Design and Development of Atenolol Orally Disintegrating Tablets by Superdisintegration Method

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ABSTRACT

The present study aims to formulate and evaluate oro dispersible tablets of Atenolol, a drug that is used for the treatment of chest pain (angina) was prepared by using superdisintegration method and also optimize the best formulation. The study involved different excipients which were tested for their compatibility with Atenolol by the FT-IR studies. Based on the results of FT-IR studies, majority of the excipients were found to be compatible with Atenolol which were used for the preparation of Atenolol oral disintegrating tablets. Oral disintegrating tablets of Atenolol were prepared by direct compression method by the addition of super disintegrants. Seven batches (F1 – F7) of oral disintegrating tablets of Atenolol were prepared by using super disintegrants like Sodium starch glycolate and Croscarmellose in variable concentrations along with other excipients for the development of optimized formulation. All the formulations were subjected to evaluation studies of weight variation, hardness, friability, drug content, Wetting time, in-vitro disintegration, in vitro-dissolution studies and are found to be within the limits.

KEY WORDS:-*Oro dispersible tablet (ODT), Atenolol, Direct compression, Superdisintegration Method, Anti angina activity.*

1. INTRODUCTION:

Most of the oral pharmaceutical dosage forms like conventional tablets and capsules are formulated to be swallowed or chewed. As a result children, bedridden patients and elderly patients have difficulty in swallowing these dosage forms. To overcome this drawback novel drug delivery systems like orally disintegrating tablets have been developed which disintegrate/dissolve/ disperse in saliva within few seconds without water. United States of America Food and Drug Administration (USFDA) define ODT as "A solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon a tongue''[1]

The principal benefits of ODT include meliorated patient compliance, improved bioavailability, rapid onset of action, pain avoidance, consumption without water, pregastric absorption, versatility, and economical. Pregastric absorption is the major capital advantage of the ODTs, which avoids hepatic first-pass metabolism of the drugs[2]

Atenolol is a beta-blocker used to treat chest pain (angina) and high blood pressure. It is also used after an acute heart attack to improve survival. High blood pressure reduction helps prevent strokes, heart attacks and kidney problems. This drug works by blocking the action of certain natural chemicals in your body such as epinephrine on the heart and blood vessels. This result in a lowering of the heart rate, blood pressure, and strain on the heart. This medication may also be used for irregular heartbeats, heart failure, migraine headache prevention, tremors.

The main objective of the study was undertaken for formulation and evaluation of oral dispersible tablets of atenolol by direct compression technique. In the present work, an attempt was made to formulate atenolol orodispersible tablet using different superdisintegrants (like croscarmellose sodium, sodium starch glycolate) in different ratios by direct compression method. The fundamental principle used in the development of the fast dissolving tablet is to maximize its pore structure[3].

2. MATERIALS AND METHODS:

The active pharmaceutical ingredient Atenolol was procured from Litaka Pharmaceuticals, Pune. The other excipients such as Sodium Starch Glycolate, Micro crystalline cellulose, and Talc were procured from SD Fine Chemicals, Mumbai. Croscarmellose sodium, Aspartame and Sodium Stearyl Fumarate were purchased from DMV, Fonterra excipients, India. Directly compressible Mannitol was purchased from Roquette Chemicals, France.

2.1 METHODS:

Standard calibration curve for Atenolol in pH 1.2 buffer

100 mg of atenolol was dissolved in small amount of pH 1.2 buffer and the volume was made up to 100 ml using the same, which is called as stock-I solution. 1 ml of the above solution is diluted to 100 ml in another volumetric flask, which is called as Stock-II solution. From this stock-II solution serial dilutions were made to obtain solutions of the drug in the concentration ranging from 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 µg/ml. The absorbance of the solutions was measured at 224.2 nm using Elico Double beam UV-visible spectrophotometer[4] A graph of concentration vs. absorbance was plotted and shown in fig 1.

