	18-21	13-15	91.25
C3	99.46	20-24	16-17	87.45
C4	98.76	24-28	16-19	84.87
C5	98.69	25-31	19-21	80.65

5. Stability studies. Stability studies data for C 1 formulation

Time	Evaluation Parameter					
	Colour	Hardness	Disintegration time	Drug Content	Dissolution time	Result
After 1 Month	White	4.00	09-11 seconds	99.28 %	94.85 %	Pass
After 2 Month	White	3.70	09-11 seconds	98.45 %	92.41 %	Pass
After 1 Month	White	3.40	12-13 seconds	98.28 %	91.56 %	Pass
After 3 Month	White	3.40	13-15 seconds	97.85 %	90.48 %	Pass
After 4 Month	White	3.20	16-18 seconds	97.65 %	90.12 %	Pass
After 5 Month	White	3.20	17-20 seconds	97.30 %	88.48 %	Pass
After 6 Month	White	3.10	18-21 seconds	97.20 %	87.32 %	Pass

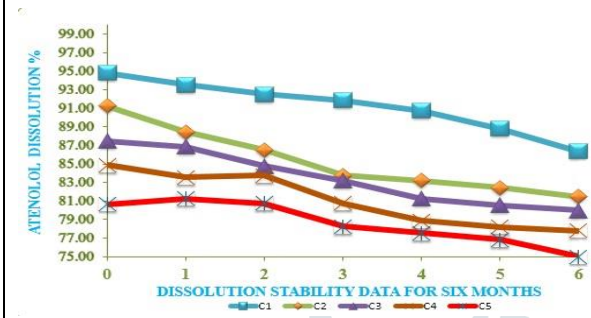
6. GRAPHS

ATENOLOL ASSAY STABILITY DATA



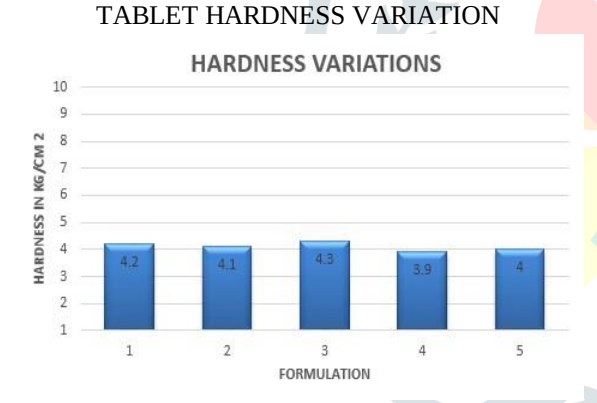
Time (Months)	Atenolol Assay Stability Data				
	C 1	C 2	C 3	C 4	C 5
0	99.62	98.25	99.46	98.76	98.69
1	99.20	98.10	99.32	98.52	98.32
2	99.12	97.95	99.08	98.32	98.10
3	98.85	97.80	98.65	98.22	97.98
4	98.45	97.75	98.32	98.02	97.88
5	98.14	97.40	98.02	97.95	97.90
6	98.10	97.10	97.90	97.85	97.65

ATENOLOL DISSOLUTION STABILITY DATA

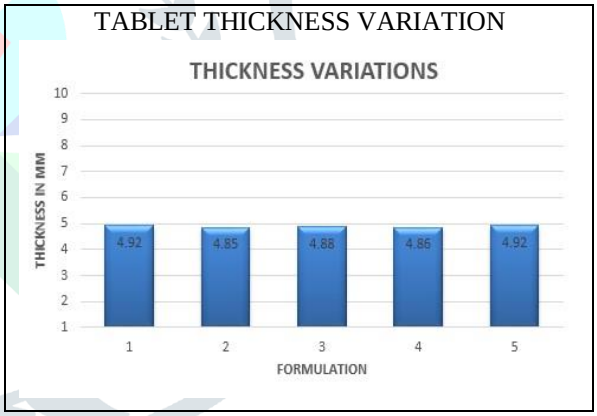


Time (Month)	Atenolol Dissolution Stability Data				
	C 1	C 2	C 3	C 4	C 5
0	94.83	91.25	87.45	84.87	80.65
1	93.52	88.45	86.85	83.54	81.25
2	92.54	86.52	84.75	83.74	80.74
3	91.84	83.74	83.21	80.74	78.25
4	90.74	83.21	81.25	78.87	77.54
5	88.82	82.45	80.54	78.21	76.85
6	86.35	81.47	80.00	77.78	75.00

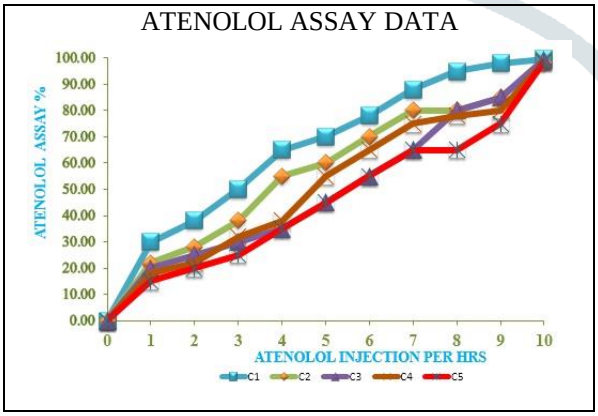
TABLET HARDNESS VARIATION



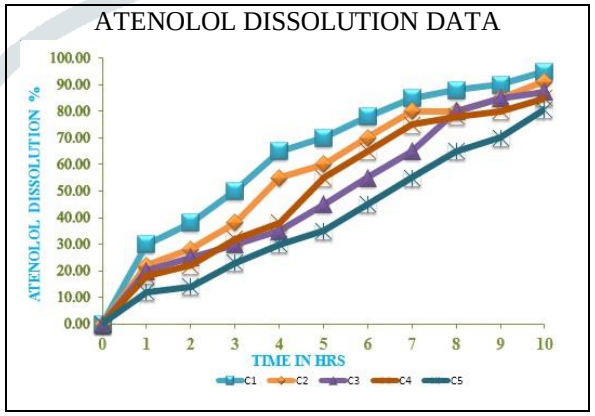
TABLET THICKNESS VARIATION



ATENOLOL ASSAY DATA



ATENOLOL DISSOLUTION DATA



6. Conclusion:

In the current efforts have been made to formulate and evaluate orodispersible tablets of Atenolol Maleate 100 mg using different super disintegrants by a direct compression method. The results disclosed that increased amount of various super disintegrants were associated with an increase in overall rate of cumulative drug release. Of all five formulations, C1formulation with 20 mg of cross carmillose sodium exhibited maximum cumulative drug release in 9-11 seconds. In addition, formulation C1 also showed short wetting time, good drug content, and fast disintegration. Stability studies conducted also revealed no any significant changes in the color, hardness, drug content uniformity, % CDR, and *in vitro*

disintegration time. Henceforth, we concluded that formulated Atenolol Maleate 100 mg ODTs can be one of the better choices for the management of hypertension enhanced patient compliance and rapid onset of action.

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