Drug-excipient interaction studies

Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned. Therefore, in the present studies Atenolol with the given polymers were analyzed for compatibility studies[5] The spectra are shown in figure 2 - 4.

2.2 Pre-compression studies[6]

All the physical parameters namely, angle of repose, bulk density, compressibility index and Hausner's ratio were performed and the results are shown in table 2

1. Angle of Repose:

It is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the given formula.

$$\theta = tan - 1\,(\frac{h}{r})$$

2. Bulk density:

It is the ratio of total mass of powder to the bulk volume of powder. Required quantity of powder blend was transferred in 100 ml graduated cylinder and the bulk density was calculated by using the formula given below.

$$\text{Bulk density} = \frac{\text{weight of powder}}{\text{Bulk volume}}$$

3. Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder. Required quantity of powder blend was transferred in 100 ml graduated cylinder which was operated for fixed number of taps until the powder bed volume has reached a minimum Tapped density using the was calculated by formula given below.

$$\text{Tapped density} = \frac{\text{Weigh of powder}}{\text{Tapped volume}}$$

4. Compressibility Index:

It is a simple test to evaluate bulk and tapped density of a powder .The formula for Carr's index is as below:

$$C.I = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} * 100$$

5. Hausner's Ratio:

Hausner's Ratio is a number that is correlated to the flow ability of a powder.

$$Hausner's\ ratio = \frac{Tapped\ Density}{Bulk\ Density}$$

2.3 FORMULATION OF ORODISPERSIBLE TABLETS OF ATENOLOL

Atenolol orodispersible tablets were prepared by direct compression method according to formulae given in the table 1. Blend can be prepared by passing the ingredients through 60-mesh sieve separately and collected. The drug and microcrystalline cellulose were mixed in small portion of both at each time and blended to get a uniform mixture and kept aside. Then the other ingredients were weighed and mixed in geometrical order and the tablets were compressed using flat face 8 mm size punch to get a tablets of 150 mg weight using ten station Rimek tablet compression machine.

Table 1 : Different Formulations of Atenolol using superdisintegrant addition method

Sr. No.	Name of the chemical used	Quantity used in mg						
		F1	F2	F3	F4	F5	F6	F7
1	Atenolol	25	25	25	25	25	25	25
2	Sodium starch glycolate	---	3	6	9	---	---	---
3	Croscarmellose sodium	---	---	---	---	3	6	9
4	Avicel pH 102	30	30	30	30	30	30	30
5	Aspartame	6	6	6	6	6	6	6
6	Sodium stearyl fumarate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Talc	3	3	3	3	3	3	3
8	Mannitol directly compressible	84.5	81.5	78.5	75.5	81.5	78.5	75.5

2.4 POST COMPRESSION STUDIES [6,7,8]

1. Weight Variation

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

2. Hardness test

Hardness of the tablet was determined by using the Monsanto hardness tester-Mumbai. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

3. Friability test

This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the Roche friabilator, rotating at 100rpm for 4min. The tablets are then taken out, dedusted and were weighed.The difference in the weight is noted and expressed as percentage.

4. Wetting Time

Circular tissue papers were placed in a petridish containing water. The prepared tablet was then carefully placed. The time required for water to reach the upper surface of the tablets and to get completely wet was noted as the wetting time. Wetting time was recorded using a stopwatch.

5. Content Uniformity

At random 20 tablets were weighed and powdered. The powder equivalent to 25 mg was weighed accurately and dissolved in 100ml of 0.1 N HCl. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatmann No.41 filter paper. Then the dilute the solution to obtain 10µg solution. The absorbance of the diluted solutions was measured at 224.2 nm by spectrophotometric method. The concentration of the drug was computed from the standard curve of the atenolol in 0.1 N HCl.

6. *In-Vitro* Disintegration Time

In- vitro disintegration time was measured by dropping a tablet in a beaker containing phosphate buffer PH 6.8. Tablets from each formulation were randomly selected and in vitro dispersion time was performed. All these studies were performed and the results are shown in table 3.

7. *In-vitro* drug release studies:

In-vitro drug release studies were carried out by using Electrolab TDT-08L USP-type II dissolution apparatus 900 ml of Phosphate buffer (pH 1.2) was placed in the dissolution flask maintained at a temperature of 37±0.5^{0}C.One tablet was placed in the flask of the dissolution apparatus and was operated to run upto 60mins at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn, filtered and again replaced with 5 ml of fresh medium. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ max is 224.2 nm using a UV-spectrophotometer. The in-vitro drug release of ODT tablets of
Atenolol were shown in table 4 and their comparison profile was shown in fig 5.

3. RESULTS & DISCUSSIONS:

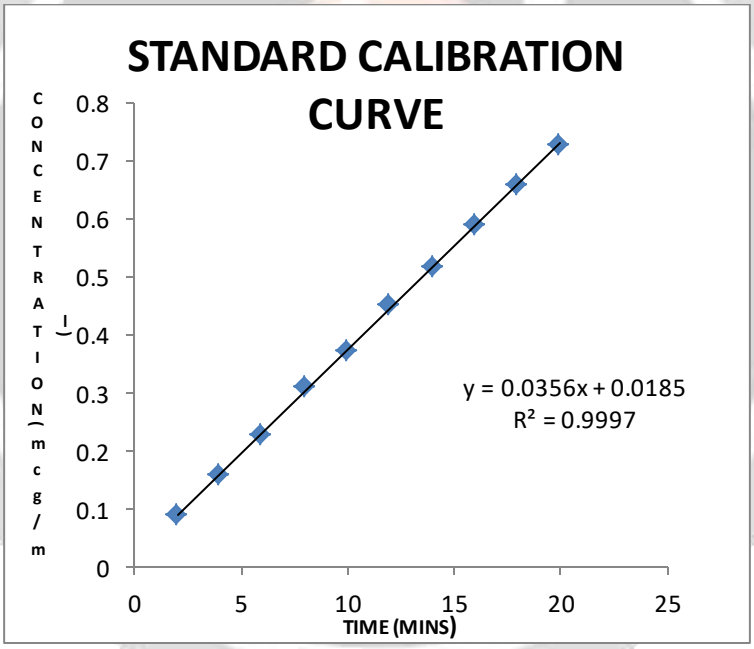

Figure 1: Standard calibration curve

3.1 FT-IR STUDIES

To study the presence of interactions between the active pharmaceutical ingredient and the selected polymers, FT-IR studies were undertaken. The The FT-IR spectra are shown in Figure 2 to 4.

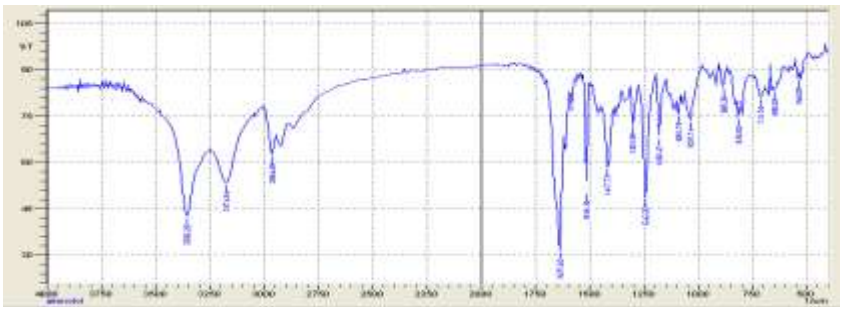

Figure 2: I.R-1: I.R. SPECTURM OF ATENOLOL (PURE DRUG)

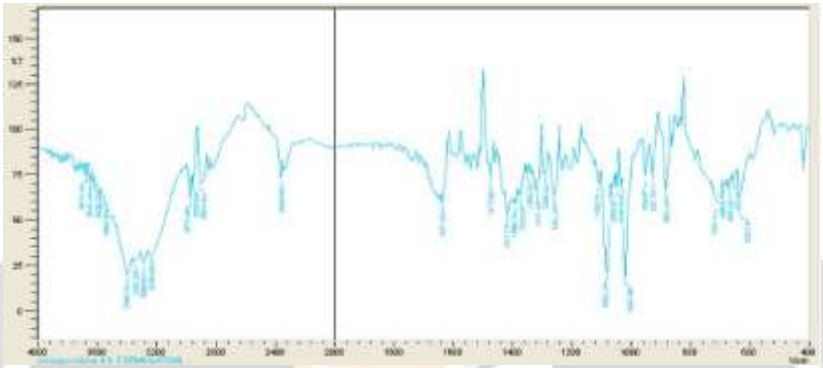

Figure 3: I.R-2: I.R. SPECTURM OF ATENOLOL FORMULATION –F7

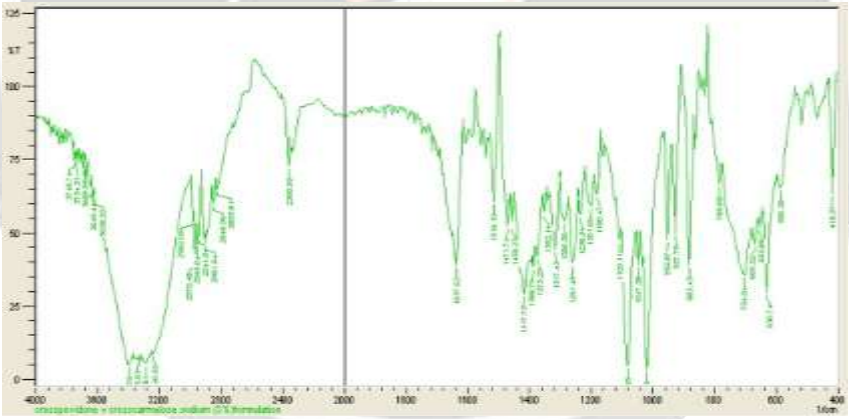

Figure 4: I.R-3: I.R. SPECTURM OF ATENOLOL FORMULATION –F4

Table 2: Pre Compression parameters of Atenolol tablet formulation

Formulation	Parameters				
	Angle of Repose (θ)*	Bulk Density (g/ml)*	Tapped Density (g/ml)*	Carr's Index. (%)*	Hausner ratio*
F1	27.50 ± 0.182	0.3913 ±0.007	0.4615±0.011	15.20 ± 1.62	1.17 ± 0.023
F2	27.42 ± 0.075	0.3913 ±0.007	0.4615±0.010	15.20 ± 1.62	1.17 ± 0.023
F3	27.54 ± 0.137	0.4186 ±0.008	0.4866 ±0.011	13.97 ± 0.282	1.16 ± 0.003
F4	28.32 ± 0.219	0.3750±0.008	0.4391 ±0.009	14.56 ± 1.80	1.16 ± 0.023
F5	27.73 ± 0.344	0.4140 ±0.014	0.4933 ±0.011	14.92 ± 1.52	1.17 ± 0.023
F6	28.33 ± 0.225	0.3833 ±0.014	0.4395 ±0.019	13.7 ± 1.89	1.15 ± 0.028
F7	27.43 ± 0.273	0.4000±0.012	0.4676 ±0.010	14.43 ± 1.92	1.16 ± 0.028

***** Mean ± S.D., n=3 (All the values are the average of three determination)

Table 3: Post Compression Parameters of Atenolol ODT

Formulations	Parameters						
	Weight variation test (%)*	Friability (%)	Hardness (kg/cm^2)*	Diameter (mm)*	Disintegration time (sec)*	Wetting Time (sec)*	Drug Content (%)*
F1	151.1±1.21	0.396	3.83±0.28	7.98±0.01	183.66±0.51	98±1.21	100.88±0.88
F2	151±1.33	0.524	3.16±0.28	7.99±0.01	65.66±0.51	60±1.73	98.72±0.44
F3	150.3±1.02	0.402	3.66±0.28	7.98±0.01	57.66±1.08	54±1.64	98.52±1.17
F4	151.5±1.01	0.530	3.83±0.28	7.97±0.02	48.33±0.51	38±1.10	98.82±1.83
F5	151.25±0.37	0.658	3.33±0.28	7.99±0.05	35.66±1.08	30±0.64	99.41±1.63
F6	150.9±1.65	0.663	3.16±0.28	7.99±0.02	29.33±1.08	28±0.64	101.17±1.78
F7	152±1.85	0.796	3.50±0.50	7.99±0.01	33.66±1.52	29±0.64	99.11±1.28

***** Mean ± S.D., n=3 (All the values are the average of three determination)

Table 4: *In-Vitro* dissolution of Atenolol tablet for Formulation-F1- F7

Time In Min	F1	F2	F3	F4	F5	F6	F7
0.5	4.60	4.86	5.19	31.49	12.72	30.93	31.42
1	18.65	59.13	51.16	59.06	84.82	87.59	93.60
1.5	26.37	74.21	72.63	73.43	89.95	92.63	94.59
2	35.56	83.71	85.97	86.52	90.93	93.73	95.60
2.5	42.97	91.03	91.14	93.27	91.88	94.82	95.78
3	53.87	93.80	92.93	94.29	94.29	96.08	98.81

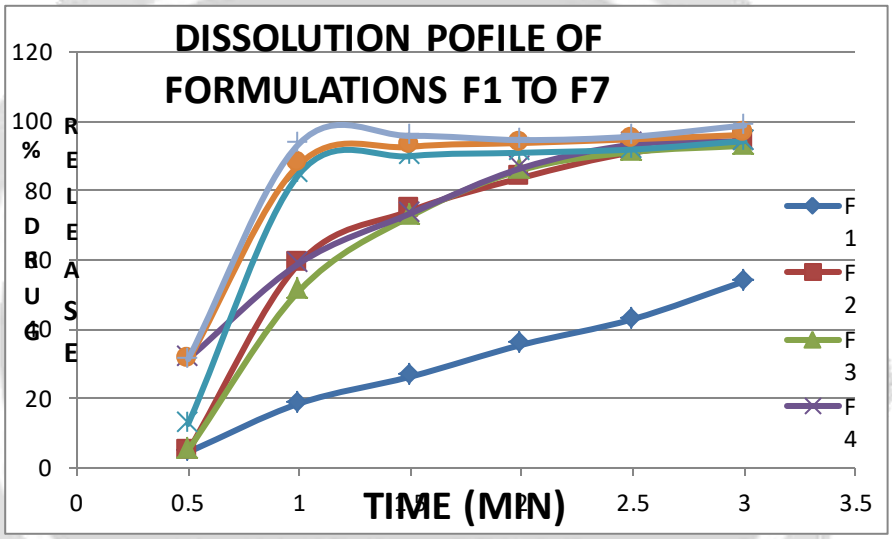

Figure 5: Comparison of % drug release of formulations F1 – F7

4. CONCLUSION

Suitable analytical method based on UV-Visible spectrophotometer was developed for Atenolol. λmax of 224.2 nm was identified by using phosphate buffer solution, pH 1.2. From the FT-IR spectra, the interference was verified and found that Atenolol did not interfere with the excipients used. Precompression studies of atenolol were performed. Oral Disintegrating tablets of atenolol were successfully prepared using Sodium Starch Glycolate and Croscarmellose sodium by using direct compression method. Post compression parameters like general appearance, weight variation, hardness, friability, in-vitro dispersion and wetting time indicate that values were within permissible limit for all formulations. In-vitro drug release study was carried out and based on the results, F 7 formulation was identified as best amongst all the other formulations and its release was found to be 93% within 1min. and it showed a constant release up to 3 min. On the basis of the results, the formulation containing CCS was considered as ideal among all other formulations used for the development of atenolol tablets.

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